Original Article

Clinicopathological Features of Young Gastric Cancer and New Inflammatory Prognostic Markers

Genç Mide Kanserinin Klinikopatolojik Özellikleri ve Yeni İnflamatuar Prognostik Belirteçler

Ahmet Gülmez[1], Mustafa Dikilitaş[2]

[1]Adana City Education and Research Hospital, Department of Medical Oncology
[2]Inonu University Faculty of Medicine. Department of Medical Oncology. Malatya

ABSTRACT

Introduction: This study aimed to evaluate the clinicopathologic features of young gastric cancer (GC) patients and to investigate the factors affecting survival (OS).
Materials and methods: In this study, the data of 55 patients diagnosed under the age of 40 were obtained by retrospective evaluation of hospital records. Clinicopathological features and some laboratory parameters of this patient group and new inflammatory prognostic markers (IPM) obtained from these parameters were evaluated.
Results: The mean age of the patients in this study was 33 years. The majority of the patients were male. Patients were evaluated according to human C-erbB2 positivity too. The identified patients as positive were only 7% of all patients. Also, the patients were evaluated for platinum sensitivity too. It was found that 30% of the patients were sensitive to platinum treatments. Also, survival times of the patients were evaluated with IPM. Neutrophil-lymphocyte ratio (NLR), mean platelet volume/platelet count, C-reactive protein/albumin ratios were calculated separately. Survival results were analyzed based on the mean values of all 3 prognostic markers. Even though there was a significant numerical difference, no statistical significance was found.
Discussion: This study was conducted to examine the clinicopathological features and survival time of young GC patients. Low C-erbB2 positivity and high platinum resistance were found among this patient population. In addition, inflammatory prognostic markers, which were found to be associated with survival in most cancers, were found to cause significant numerical differences in terms of survival in our study.

Keywords: Young Gastric Cancer, Prognosis, Novel Prognostic Markers

ÖZET

Giriş: Bu çalışma genç mide kanseri (GC) hastalarının clinicopathologic özelliklerini değerlendirmek ve sağ kalıma (OS) etki eden faktörleri araştırmayı amaçladı.
Gereç ve yöntemler: Bu çalışmada, hastane kayıtlarının retrospektif olarak değerlendirilmesi ile 40 yaş altı tanı almış 55 hastanın verileri elde edilmiştir. Bu hasta grubunun klinikopatolojik özellikleri ve bazı laboratuvar parametreleri ile bu parametrelerden elde edilen yeni inflamatuar prognostik belirteçler (IPM) değerlendirildi.
Bulgular: Çalışmamızda hastaların ortalama yaşı 33'tü. Erkek hastaların sayısı çoğunluktaydı. Hastalar C-erbB2 pozitifliğine göre de değerlendirildi. Pozitif olarak saptanan hastalar, tüm hastaların sadece %7'siydi. Hastalar aynı zamanda platin duyarlılığı açısından da değerlendirildi. Hastaların %30'unun platin tedavilerine karşı duyarlı olarak saptandı. Hastaların SK süreleri inflamatuar prognostik belirteçler eşliğinde de değerlendirildi. Nötrofil-lenfosit oranı (NLR), ortalama platelet volümü/platelet sayısı (MPV/platelet sayısı), C-reaktif protein/albümin oranları (CAR) ayrı ayrı hesaplandı. Her 3 prognostik belirtecin de ortalama değerleri baz alınarak SK sonuçları incelendi. Bu değerler ve SK arasında rakamsal olarak belirgin farklılık olmasına rağmen istatistiksel bir anlamlılık saptanmadı. **Tartışma:** Bu çalışma genç mide kanseri hastalarının klinikopatolojik özelliklerini ve SK sürelerini

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incelemek için yapılmıştır. Çalışmamız sonucunda bu hasta grubunda düşük C-erbB2 pozitiflik oranı ve yüksek platin direnci olduğu saptanmıştır. Ayrıca çoğu kanserde sağkalımla ilişkili olduğu saptanan inflamatuar prognostik belirteçlerin, çalışmamızda da SK açısından belirgin rakamsal farklılık oluşturduğu görülmüştür.

Anahtar kelimeler: Genç Mide Kanseri, Prognoz, Yeni Prognostik Belirteçler

Introduction

Gastric cancer (GC) is an important cancer worldwide. It is estimated that there will be more than 1,000,000 new cases and 783,000 deaths for GC in 2018. This makes GC the fifth most frequently diagnosed cancer worldwide and the third most common cause of cancer death [1]. Gastric cancer shows a marked variation for age at diagnosis. Gastric cancer is usually detected more frequently in older people in the United States, and the average age at diagnosis is 68. More than 95% of all newly diagnosed GC patients are over the age of 40 [2]. According to literature, patients under the age of 40 are referred to as young GC. Although few patients with young GC are seen in the literature, young GC patients have started to be seen more frequently in recent years. This situation can be caused by many different reasons. In addition to the development of cancer screenings and diagnostic procedures, the fact that people come into contact with carcinogens from an earlier age can be counted among the reasons for this situation.

Young adult patients with GC face unique challenges such as tumor biodiversity, differences in treatment efficacy, tolerance and compliance with treatment, fertility preservation, and psychosocial considerations associated with premature death [3-4]. There are some variation in the specific threshold used to define young adult GC patients. Large study groups, such as the National Cancer Institute [5], used age 39 as the upper limit to define young adult GC. Diffuse type GC is more common in this group of young adults. These patients are diagnosed later than elderly patients and have a more aggressive tumor biology [6].

In this study that we have completed, we evaluated the clinico-pathological features, treatments they received, and responses to these treatments in patients aged 40 years and younger. In addition, we aimed to evaluate some laboratory parameters, progression-free survival (PFS) and overall survival (OS) data of these patients.

Materials and Methods

In this study, we retrospectively evaluated GC patients who were diagnosed pathologically in our hospital between 2010 and 2020. When the hospital records were examined, it was seen that the number of young adult GC patients diagnosed between these years was 55. Gender, ECOG (Eastern Cooperative Oncology Group) performance status, predominant complaint at the time of diagnosis, diagnosis method, TNM stage at the time of diagnosis [7], surgical procedure and surgical technique, treatment modalities, hemoglobin (Hb), neutrophil (Neu) of the patients in our study, lymphocyte (Lym), platelet (Plt), albumin (Alb), total protein (Tp), C-reactive protein (CRP) results were obtained from hospital records. NLR was calculated as absolute neutrophil count / absolute lymphocyte count. MPR was calculated as mean platelet volume/absolute platelet count. CAR; It was calculated by taking the ratio of CRP to albumin. If patients receiving chemotherapy received platinum-based therapy, the platinum sensitivity of these patients was also evaluated. Treatment response assessment in metastatic patients was performed according to the Criteria for Evaluation of Response in Solid Tumors (RECIST) version 1.1 using magnetic resonance imaging (MRI), computed tomography (CT), or Positron Emission Tomography (PET/CT) at 6-8 week intervals. Patients who received adjuvant therapy were included in the follow-up after the end of the targeted treatment period. This study has ethics committee approval dated 29.09.2020 and numbered 2020-979. All procedures performed in studies involving human participants comply with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and later amendments or comparable ethical standards.

Statistical Analysis

Clinicopathological features were evaluated. Overall survival (OS) was calculated as the time from diagnosis to death from any cause. Overall survival was assessed using the Kaplan Meier method and compared using log-rank tests. Statistical analyzes were performed with IBM SPSS Statistics for Windows (version 22.0. Armonk, NY). A p value less than 0.05 was considered statistically significant. Patient survival was determined as mean ± standard deviation and was written in months.

Results

In this study, a total of 55 patients were evaluated in accordance with the inclusion and exclusion criteria. The patients were evaluated according to the complaint of predominance at the time of admission to the hospital. The predominant complaint was abdominal pain in 36 (65%) patients, and nausea and vomiting in 12 (27%) patients. Less common causes were weight loss in 5 (9%) patients and admission to the hospital with bleeding symptoms in two (4%) patients. When evaluated as a diagnosis method; 49 (89%) of the patients were diagnosed by endoscopy, while six (11%) patients were diagnosed by surgery. Patients were evaluated for differentiation from biopsy or postoperative pathology reports. Of the patients, five (9%) patients were diagnosed as well differentiated, seven (13%) patients moderately differentiated, 11 (20%) patients poorly differentiated, 18 (33%) patients with signet ring cell, and 14 (25%) patients with poorly cohesive carcinoma. The patients were also evaluated in terms of cerbB2 as a result of staining with immuno-histochemical evaluation. 37 (67%) of these patients were found to be cerbB2 negative. It was evaluated as +1 positive in 10 (19%) of the patients, +2 positive in four (7%) and +3 positive in four (7%) patients. The clinical and demographic data of these patients are shown in Table-1. The total number of patients who were considered locally advanced and operated for curative purposes was 35 (64%). On the other hand, the number of patients who were metastatic at the time of diagnosis was 20 (36%). When the patients were evaluated as surgical and non-surgical, it was seen that 40 (73%) patients were operated and 15 (27%) were not operated. While 35 of these operated patients were operated for curative purposes as previously stated, 5 patients were operated for palliative purposes. Subtotal gastrectomy was performed in 26 (65%) of 40 patients who underwent surgery, while total gastrectomy was performed in 14 (35%) patients. When the patients are classified according to the type of chemotherapy they receive; It was seen that five (9%) patients received neoadjuvant

Table 1. Demographic Data and Clinicopathological Characteristics of the Patients

	Number of Patients (n=55)	(%)
Age		
Median Age	33	
Range	(18-40)	
Gender		
Male	31	56
Female	24	44
ECOG		
0	15	27
1	21	38
2	19	35
Dominant Complaint		
Abdominal Pain	36	65
Nausea and Vomiting	12	22
Weight Loss	5	9
Bleeding	2	4
Diagnostic Method		
Endoscopy	49	89
Surgery	6	11
Subtype-Differential		
Well Differentiated	5	9
Poor Differentiated	7	13
Middle Differential	11	20
Ring Cell	18	33
Poorly Cohesive	14	25
CerbB2		
Negative	37	67
+1	10	19
+2	4	7
+3	4	7
Stage at Diagnosis		
Stage II	5	9
Stage III	30	55
Stage IV	20	36

Table 2. Surgical Characteristics and Treatments of the Patients

	Number of Patients (n 55)	(%)
Indication of Surgery		
Curative Approach	35	64
Palliative Approach	5	9
No Surgery	15	27
Type of Surgery		
Subtotal Gastrectomy	26	65
Total Gastrectomy	14	35
Lymph Node Dissection		
D1	4	10
D2	31	77
Unknown	5	13
Chemotherapy Reason		
Neoadjuvant	5	9
Adjuvant	27	49
Palliative	16	29
Could not get	5	9
No indication	2	4
Chemotherapy Type		
FUFA	11	23
FOLFOX	22	46
DCF	10	21
FLOT	3	6
EOX	2	4
Chemoradiotherapy	18	37,5
Completing Systemic Treatment	30	62,5
Platinum Sensitivity	11	30

FUFA: Fluorouracil/Folinic Acid, FOLFOX: Oxaliplatin Plus İnfusional 5-FU And Leucovorin, DCF: Docetaxel, Cisplatin and Fluorouracil, FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel, EOX: Epirubicin, Oxaliplatin, And Capecitabine

chemotherapy, 27 (49%) patients received adjuvant chemotherapy, and 16 (29%) patients received palliative chemotherapy. Although five (9%) patients had indication for treatment, they could not receive treatment due to poor performance status, and two (4%) patients had no indication for treatment. The patients were also evaluated according to the type of chemotherapy. 11 (23%) patients were treated with FUFA, 22 (46%) patients with FOLFOX, 10 (21%) patients with DCF, three (6%) patients with FLOT, and two (4%) patients with EOX. The patients were also evaluated according to the planned systemic treatment completion status. While 30 (62.5%) of 48 patients who started systemic treatment completed the planned treatment period, it was observed that the planned treatment period could not be reached in 18 (37.5) patients. The data from 37 patients treated with platinum agents were also re-evaluated for platinum sensitivity. The times determined for platinum sensitivity; at least 6 months after the end of treatment for metastatic disease, and 12 months after the end of treatment for patients who received adjuvant or neoadjuvant therapy. When evaluated with these criteria, a total of 11 (30%) patients were found to be platinum sensitive. The operation information of the patients and the systemic treatments of their received are shown in Table-2.

Some laboratory parameters of the patients were also evaluated. Patients were evaluated as neutrophil-lymphocyte ratio (NLR). The mean value was determined as 5.60 (0.99-21.20). The mean value for the evaluation of MPV/Platelet ratio, another inflammatory prognostic marker, was found to be 0.049 (0.011-0.450). Similarly, the mean ratio of CRP/Albumin, an inflammatory prognostic marker, was 1.38 (0.016-7.42). The relationship between inflammatory prognostic markers and OS is shown in Table 3.

Discussion

Gastric cancer patients are usually diagnosed over the age of 40. However, the frequency of GC patients under the age of 40 has been increasing in recent years, especially in western societies. And these patients are mostly diagnosed in the 30-39 age range [8]. In a previously published article, it was shown that young GC patients were diagnosed at a more advanced stage and their survival was worse [9]. The reasons for this poor prognosis are controversial. Some authors argue that GC diagnosed at an early age has genetic origins and therefore has a more aggressive course. According to another view, in many countries of the world, especially in countries where GC is endemic, young patients cannot be detected early due to inadequate screening programs and therefore the prognosis of these patients is worse. Possibly, both hypotheses may account for the poor course of these patients.

Table 3. Inflammatory Prognostic Markers and Survival Times

	Overall Survival-Month (OS)	Min	Max	p value
		%95 CI		
NLR				
<5,6 (n 18)	12,44±7,40	8,92	15,6	p>0,05
>5,6 (n 14)	7,08±4,72	5,11	9,27	
MPV/Platelet				
<0,049 (n=26)	9,73±7,20	7,02	12,78	p>0,05
>0,049 (n=6)	11,66±5,15	5,10	9,15	
CRP/albumin				
<1,38	11,18±4,93	8,95	13,38	p>0,05
>1,38	8,70±6,71	3,48	5,92	

NLR: Neutrophil-Lymphocyte Ratio, MPV: Mean Platelet Volume, CRP: C-Reactive Protein

Young GC has not been clearly defined yet. In previous studies, there are studies based on the age of 50, 40, and 34 years [10]. This definition of young GC varies due to the development level and life expectancy of the countries. In this study, we classified patients aged 40 years and younger as young GC. The mean age of the patients in this study was 33 years. More than half of the patients were male patients. In a previous study, the fact that GC seen at a young age was more common in women was attributed to hormonal changes. In addition, it has been stated that the reason for the excess of male cancer detected at advanced age is exposure to carcinogens more than women [10]. However, there is no clear cause and effect relationship related to this situation. Because the number of male patients was found to be higher in different series studies performed on young GC patients. In the same study, diffuse histology and poorly differentiated tumors were observed to be more common in younger patients. However, no difference was found regarding the diagnosis of younger patients at a later or more advanced stage. In addition, it has been observed that young GC patients have a shorter DFS period [10].

In another study, almost 5000 patients were evaluated and patients younger than 40 years of age were classified as young GC. There were 136 patients in this group. In this study, no difference in OS was found between younger patients and older patients. However, it has been reported that the performance status of young patients is better than that of elderly patients, and the complication rates after surgery are lower than those of the elderly. In addition to this situation, as in previous studies, pathologically worse differentiated tumors were found to be more common in younger patients. In addition, in this study, it was observed that the frequency of lymph node metastasis in young patients was higher than in patients over 40 years of age [11]. The reason why both OS and DFS durations were not different from patients aged >40 years in this study may be that the systemic treatments they received were more potent due to the better performance status of the younger patients. Another meta-analysis involving young GC patients was published in 2020. According to this study, the clinicopathologic features of GC patients diagnosed under the age of 40 were evaluated in 19 different studies between 2010 and 2019. In the light of these studies, the rate of female patients, the rate of diffuse type GC, the rate of poorly differentiated GC, and the rate of diagnosis at a more advanced stage were found to be higher in younger GC patients [12].

The standard treatment for Her-2 positive advanced GC is a combination of trastuzumab and platinum-based chemotherapy. The study that made this treatment standardized is the

ToGA study [13]. As mentioned in this study, Her-2 amplification or over-expression varies between 7-34%. However, Her-2 positivity rate was found to be only 7% in this study. This low Her-2 positivity rate also reduces the treatment options that can be used in young GC patients. Unfortunately, in this study that we have completed, the number of patients who can use the Her-2 targeted therapy option is extremely low.

Recently, treatment options without the use of conventional chemotherapy have been developed for some types of cancer. However, in treatment-naive and especially platinum-sensitive GC patients, a systemic treatment plan cannot be made without the use of platinum-based chemotherapy. However, platinum resistance in some patients renders these treatments ineffective. Many studies investigating which patients have resistance to these treatments have been reported in the literature [14,15]. In this study, approximately 70% of the patients had platinum resistance. Such a high level of platinum resistance in young GC patients may explain the poor prognosis of the patients. Investigation of the causes of platinum resistance in young GC patients; It should be the main subject of future studies both for genomic polymorphisms that can explain the pathogenesis of the disease and to aim to increase the extremely poor survival of the disease.

Due to both platinum resistance and low rate of Her-2 positivity, the treatment options available in young GC patients are decreasing. At this stage, immunotherapy treatments, which have gained importance in recent years, can be considered as an option. There is no clear biomarker for immunotherapy yet. Previous studies have shown that immunotherapies are beneficial in patients with high microsatellite instability (MSI-H), regardless of tumor type. With this demonstrated clinical benefit, pembrolizumab treatment has been approved by the American Food and Drug Administration (FDA) in patients with MSI-H [16]. However, according to a previous meta-analysis, there is a lower rate of MSI-H/dMMR in early young GC patients than in advanced age GC patients [17]. All these situations prove that young GC patients are more difficult patients and that more research is needed in this area.

Inflammatory prognostic markers are especially important in predicting the prognosis of the disease. Recently, it has been studied in almost all cancer types. As a result of studies supporting each other, they have become important parameters used in clinical practice. These parameters have also recently been studied in GC. It was evaluated in one study in patients with stage III GC, which included a total of 225 patients. C-reactive protein/albumin ratio (CAR) and platelet lymphocyte ratio (PLR) were found to be independent markers that affect overall survival [18].

There is also a meta-analysis result in patients with GC. The data from 41 studies published between 2007 and 2020 were analyzed [19]. According to this meta-analysis, which included a total of 18,348 patients, the increased NLR value was confirmed to be a negative prognostic marker for OS. Certain cut-off values were used for the inflammatory prognostic markers mentioned in these studies. These cut-off values were determined based on the average value of the patients in some studies, a target value was determined in some studies, and Roc Curve analysis was performed in some studies. However, the number of patients should be sufficient for Roc curve analysis. In this study, which we completed, the mean values of the patients were calculated due to the small number of patients and this mean value was taken as the cut-off value. A significant numerical difference was found in all three inflammatory prognostic markers in overall survival calculated with these values. However, this numerical difference was not statistically significant due to the insufficient number of patients.

The shortcomings of our study are the small number of patients, data from a single center, and being a retrospective study. The strengths of our study are that there are very few young

GC studies in the world. Another strength is that it is the first study to evaluate all three inflammatory prognostic markers in young GC patients. It is important to confirm with larger patient numbers. Considering all these data, early-stage GC is an important problem that should be emphasized. In this patient group, new treatment options are needed because of the poor biological behaviour of the disease and less use of targeted therapy agents.

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Corresponding author e-mail: doktor.ahmetgulmez@gmail.com

Orcid ID:
Ahmet Gülmez 0000-0002-3353-344X
Mustafa Dikilitaş 0000-0002-3763-7529

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Original Article

False-positive MRI Findings in Breast Cancer After Neoadjuvant Chemotherapy and Correlation Between Tumor Response Patterns and HER2 Status

Meme Kanserinde Neoadjuvan Kemoterapi Sonrası Yanlış-Pozitif MRG Bulguları ve Tümör Yanıt Paternleri ile HER2 Durumu Arasındaki Korelasyon

Aydan Avdan Aslan[1], Servet Erdemli[2], İbrahim Halil Erdoğdu[3], Serap Gültekin[1], Cihan Uras[4], Fatma Tokat[5], Ali Arıcan[6], Leyla Özer[6], Kemal Behzatoğlu[5], Nezih Meydan[7], Füsun Taşkın[2]

[1]Department of Radiology, Gazi University, Ankara, Turkey.
[2]Department of Radiology, Acıbadem M.A.A. University, İstanbul, Turkey.
[3]Department of Pathology, Adnan Menderes University School of Medicine, Aydın, Turkey
[4]Department of General Surgery, Acıbadem M.A.A. University, Istanbul, Turkey
[5]Department of Pathology, Acıbadem M.A.A. University, Istanbul, Turkey
[6]Department of Medical Oncology, Acıbadem M.A.A. University, Istanbul, Turkey
[7]Department of Medical Oncology, Adnan Menderes University, Aydın, Turkey

ABSTRACT

Objective: To demonstrate false-positive MRI findings after neoadjuvant chemotherapy (NAC) in patients with pathologic complete response (pCR) and investigate the correlation between post-NAC MRI findings and tumor response patterns based on human epidermal growth factor receptor 2 (HER2) status.

Methods: This retrospective multicenter study enrolled 118 patients with breast cancer who received NAC and achieved pCR. Tumors were evaluated with MRI pre- and post-NAC. MRI evaluation included lesion characteristics, kinetic curve analysis, background parenchymal enhancement (BPE), and post-NAC changes of MRI features. Tumor response patterns were also assessed and categorized based on MRI findings. Tumor response patterns and post-NAC MRI findings were correlated with HER2 status.

Results: The residual MRI findings following NAC differed significantly between HER2+ and HER2− groups (p=0.02). The most frequent false-positive MRI finding was focus and foci in HER2+ tumors, whereas non-mass enhancement (NME) in HER2− group. The presence of ductal carcinoma in situ (DCIS) and fibrosis in surgical pathology is significantly associated with NME on post-NAC MRI (p<0.001). Axillary pCR was achieved significantly higher in the HER2+ group (p=0.04).

Conclusion: Although MRI is considered the most reliable method for evaluating tumor response after NAC, over and underestimation is still possible. This study revealed that tumor response patterns and post-NAC MRI findings differ according to HER2 status. The diagnostic accuracy of post-NAC MRI is evolving by understanding the underlying mechanisms and tumor biology.

Keywords: neoadjuvant chemotherapy, magnetic resonance imaging, breast cancer, pathologic complete response

ÖZET

Amaç: Bu çalışmada patolojik tam yanıtlı (pTY) meme kanseri hastalarında neoadjuvan kemoterapi (NAK) sonrası yanlış-pozitif MRG bulgularını ortaya koymayı ve tümör yanıt paternleri ile insan epidermal büyüme faktörü reseptörü 2 (HER2) pozitifliği ile arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çok merkezli çalışmaya, Ocak 2016 ile Eylül 2020 tarihleri arasında NAK alan ve pTY elde eden meme kanseri tanılı118 hasta dahil edildi. Hastaların NAK öncesi ve sonrası MRG bulguları kayıt edildi. Tümör yanıt paternleri kategorilere ayrıldı. HER2 pozitifliği ile post-NAK MRG bulguları ve tümör yanıt paternleri arasındaki ilişki istatistiksel olarak analiz edildi.

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Bulgular: Post-NAK MRG bulguları HER2+ ve HER2− grupları arasında istatistiksel olarak anlamlı farklılık gösterdi (p=0.02). HER2+ tümörlerinde en sık yanlış-pozitif MRG bulgusu odak kontrast tutulumu iken, HER2− grubunda kitle dışı kontrastlanma (KDK) idi. Cerrahi patolojide duktal karsinoma in situ (DKİS) ve fibrozis varlığı ile post-NAK MRG'de KDK anlamlı olarak ilişkili bulundu (p<0,001). Aksiller pTY, HER2+ grubunda anlamlı derecede daha yüksek elde edildi (p=0.04).
Sonuç: MRG, NAK sonrası tümör yanıtını değerlendirmede en güvenilir yöntem olarak kabul edilse de, yanlış-pozitif ve yanlış-negatif sonuçlar elde edilebilmektedir. Bu çalışma, tümör yanıt paternlerinin HER2 durumuna göre farklılık gösterdiğini ortaya koymuştur. Bu alanda yapılacak yeni çalışmaların tümör biyolojisini anlamaya yardımcı olacağı ve NAK sonrası MRG'nin tanısal doğruluğunu arttırmaya yardımcı olacağı düşünülmektedir.

Anahtar Kelimeler: neoadjuvan kemoterapi, manyetik rezonans görüntüleme, meme kanseri, patolojik tam yanıt

Introduction

Neoadjuvant chemotherapy (NAC) has become the standard treatment in locally advanced breast cancer, and its use has been increasing recently [1]. NAC has also gained acceptance as an alternative therapeutic option in early-stage breast cancer, considering the studies reported no significant difference in survival rates and disease progression between patients who received neoadjuvant and adjuvant chemotherapy [2].

NAC enables breast-conserving surgery with a better surgical outcome in patients with large tumors by downstaging both primary tumor and axillary nodes. As pathologic complete response (pCR) is associated with better disease-free and overall survival, NAC provides valuable prognostic information in patients who achieved pCR [3, 4]. Other potential advantages of NAC over adjuvant chemotherapy include the ability to evaluate the efficacy of selected systematic therapy in vivo.

Accurate ascertainment after NAC is vital to evaluate tumor response and appropriate surgical planning. In the current medical practice, clinical examination and radiological modalities (mammography, ultrasound, and/or magnetic resonance imaging (MRI)) cannot exclude the presence of a residual tumor and surgical treatment must be applied even in the patients with clinical and radiological complete response [5]. As dynamic-contrast enhanced MRI provides information about morphology and function of the tumor, it has been shown that MRI is the most accurate imaging modality to assess tumor response to NAC [6].

Even though MRI is considered the most reliable method in evaluating tumor response following NAC, over and underestimating residual tumor is still possible. Several studies have shown that post-chemotherapy changes in the breast is the major cause of the discordance between pathology and MRI [7, 8]. Besides, tumor response patterns post-NAC are heterogenous and varies depending on subtype and Ki-67 index. Studies have shown that the diagnostic performance of MRI following NAC is better in human epidermal growth factor 2 (HER2) positive tumors with a high Ki-67 index [9-11]. Ballesio et al. evaluated the relation between molecular subtypes and tumor response patterns and demonstrated that concentric pattern is significantly correlated with HER2+ tumors [12]. To our knowledge, no study has investigated false-positive MRI findings following NAC.

Based upon the limited body of knowledge, we aimed to demonstrate false-positive MRI findings after NAC in patients with pCR and investigate the correlation between post-NAC MRI findings and tumor response patterns based on HER2 status.

Materials and Methods

Study population

From January 2016 to September 2020, a total of 292 consecutive women with breast cancer treated with NAC and achieved pCR were reviewed. Inclusion criteria were as follows:

(1), invasive breast cancer histologically proven with image-guided core needle biopsy before NAC; (2), underwent breast MRI pre- and post-NAC; (3), presence of residual contrast enhancement in tumor bed at MRI after NAC; (4), underwent surgery (breast-conserving or modified radical mastectomy) following NAC. According to these eligibility criteria, 118 patients were included in this study. This retrospective study involving three centers was approved by Local Ethics Committee and informed consent was waived (2021-01/07).

Treatment protocol

The NAC regimen included a combination of epirubicin/adriamycin and cyclophosphamide (4 cycles) and taxanes (4 to 12 cycles). Pertuzumab or Transtuzumab was also administered in HER2+ patients. Carboplatin was also applied in patients with BRCA mutation.

After completing NAC, surgery was performed for all patients.

MRI Acquisition and Evaluation

MRI scan was performed in three tertiary referral centers using 1.5T (Achieva, Philips Medical Systems, The Netherlands or Magnetom Aera, Siemens Healthinieers, Erlangen, Germany) or 3T (Skyra, Siemens Healthinieers, Erlangen, Germany) MRI systems with a dedicated 7- or 16-channel bilateral breast coil. Breast MRI protocol comprised high-resolution precontrast and dynamic contrast-enhanced imaging in axial plane including one pre-contrast and five or six post-contrast image sets after administration of gadolinium-based contrast agent. MRI scans were performed prior to NAC therapy and immediately before the surgery. MRI studies were evaluated using fifth edition of BI-RADS lexicon by four breast radiologists with 4 to 20 years of experience in breast imaging. For the patients with multifocal and multicentric disease largest tumor was accepted as index lesion. Largest diameter of tumor at peak enhancement was accepted as tumor size. Tumor response pattern following NAC was grouped according to the classification suggested by Kim et al [13].

Histopathological Evaluation

Before NAC, all patients underwent US-guided core needle biopsy procedure and invasive breast cancer diagnosis was confirmed histologically. Tumor histology and Ki-67 index were assessed using core biopsy samples. Ki-67 index was classified into three groups; ≤15%, 16-39% and ≥40% [14]. Estrogen receptor (ER) and progesterone receptor (PR) were assessed as negative if there was <10% nuclear staining. Human epidermal growth factor receptor 2 (HER2) was considered as positive if there was 3+ staining and negative if the staining score was 0 or 1+. In case of 2+ score, HER2 gene amplification testing was performed using fluorescent in situ hybridization. Patients were grouped into four categories according to hormone receptor (HR) and HER2 status: HR+/HER2−, HR+/HER2+, HR−/HER2+ and HR−/HER2−.

After NAC, surgery was performed for all patients and surgical specimen was evaluated for pCR. pCR was defined as absence of invasive cancer regardless of ductal carcinoma in situ or metastatic lymph node presence.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (version 22; IBM, USA). The categorical variables were expressed as counts and percentages, and the continous variables were expressed as means and ranges. Categorical variables were compared based on HER2+ status using Chi-square or Fisher’s exact test. P values <0.05 were considered statistically significant.

Results

Study population and pre-NAC clinico-pathologic characteristics

This study included 118 breast cancer patients who received NAC consecutively. The median age was 47.0 (range: 27-85). The majority (66.7%) of the patients were premenopausal. Regarding molecular subtype, 43 (36.5%) tumors were HR+ HER2+, 34 tumors (28.8%) were HR− HER2+, 24 tumors (20.3%) were HR+ HER2−, and the remaining 17 (14.4%) were triple-negative. The mean tumor size by MRI before NAC was 30.4 mm (range:9-78 mm). Twelve patients (10.1%) had multifocal carcinoma, and one patient (0.8%) had bilateral invasive breast cancer. The histopathological analysis of surgical specimen revealed 103 (87.3%) invasive ductal carcinoma, seven (5.9%) invasive lobular carcinoma, three (2.5%) invasive ductal and lobular carcinoma, two (1.7%) invasive medullary carcinoma and one (0.8%) invasive mucinous. The majority of the patients (78.8%) were axillary node positive at presentation. The baseline clinico-pathological characteristics of patients were summarized in Table 1.

MRI findings of tumors before and after NAC

The mean tumor size by MRI after NAC was 9.9 mm (range:3-55 mm). The most frequent MRI findings at presentation were mass and non-mass enhancement (NME) in HER2+ and HER2− groups. The MRI findings following NAC differed significantly between HER2+ and HER2− groups (p=0.02). The most frequent false positive MRI finding was focus and foci in HER2+ tumors, whereas NME in HER2− group (Figure 1). In pre-NAC MRI peritumoral edema was significantly associated with HER2+ tumors (p=0.04). Pre- and post-NAC, the presence of the metastatic lymph nodes by MRI was similar in both groups (p>0.05). The most frequent enhancement curve pattern was type 3 at presentation, whereas the majority of tumors presented type 1 and type 2 enhancement curve pattern after NAC in both groups (p>0.05). Pre- and post-NAC MRI findings of tumors based on HER2 status were summarized in Table-2.

Changes of MRI features and pathologic findings after NAC

The majority of post-NAC tumor size by MRI was smaller than tumor size at presentation. Following NAC, three tumors (7.3%) in HER2− group and one tumor (1.3%) in HER2+ group showed increase in size. The post-NAC MRI finding was NME in all tumors that increased in size. Regarding the tumor size pre- and post-NAC, ≥50% reduction in size was significantly associated with HER2+ tumors (p<0.001). In pathologic evaluation, fibrosis in tumor bed was found more often in the HER2− group without significant difference (p=0.10). Presence of DCIS and fibrosis in surgical pathology was significantly associated with NME on post-NAC MRI (p<0.001). A high-risk lesion with atypia in the surgical specimen was found more likely in the HER2+ group, whereas failed to reach a significant difference (p=0.06). Axillary pCR was achieved significantly higher in the HER2+ group (p=0.04). There was no significant difference

Table 1. Baseline clinicopathological characteristics of patients (n=118)

	All patients (n=118)
Median age, years (range)	47.0 (27-85)
Menopausal status	
Premenapausal	80(67.8)
Postmenapausal	38(32.2)
Basal MRI mean tumor size, mm (range)	30.4 (9-78)
Histologic type	
IDC	103(87.3)
ILC	7(5.9)
IDC+ILC	3(2.5)
Medullary carcinoma	2(1.7)
Mucinous carcinoma	1(0.8)
Other	2(1.6)
Molecular subtype	
HR+/HER2-	24(20.3)
HR+/HER2+	43(36.4)
HR-/HER2+	34(28.8)
HR-/HER2-	17(14.4)
Ki-67 index	
≤15%	5(4.2)
16-39%	57(48.3)
≥40%	56(47.5)
Node status at presentation	
Negative	25(21.2)
Positive	93(78.8)

Age presented as median (range) and tumor size presented as mean (range). All other variables are numbers of patients (percentages). MRI=Magnetic resonance imaging, IDC=Invasive ductal carcinoma, ILC=Invasive lobular carcinoma, HR=Hormone receptor, HER2=Human epidermal growth factor receptor 2

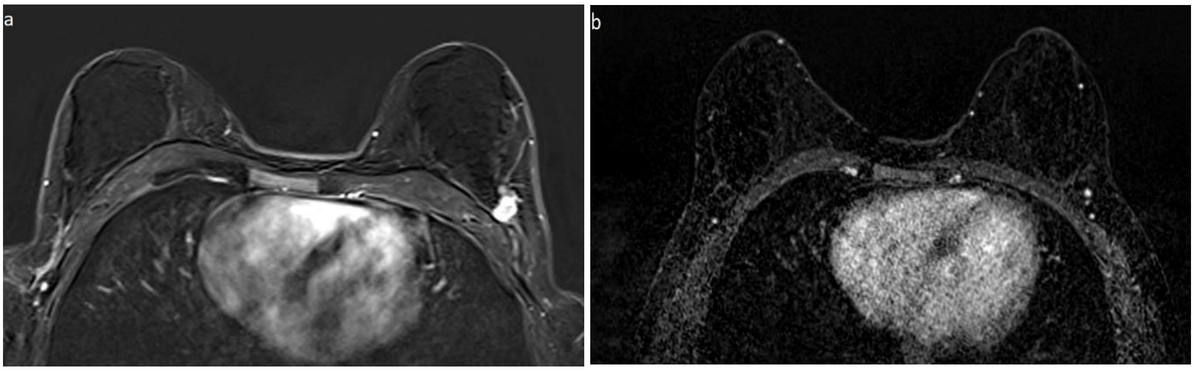

Figure 1. 36-year-old woman with invasive ductal carcinoma (hormone receptor-positive and HER2-positive)
(a) Axial substracted postcontrast T1-weighted image shows an irregular enhancing mass of left breast before chemotherapy.
(b) After completion of neoadjuvant chemotherapy, axial subtracted postcontrast T1-weighted image shows an enhancing focus at the original tumor site, which turned out to be a false-positive finding. No tumor or fibrosis was detected in the specimen after surgery.

Table 2. MRI findings based on HER2 status before and after NAC

	Before NAC			After NAC		
	HER2+(n=77) (65.2%)	HER2−(n=41) (34.7%)	p	HER2+(n=77) (65.2%)	HER2−(n=41) (34.7%)	p
BPE						
Minimal	21(27.3)	6(14.6)	0.36	39(50.6)	12(29.3)	0.04*
Mild	37(48.1)	20(48.8)		30(39.0)	20(48.8)	
Moderate	17(22.1)	13(31.7)		7(9.1)	9(22.0)	
Marked	2(2.6)	2(4.9)		1(1.3)	0(0)	
MRI finding						
Mass	41(53.2)	22(53.7)	1.0	11(14.3)	2(4.9)	0.02*
NME	1(1.3)	0(0)		32(41.6)	25(61.0)	
Mass+NME	35(45.5)	19(46.3)		1(1.3)	3(7.3)	
Focus	0(0)	0(0)		33(42.9)	11(26.8)	
Peritumoral edema						
Present	37(48.1)	12(29.3)	0.04*	4(5.2)	2(4.9)	1.0
Absent	40(51.9)	29(70.7)		73(94.8)	39(95.1)	
Axillary LAP						
Present	61(79.2)	32(78.0)	0.88	14(18.2)	9(22.0)	0.62
Absent	16(20.8)	9(22.0)		63(81.8)	32(78.0)	
Kinetic curve type						
1	1(1.3)	0(0)	1.0	47(61.0)	25(61.0)	1.0
2	20(26.0)	11(26.8)		29(37.7)	16(39.0)	
3	56(72.7)	30(73.2)		1(1.3)	0(0)	

Data are presented as n(%).
**p* values less than 0.05 regarded as statistically significant.
BPE=Background parenchymal enhancement, NAC=Neoadjuvant chemotheraphy, HER2=Human epidermal growth factor receptor 2, NME=Non-mass enhancement, LAP=Lymphadenopathy

Table 3. Changes of MRI features and pathologic findings based on HER2 status after NAC

	HER2+(n=77)	HER2−(n=41)	p
Tumor size difference in MRI			
≥50% reduction	68(88.3)	22(53.7)	<0.001*
<50% reduction	8(10.4)	16(39.0)	
Increase	1(1.3)	3(7.3)	
Tumor response pattern			
Concentric shrinkage	14(18.2)	4(9.8)	0.10
Crumble	6(7.8)	3(7.3)	
Focus or NME	48(62.3)	22(53.7)	
Diffuse enhancement	9(11.7)	12(29.3)	
BPE decrease (in categories)			
0	50(64.9)	28(68.3)	0.88
1	24(31.2)	11(26.8)	
2	3(3.9)	2(4.9)	
Tumor bed; fibrosis			
Present	28(36.4)	9(22.0)	0.10
Absent	49(63.6)	32(78.0)	
Tumor bed; DCIS			
Present	13(16.9)	10(24.4)	0.32
Absent	64(83.1)	31(75.6)	
Lesion with atypia in surgical specimen			
Present	21(27.3)	5(12.2)	0.06
Absent	56(72.7)	36(87.8)	
Axillary pathologic response			
Complete response	65(84.4)	28(68.3)	0.04*
Partial response	12(15.6)	13(31.7)	

Data are presented as n(%).
**p* values less than 0.05 regarded as statistically significant.
HER2=Human epidermal growth factor receptor 2, BPE=Background parenchymal enhancement, NME=Non-mass enhancement, DCIS=Ductal carcinoma in situ

regarding the frequency of residual in situ component in the surgical specimen and the degree of BPE reduction at MRI between groups. Changes in MRI features and pathologic findings following NAC were summarized in Table 3.

Discussion

In recent years, the use of NAC in breast cancer has become widespread. MRI is considered the most accurate method for evaluating tumor response after NAC; however, post-NAC MRI assessment may be challenging due to the heterogeneity of tumor response and the possibility of over and underestimation. To our knowledge, this study is the first study reporting false-positive MRI findings post-NAC and tumor response patterns based on molecular subtypes in breast cancer patients who achieved pCR. Our results revealed that residual MRI findings differ according to HER2 status. HER2+ tumors mostly present with focus or foci after NAC whereas non-mass enhancement more likely found in HER2− tumors.

The efficacy of NAC in breast cancer varies according to molecular subtypes. Studies have shown that HER2+ and triple-negative tumors are more responsive to chemotherapeutics due to their high cellular proliferation [15, 16]. Targetted agents used in the HER2+ group also increase this effectiveness. In agreement with the previous results, the majority of our study population (79.6%) consist of HER2+ and triple-negative breast cancer.

In a multicenter study, the overall accuracy of MRI after NAC was reported as 74% [17]. In a retrospective study with 98 patients, Choi et al. reported false positive rate of post-NAC MRI as 47% [18]. Confounding factors in radiology-pathology discordance should be taken into consideration to avoid inappropriate surgical planning. Post-chemotherapy changes including fibrosis, inflammation, and necrosis can mimic residual tumor and thereby may cause false-positive results on imaging. Molecular subtype, tumor size and chemotherapy regimen are also among the factors that influence the diagnostic performance of MRI. Studies have shown that the diagnostic accuracy of MRI was higher in HER2+ and triple negative tumors than hormone receptor-positive breast cancer. MRI-pathology discordance was also higher in tumors with >5 cm size and in tumors with low Ki-67 index [19]. Tumors presented with non-mass enhancement (NME) at pre-NAC MRI were also associated with lower diagnostic performance [20]. Furthermore, a decrease in contrast enhancement at post-NAC MRI resulting from the antiangiogenetic effect of taxanes may cause underestimation of residual tumor.

Another challenge in evaluating the post-NAC residual tumor is the heterogeneity of the tumor response patterns. Ballesio et al. evaluated MRI-based tumor shrinkage patterns (concentric, nodular and mixed pattern) and investigated its relationship between pCR rates and molecular subtypes. Results showed that concentric pattern is significantly associated with pCR and HER2+ subtype. However, mixed pattern is significantly associated with Luminal A tumors and non-pCR [12]. In our study, foci and NME was the most frequent response pattern post-NAC without significant difference according to HER2 status. This discrepancy may be attributable to the difference in the study populations and that only patients who achieved pCR were included in our study. Moreover, Lee et al. revealed that tumor response patterns differ histopathologically according to molecular subtypes [21]. According to this study, fibrosis within tumor bed was found more frequently in HR+ tumors which is in line with our results.

Imaging biomarkers based on MRI can be used in order to increase the diagnostic accuracy of post-NAC MRI. Studies have shown that decrease in background parenchymal enhancement (BPE) after NAC is correlated with pCR [22, 23]. Oh et al. also revealed that no significant correlation between post-NAC BPE decrease and molecular subtypes, which is consistent with our results [22]. In a retrospective study, Kim et al. used lesion-to-background parenchymal signal enhancement ratio (SER) on MRI in ≤ 5 mm lesions, and their results indicate that SER≤1.6 criterion significantly improves specificity to distinguish pCR from a residual tumor [24]. In regard to apparent diffusion coefficients (ADC), high ADC values post-NAC is associated with pCR. Santamaria et al. reported that pre- and post-NAC ADC ratio was >1.5 in 86% of patients who achieved pCR [25].

Our study has some limitations. First, this was a multi-center study thus MRI scans were performed with different MRI systems which could affect MRI assessment. Second, interobserver variability was not assessed even though MRI evaluation was made by two radiologists to reach consensus in ambiguous cases. At last, the definition of pCR may have an influence on MRI accuracy, and pCR was defined as the absence of invasive tumor regardless of DCIS presence in this study. However, Santamaria et al. revealed that pCR definition has no significant effect on the post-NAC MRI accuracy [26].

In conclusion, each breast tumor shows different response characteristics to NAC, and the diagnostic accuracy of MRI following NAC is evolving by understanding the underlying mechanisms and tumor biology. Our study revealed that tumor response patterns and post-NAC MRI findings differ according to HER2 status. It should be noted that focus and foci are the most frequent false-positive MRI finding in patients with pCR, particularly in HER2+ cases. With the help of further information in this field, avoidance of post-NAC surgery might be possible with an accurate prediction of pCR.

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Corresponding author e-mail: aydanavdanaslan@gmail.com

Orcid ID:
Aydan Avdan Aslan 0000-0002-7169-5933
Servet Erdemli 0000-0001-5545-768X
İbrahim Halil Erdoğdu 0000-0002-5445-2649
Serap Gültekin 0000-0001-6349-3998
Cihan Uras 0000-0002-6838-2311
Fatma Tokat 0000-0002-6976-1567
Ali Arıcan 0000-0002-6099-2000
Leyla Özer 0000-0001-8763-5268
Kemal Behzatoğlu 0000-0002-9843-9825
Nezih Meydan 0000-0003-4100-5804
Füsun Taşkın 0000-0001-7985-3660

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Original Article

How are the Results of Allogeneic Stem Cell Transplantation in Elderly Patients? A Single-Center Experience

Yaşlı Hastalarda Allojeneik Kök Hücre Nakli Sonuçları Nasıl? Tek Merkez Deneyimi

Ayse Uysal[1], Mehmet Ali Erkurt[2], İrfan Kuku[2], Emin Kaya[2], İlhami Berber[2], Ahmet Sarıcı[2],
Soykan Biçim[2], Ahmet Kaya[2], Emine Hidayet[2]
[1]Fırat University School of Medicine, Hematology Department, Elazığ, Turkey
[2]İnönü University, Turgut Özal Medical Center, Adult Hematology Department, Malatya, Turkey

ABSTRACT

Aim: In this study, we aimed to present allogeneic hematopoietic stem cell transplantation (allo-HSCT) experience in elderly patients with hematological malignancy.

Materials and methods: Thirty-five patients aged 60 years and older who underwent allo-HSCT between 2017 and 2021 were retrospectively analyzed. Patient's demographic/clinical features, and the outcomes of transplantation were reviewed.

Results: The median age was 63 (range, 60-74) years and 25 (77,1%) were male. Twenty-seven (60%) were diagnosed with AML, followed by MDS (n:7, 20%). Twenty-three (65,8%) patients had intermediate, and 6 (17,1%) patients had a high hematopoietic cell transplantation-specific comorbidity index score. Karnofsky performance status of ≥ 90% was detected in 15 (42,9%) patients. Busulfan plus fludarabine plus anti-thymocyte globulin was used mainly as a reduced-intensity conditioning regimen, which was used in 18 (51,4%) patients. The median duration of neutrophil and platelet engraftments were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The median follow-up time was 4 months (range, 0-51), with the OS rate %14,2. The transplant-related mortality rate within the first 30 days after allo-HSCT was detected in 10 patients (28,6%) due to infection and/or GvHD. Response assessment could be performed in 25 (71,4%) patients after transplantation. The duration of PFS was 6 (range, 1-51) months in patients with response evaluation. The rate of PFS was 72% in 1 years and 5 (14,2%) patients were still alive with complete response at the last visit.

Conclusion: Reduced-intensity conditioning regimen has provided the advantage in allo-HSCT, for elderly patients with hematological malignancies such as AML and MDS.

Keywords: allogeneic hematopoietic stem cell transplantation, elderly patients, reduced-intensity conditioning regimen

ÖZET

Amaç: Biz bu çalışmada 60 yaş ve üzerindeki hematolojik malignitesi olan hastalarda allo-HSCT deneyimini ve sonuçlarını sunmayı amaçladık.

Gereç ve yöntemler: 2017-2021 yılları arasında allo-HSCT uygulanan 60 yaş ve üstü 35 hasta retrospektif olarak analiz edildi. Hastaların nakil anındaki demografik ve klinik özellikleri ile nakil sonuçları incelendi.

Bulgular: Ortanca yaş 63 (60-74) ve 25'i (%77,1) erkekti. Yirmi yedi (%60) hasta AML, 20 (%20) hasta MDS tanılıydı. Yirmi üç (%65,8) hastada orta, altı (%17,1)' sında yüksek hematopoietik hücre transplantasyonu spesifik komorbidite indeks skoru vardı. 15 (%42,9) hastada Karnofsky performans durumu ≥%90 olarak saptandı. Busulfan, fludarabin ve anti-timosit globulin kombinasyonu en sık kullanılan RIC rejimiydi ve 18 (%51,4) hastada kullanıldı. Ortanca nötrofil ve trombosit engraftman süresi sırasıyla 18 (11-27) ve 18 (11-33) gündü. Ortanca takip süresi 4 aydı (aralık, 0-51), toplam sağkalım oranı %14,2. Allo-HSCT' den sonraki ilk 30 gün içinde transplanta bağlı ölüm oranı enfeksiyon ve/veya GvHD nedeniyle 10 hastada (%28,6) tespit edildi. Nakil sonrası 25 (%71,4) hastada yanıt değerlendirmesi yapılabildi. Yanıt değerlendirmesi yapılan hastalarda PFS süresi 6 (dağılım, 1-51) aydı. PFS oranı 12 ayda %72 idi. Son kontrolde 5 (%14,2) hasta tam yanıtla halen yaşıyordu.

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Sonuç: Azaltılmış yoğunluklu şartlandırma rejimi, özellikle AML ve MDS gibi hematolojik maligniteleri olan yaşlı hastalarda allo-HSCT' de önemli bir avantaj sağlamıştır.

Anahtar Kelimeler: allojeneik hematopoietik kök hücre nakli, yaşlı hastalar, düşük yoğunluklu hazırlama rejimi

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the important treatment option for many hematological malignancies and benign hematological disorders [1]. However, complications such as post-transplant infection and graft versus host disease (GvHD) increase the rate of transplant-related mortality (TRM) and morbidity [2]. In the literature, high TRM (50%) rates have been reported [3]. Furthermore, many hematological malign diseases significantly affect the elderly. The median age at diagnosis is over 60 years in disease such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)in which allo-HSCT is very important [4-6]. Therefore, allo-HSCT as a salvage or consolidation treatment option could be used limitedly as a treatment option in elderly patients with multiple comorbidities [7].

The performance status and comorbidity are other factors determining the eligible transplant candidate and affecting the transplant outcome [8]. Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) is used widely before the transplantation for transplant-risk assessment. Patients are stratified into 3 (score 0, 1–2, or ≥3) categories according to the HCT-CI. The TRM rate is found to be high in those with a score of 3 and above. [9]. Karnofsky performance score (KPS) is determined by evaluating functional abilities to perform routine daily activities. Generally, KPS below 60-70% is considered an exclusion factor for transplantation [8, 10].

Myeloablative conditioning regimen (MAC) could not be used in elderly and frail patients due to the significant risk of adverse effect. However, a reduced-intensity conditioning (RIC) regimen has shown significant benefits in TRM and morbidity [11-13]. In addition, TRM rates were reduced with the determination of the eligible transplant candidate, the development of GvHD prophylaxis, and the improvement in post-transplant supportive and infection therapy[4, 5, 14].

In this study, it was aimed to review allo-HSCT experience and outcomes in elderly patients who were 60 years old and older with hematological malignancy disorders.

Materials and Methods

We retrospectively analyzed 35 patients who were 60 years and older and underwent allo-HSCT between 2017 and 2021. The age, gender, performance score, comorbidity, disease status at the transplantation, number of treatment lines before the transplantation, donor type, the conditioning regimen, the quantity of CD34+ stem cells infused, the duration of neutrophil/platelet engraftment, the presence of febrile neutropenia/acute-chronic graft versus host disease, TRM, and duration of hospitalization, progression-free survival (PFS) and overall survival (OS) were examined. All data were collected from the hospitals' registries and patients' clinical notes.

Performance status was evaluated with KPS, and comorbidity status was evaluated with HCT-CI. The HCT-CI were each separated into 3 risk groups low (0), intermediate (1-2), and high (≥ 3) risk [9, 10].

Neutrophil engraftment duration was defined as the time from the first day of allo-HSCT to the first of three consecutive days with absolute neutrophil counts ≥0.5×10^9/L. Platelet engraftment duration was defined as the time from the first day of allo-HSCT to the first of three consecutive days with platelet counts of more than 20×10^9/L without transfusion. Febrile neutropenia was defined as the combination of granulocyte counts below 500 cells/µl and temperature over 38 oC. Acute GvHD was evaluated according to the revised Glucksberg scale. Chronic GvHD was diagnosed and staged according to the National Institutes of Health (NIH) Consensus Criteria[15, 16].

Transplant-related mortality was defined as death within the first 30 days after allo-HSCT without any evidence of disease relapse or progression. Progression-free survival was defined as the time from initiation of transplantation to the occurrence of disease relapse or death. Overall survival was defined from the first day of allo-HSCT to death from any cause.

This study was conducted with approval by the Ethics Committee of Inonu University with approval number 2021/2875 and was carried out by the principles of the Helsinki Declaration.

Statistical analysis

Numbers and percentages were used for categorical data in descriptive analyses. Continuous data were classified as parametric and non-parametric with skewness–kurtosis, Kolmogorov–Smirnov test, standard deviation/mean percentages, and histogram graphics with regular distribution lines. For parametric and non-parametric data, mean±standard deviation and median(min-max) values were used, respectively. For univariate analysis overall survival was calculated by Kaplan-Meier method and log-rank test was performed. Cox regression analysis was performed to determine significant predictors of age and the dose of CD34+ stem cells variables. Values of $p<0.05$ were accepted as statistically significant. All data analyzes were performed using Statistical Package for Social Sciences (SPSS) version 22.0 (Armonk, NY: IBM Corp.).

Results

Twenty-five (77,1%) of them were male. The median age at the time of transplantation was 63 (range, 60-74) years, and only two (5,7%) patients were older than 70 years old. Thirty-one (n:27, 60%) were diagnosed with AML, followed by MDS (n:7, 20%). Thirteen (48,1%) of 27 patients with AML had a complete response (CR) at the time of allo-HSCT. Twenty-three (65,8%) patients had intermediate, and six (17,1%) patients had a high hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score. The comorbidities were pulmonary dysfunction (17,1%), cardiac disease (14,2%), infection (14,2%), diabetes mellitus (11,4%), psychiatric disturbance (5,7%), arrhythmia (2,8%), cerebrovascular disease (2,8%), and rheumatologic disease (2,8%). Karnofsky performance status of ≥90% was detected in 15 (42,9%) patients. The demographic and clinical characteristics of the patients were presented in Table 1.

The median time from diagnosis to allo-HSCT was three (1-75) months. The HLA-matched sibling donor (MSD) was used most frequently as the donor type, which was used in 28 (80%) patients. A reduced conditioning regimen was used most frequently as the conditioning regimen, which was used in 31 (88,6%) patients. Busulfan plus fludarabine plus anti-thymocyte globulin (ATG) regimen was primarily used as a reduced-intensity regimen, which was used in 18 (51,4%) patients. Treosulfan plus fludarabine plus ATG therapy and fludarabine plus amsacrine plus cytarabine (FLAMSA) therapy were the other RIC regimens were used in nine (25,7%) and four (11,4%) patients, respectively. Busulfan plus cyclophosphamide was used as the MAC regimen, which was used in only

Table 1. The demographic and clinical characteristics of the patients at the time of transplantation

	N:35
Median age (range)	63 (60-74)
Gender, n (%)	
Male	27 (77,1)
Female	8 (22,9)
Disease type, n (%)	
AML	21 (60)
MDS	7 (20)
ALL	2 (5,7)
PMF	2 (5,7)
Others	3 (8,6)
Disease status, n (%)	
CR	18 (51,4)
PR	6 (17,1)
Refractory	11 (31,4)
The median time from diagnosis to transplant, (range), months	3 (1-75)
The median prior therapy line, (range)	1 (0-3)
Karnofsky performance score, n (%)	
≥90	15 (42,9)
<90	20 (57,1)
HCT-CI, n (%)	
Low	6 (17,1)
Intermedia	23 (65,8)
High	6 (17,1)
LDH, n (%)	
Normal	13 (37,1)
High	22 (62,9)
CRP, n (%)	
Normal	29 (82,9)
High	6 (19,1)
Cytomegalovirus serologic status, n (%)	
Positive	34 (97,1)
Negative	1 (2,9)

ASCT; autologous stem cell transplantation, AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, CR; complete response CRP; C-reactive protein, HCT-CI; hematopoietic cell transplantation-specific comorbidity index, LDH; lactate dehydrogenase, MDS; myelodysplastic syndrome PMF; primary myelofibrosis, PR; partial response

four (11,4%) patients. Cyclosporine A plus methotrexate combination was used in all patients due to GvHD prophylaxis.

The stem cell source was peripheral blood in all patients. The median counts of infused stem cells were 8,1x10^{6}/kg (range, 5,1-19,4x10^{6}/kg). The median duration of neutrophil engraftment and platelet engraftment were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The neutrophil and platelet engraftments did not occur in 11 (11,4%) and 11 (11,4%) patients, respectively. Febrile neutropenia was detected in 25 (71,4%) patients. The median time of hospitalization was 19 (range, 1-50) days. Transplantation characteristics and post-transplantation outcomes were shown in Table 2.

Table 2. Peritransplantation features and outcome of transplantation

	N: 35
Donor type, n (%)	
Matched related	28 (80)
Matched unrelated	5 (14,3)
Haploidentical	2 (5,7)
Conditioning regimen n (%)	
Myeloablative	4 (11,4)
Reduced induced	31 (88,6)
The median count of infused CD34+stem cell ×10^{6}/kg (range)	8,1 (5,1-19,4)
The median time to neutrophil engraftment (range), day	18 (11-27)
The median time to platelet engraftment (range), day	18 (11-33)
The rates of febrile neutrophile, n (%)	
Yes	25 (71,4)
No	10 (28,6)
The median duration of hospitalization (range), day	19 (1-50)
Transplant-related mortality, n (%)	
Yes	15 (42,8)
No	20 (57,2)
Disease status after transplantation	
CR	18 (51,4)
PR	2 (5,7)
Refractory/relaps	5 (14,3)
Not detectable	10 (28,6)
Acute GvHD status, n (%)	
Yes	10 (28,6)
Chronic GvHD status, n (%)	
Yes	3 (8,3)

CR; complete response, GvHD; graft versus host disease, PR; partial response

The median follow-up time was 4 months (range, 0-51), with the OS rate %14,2. The median OS was 4 months (95% CI: 2,1-5,8). The transplant-related mortality rate within the first 30 days after allo-HSCT was detected in 10 patients (28,6%) due to infection and/or GvHD. The age at the time of transplantation, gender, HCT-CI score, Karnofsky performance status, disease status at time of transplantation, the conditioning regimen, and

Table 3. The univariate analyses for overall survival

Variables	Median overall survival (months)	95% CI	p valuable
Gender			
Male	4,00	2,31-5,69	.889
Female	1,00	0-4,70	
Age*	0,969	0,842-1,115	.658
HCT-CI			
Score 0	4,00	0,60-7,40	
Score 1-2	4,00	2,45-5,55	.820
Score ≥3	1,00	0-3,40	
Karnofsky performance score			
<90%	4,00	0,21-7,79	.273
≥90%	2,00	0-6,38	
Disease status at the time of allo-HSCT			
Complete and partial response	4,00	0-8,78	.215
Refractory/progression	3,00	0-7,16	
The conditioning regimen			
Myeloablative	4,00	0-9,88	.424
Reduced induced	4,00	1,34-6,66	
The dose of CD 34 stem cell dose*	1,072	0,951-1,210	.254

HCT-CI; hematopoietic cell transplant comorbidity index, allo-HSCT; allogeneic hematopoietic stem cell transplantation
*Hazard ratio (95% confidence interval)

the dose of infused CD34+ stem cells were not statistically significantly associated with OS (Table 3).

Response assessment could be performed in 25 (71,4%) patients after transplantation. Ten (28,6%) patients died before a response assessment could be performed. The rate of PFS was 72% in 12 months. At the last follow-up, five (14,2%) patients were still alive with CR. Only three (10%) deaths were related to relapse/progressed disease.

Acute GvHD occurred in 10 (28,6%) patients as only gastrointestinal acute GvHD in four(11,4%) patients, only skin acute GvHD in five(14,2%) patients, and both gastrointestinal and liver acute GvHD in one (2,8%) patient. Grades III/IV acute GvHD occurred in six (17,1%) patients. Chronic GvHD occurred in three (8,3%) patients (one limited and two extended) surviving more than 100 days after allo-HSCT.

Discussion

Allo-HSCT can be used limitedly as a treatment option in elderly patients with comorbidities. However, in recent years, it has been more preferred in elderly patients due to the improvement of the conditioning regimens, the determination of prognostic factors before transplantation, and the improvement in post-transplant supportive treatments. In this retrospective study, 35 patients older than 60 years were evaluated who underwent allo-HSCT.

Comorbidity and performance status are the determining factors in selecting eligible patients in allo-HSCT. Sorror et al. presented the impact of HCT-CI and KPS on NMA allo-HCST outcomes and emphasized that both HCT-CI 3 and above scores and KPS percentages 80% or less were found to be important predictor of grade 3-4 toxicities and higher mortality (HCT-CI score: p=0.004, p=0.0002 and KPS: p=0.05, p=0.002, respectively). Furthermore, high HCT-CI scores were statistically significantly associated with increased NRM (p=0.0002) [17]. Other studies demonstrated that the HCT-CI score was a significant prognostic impact on OS (2-year OS, 58%, 53%, and 43% for scores 0, 1-2, and ≥3, respectively, p =0.004)[18]. In our study, 6 (17,1%) patients had low HCT-CI scores, 23 (65,8%) patients had intermediate HCT-CI scores, and six (17,1%) patients had high HCT-CI scores, whereas 20 (57,1%) patients had a KPS of

<90%. However, the comorbidity and KPS status in terms of overall survival could not be compared as they were small and heterogeneous groups.

Non-myeloablative (NMA) or RIC regimens are often preferred over myeloablative regimens to reduce toxicity for elderly patients in allo-HSCT. Wallen et al. presented the results of allo-HSCT with myeloablative regimens in adults 60 years of age and older. They evaluated 52 patients with a median age of 62.8 years who underwent allo-HSCT with MAC regimens. In their study, TRM rates at 100 days and 3 years are 27% and 43%, respectively. Grade ≥3 GVHD and extensive chronic GVHD occurred 20% and 53%, respectively [19]. However, the outcomes of allo-HSCT in elderly patients (median age, 69 years; range, 66-77) who underwent allo-HSCT using the RIC regimen were presented by Hsu et al. Most patients (85%) had received fludarabine/melphalan-based RIC regimen. The incidence of TRM mortality was 11,5% at 100 days. The grades II to IV GVHD at day 100 and 6 months was 29,5% and 34,5%, and chronic GVHD at 6, 12, and 24 months was 2.5%, 5.2%, and 6.3%, respectively[5]. In our study, the RIC regimen was used in 31 (88,6%) patients, and TRM was detected in 10 patients (28,6%) within the first 30 days after allo-HSCT. Acute GvHD occurred in 10 (28,6%) patients. Grades III/IV acute GvHD occurred in six (17,1%) patients. Chronic GvHD occurred in three (8,3%) patients. Although our TRM rates were higher than the literature, the outcome of both acute and chronic GVHD rates were similar with the literature. We attribute this to the frail of our cohort because most of them (57,1%) had KPS below 90% and majority of them (82,9%) had moderate and high HCT-CI score.

Although TRM is low with RIC regimens, the risk of relapse is more than with myeloablative therapies, as a disadvantage. Scott et al. presented the long-term follow-up of the study that MAC compared with RIC for AML and MDS. They reported that the risk of relapse was high in the RIC regimen compared to the received MAC (hazard ratio, 4.06; 95% CI, 2.59 to 6.35; p <0.001) [11]. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation presented the comparative outcome of RIC and MAC regimen in HLA identical sibling allo-HSCT for patients older than 50 years with AML. They reported that the relapse rate was statistically significantly higher in the RIC group (RIC: 41% vs. MAC: 24%, p<0.0001) [20]. However, a phase 3 study compared the treosulfan-based conditioning regimen with the busulfan-based conditioning regimen in older patients with AML or MDS. The relapse or progression rates were detected at 20% and 21%, respectively. There was no significant difference between the two groups regarding recurrence or progression (p=0,50) [21]. In our study, the rate of PFS was 72%, and the progression rate was 14,3% in 12 months. Busulfan plus fludarabine or treosulfan plus fludarabine were used mainly as the conditioning regimen in our study, and our relapse rates were consistent with this phase 3 study.

In the RIC regimen, fludarabine is combined with an alkaline agent such as melphalan, busulfan, treosulfan, and thiotepa or with total body irradiation (TBI). The dose of alkylating agents or TBI is reduced in the RIC regimens, and thus the duration of cytopenia is shortened compared to MAC regimens[22, 23]. A study about the outcome of older patients who underwent allo-HSCT using RIC regimens reported the median time to neutrophil and platelet engraftment were 13 days (range, 8 to 37) and 17 days, respectively[5]. In a randomized and phase 3 trial, treosulfan plus fludarabine was compared with busulfan plus fludarabine for older patients with AML or MDS who underwent allo-HSCT. At day 28 after HSCT, neutrophil engraftment was achieved 96.8% in treosulfan-treated patients and 96.2% in busulfan-treated patients (p=0.34). Platelet engraftment was achieved in 97% and 98% of patients, respectively (p=0.077)[21]. In our study, busulfan and treosulfan-based conditioning regimens were mainly used (51,7%vs.25,7%, respectively). The median time of neutrophil engraftment and platelet engraftments were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The neutrophil and platelet engraftments did not occur in 11 (11,4%) and 11 (11,4%) patients, respectively. The duration of engraftment was consistent with the literature, but our engraftment rates were lower than the literature. This difference was thought to be due to infection-related deaths in the early transplant period (first 30 days after allo-HSCT).

The small and heterogeneous population was the most significant limitation of our study. Therefore, subgroup and comparison analyses were not performed. Another limitation was that it was a retrospective study.

In conclusion, RIC and NMA regimens provide a significant advantage for patients with advanced age with hematological malignancies such as AML and MDS, which have an essential role in the treatment of allogeneic transplantation. However, comorbidities and transplant-related mortality such as GVHD or infection still pose a significant transplant disadvantage for allo-HSCT in elderly and frail patients

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Corresponding author e-mail: erkurtali@hotmail.com

Orcid ID:
Ayse Uysal 0000-0002-5581-8104
Mehmet Ali Erkurt 0000-0002-3285-417X
İrfan Kuku 0000-0001-6126-0816
Emin Kaya 0000-0001-8605-8497
İlhami Berber 0000-0003-3312-8476
Ahmet Sarıcı 0000-0002-5916-0119
Soykan Biçim 0000-0001-7498-344X
Ahmet Kaya 0000-0002-0742-4629
Emine Hidayet 0000-0003-3121-7387

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Original Article

Risk Factors Associated with Progression of Myelodysplastic Syndrome: 13 Years of Experience from a Single Center

Miyelodisplastik Sendromun Progresyonu ile İlişkili Risk Faktörleri: Tek Merkezden 13 Yıllık Deneyim

Emine Gültürk
Department of Hematology, Bakırköy Dr Sadi Konuk Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Aim: We aimed to assess the accuracy of the most widely-accepted prognostic classification systems in patients with myelodysplastic syndromes (MDS), and to investigate various parameters with respect to their association with MDS progression.

Material and Methods: Fifty-five patients diagnosed with MDS (January 1999 to December 2012) were reviewed retrospectively. Demographic characteristics, comorbidities, laboratory and pathological results, risk classifications (pathological and prognostic) at MDS diagnosis, treatment features, data regarding patient survival, and acute myeloid leukemia (AML) conversion were examined.

Results: Thirty-five male and 20 female patients (mean age: 70.95±9.80 years) were included. Twenty-four (43.46%) patients were defined to have had progression. Having an ECOG-PS score of ≥2 (OR: 6.939, 95%CI: 1.527-31.526; p=0.012) and being classified as 'high' or 'very high' risk according to the WPSS (OR: 10.115, 95%CI: 2.293-44.614; p=0.002) were found to be the only factors independently associated with MDS progression.

Conclusion: Although univariate differences were observed for various parameters, MDS progression was independently associated with ECOG-PS and WPSS class. It appears that singular classification systems are insufficient to predict MDS progression.

Keywords: Myelodysplastic syndrome, progression, prognostic factors, prognostic classification systems

ÖZET

Amaç: Miyelodisplastik sendrom (MDS) tanılı hastalarda en yaygın olarak kabul edilen prognostik sınıflandırma sistemlerinin doğruluğunu değerlendirmeyi ve MDS progresyonu ile ilişkisine göre çeşitli parametreleri araştırmayı amaçladık.

Gereç ve Yöntem: MDS tanısı konan 55 hasta (Ocak 1999-Aralık 2012) geriye dönük olarak incelendi. Demografik özellikler, komorbiditeler, laboratuvar ve patolojik sonuçlar, MDS tanısında risk sınıflamaları (patolojik ve prognostik), tedavi özellikleri, hasta sağkalımı ile ilgili veriler ve akut miyeloid lösemi (AML) dönüşümü incelendi.

Bulgular: Otuz beş erkek ve 20 kadın hasta (ortalama yaş: 70.95±9.80 yıl) dahil edildi. Yirmi dört (%43.4) hastada progresyon olduğu belirlendi. Sadece ECOG-PS skorunun ≥2 olması (OR: 6.939, %95 GA: 1.527-31.526; p=0.012) ve WPSS'ye göre 'yüksek' veya 'çok yüksek' riskli olarak sınıflandırmanın (OR: 10.115, %95) GA: 2.293-44.614; p=0.002), MDS progresyonu ile bağımsız olarak ilişkili faktörler olduğu belirlendi.

Sonuç: Çeşitli parametreler için tek değişkenli farklılıklar gözlemlenmesine rağmen, MDS progresyonu bağımsız olarak ECOG-PS ve WPSS sınıflandırması ile ilişkilendirilmiştir. Sınıflandırma sistemlerinin tek başına MDS progresyonunu tahmin etmede yetersiz olduğu görülmektedir.

Anahtar Kelimeler: Miyelodisplastik sendrom, progresyon, prognostik faktörler, prognostik sınıflandırma sistemleri

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Introduction

Hematopoietic cell transplantation is accepted Myelodysplastic syndrome (MDS) defines a group of diseases in which stem cell clonal disorders lead to bone marrow (BM) dysplasia and ineffective hematopoiesis. They have a high risk of progression to acute myeloid leukemia (AML) [1,2]. Annual MDS incidence is about three to four cases per 100,000 people, with a higher incidence in men and after the age of 80 years [3].

Since MDS demonstrates considerable clinical, pathological and cytogenetic heterogeneity, factors affecting survival and prognosis are highly variable [4]. Therefore, various classification systems have been developed, including pathological classification systems such as French-American-British co-operative group (FAB) and the World Health Organization (WHO) classifications. Also, various prognostic models have also been developed, such as the International Prognostic Scoring System (IPSS; and its revision, IPSS-R), the WHO classification-based Prognostic Scoring System (WPSS), and MD Anderson Cancer Center (MDACC) Risk Model [2,5-9]. Grading in these systems are made largely by considering chromosomal abnormalities, cytopenia, and BM blast percentages [10]. Patient comorbidities, physical performance status, various blood and BM parameters, treatment requirements at the time of diagnosis, and during the course of MDS are also likely to affect overall survival (OS) and progression [11-13]. The factors that determine the pathogenesis and progression of MDS have not been clarified [4] and considering that classification systems alone appear to be insufficient to predict the progression of this disease, it is evident that there is a need for further data to assess risk factors associated with progression in MDS [14].

In this study, we aimed to assess the accuracy of widely-accepted prognostic classification systems in MDS, and to investigate the roles of various parameters, many of which have not yet been included in these systems, in predicting MDS progression.

Methods

Study features and ethics

This retrospective study was conducted between January 1999 to December 2012 at the Department of Hematology, Faculty of Medicine, İstanbul University. The ethical approval of the study was obtained from the Clinical Research Ethics Committee of Istanbul University.

Participants

The files of 215 patients over the age of 18 who were diagnosed with MDS were reviewed retrospectively. Fifty-five patients whose files were sufficient for the study and who were followed up regularly in the outpatient clinic were included in the study. Patients with missing or inaccessible data were excluded.

Data collection instruments

Demographic characteristics of patients, comorbidity information, laboratory results, all histopathological information, and physical performance status were recorded. The results of classification systems listed below (at diagnosis of MDS), treatment, and follow-up data regarding survival and AML progression during disease course were obtained from hospital records.

MDS pathological classification

For MDS pathological grading, both the FAB classification [5,15] and the 2008 WHO classification [6] were used. There were 5 major groups according to the FAB classification system: Refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML) [5,15]. Using the 2008 WHO classification, MDS was grouped according to the findings of peripheral blood and BM as follows: Refractory cytopenia with unilineage dysplasia (RCUD), RARS, refractory cytopenia with multilineage dysplasia

(RCMD), RAEB-1, RAEB-2, MDS-unclassified (MDS-U), and isolated del(5q)-associated MDS [6].

MDS prognostic risk classification

Patients were classified in terms of prognostic risk using the IPSS, IPSS-R, WPSS, and MDACC models [7-9,16]. We used the 2011 revised version of the WPSS, that is, the original criterion of "transfusion requirement" was replaced by "severe anemia" (Hb<9g/dl in men, Hb<8g/dl in women) [9]. The patients were divided into 4 risk groups according to IPSS and MDACC (low, intermediate-1, intermediate-2, high), and 5 risk groups according to IPSS-R and WPSS (very low, low, intermediate, high, very high) [7-9,16].

Bone marrow assessment

Histopathological results of BM biopsy specimens were evaluated in terms of cellularity and dysplasia. Cellularity was categorized as “hypercellular, normocellular, hypocellular”; Dysplasia was categorized as “dysplasia in one, two or three cell line(s)” [17]. The European Myelofibrosis Network (EUMNET) scoring system was used to classify BM fibrosis which establishes 4 subgroups: MF-0, MF-1, MF-2, MF-3 [18].

Cytogenetic risk classification

Cytogenetic prognosis grouping was made according to the IPSS, and patients were divided into 3 risk groups as "good, moderate, poor" according to pre-specified chromosomal anomalies [1]. Patients with cytogenetically normal findings and those with del(5q), del(20q) or -Y were placed in the "good" subgroup, patients with complex (>2) abnormalities and chromosome 7 abnormalities were classified in the "poor" subgroup, and patients with other cytogenetic abnormalities were classified in the "moderate" subgroup.

Performance status assessment

The ECOG-PS was used to assess patients’ performance status at MDS diagnosis. In this scoring system, patients are classified according to their physical performance status in 6 degrees with the highest being 0 (fully active) and the lowest being 5 (dead) [19].

Progression criteria

Presence of at least one of the following 3 criteria was accepted to show MDS progression; (i) Conversion to AML, (ii) Death due to conversion to AML and/or BM failure, (iii) Later development of signs of BM failure that were not present at the beginning (i.e. Hb<9g/dl in men and <8g/dl in women, neutrophils count <0.8 x 10^9/L, platelet count <100 x 10^9/L). Progressive MDS cases were abbreviated as PG (presence of progression group), and non-progressive cases as non-PG (absence of progression group).

Statistical Analysis

All analyses were performed on SPSS version 25 (IBM, Armonk, NY, USA) with a significance threshold of <0.05 for p value. We employed the Shapiro-Wilk test to determine normality of distribution in numerical variables. Mean ± standard deviation or median (1st quartile-3rd quartile) summaries were used to describe numerical variables, in the presence and absence of normal distribution, respectively. Absolute and relative frequencies were reported for categorical variables. Numerical data were compared between groups by employing the independent samples t-test (normal distribution) or the Mann-Whitney U test (non-normal distribution). Chi-square tests were used to compare the distribution frequencies of categorical variables between groups, and the Fisher's exact test was utilized when assumptions for Pearson or continuity correction were not met. Variables’ prediction performance were assessed by using Receiver Operating Characteristic (ROC) curve analysis. Optimal cut-off points were determined by using Youden index. Multiple logistic regression analysis (forward conditional method) were performed to determine the best predictive factors associated with progression.

Results

Thirty-five male and 20 female patients were included in our study, and the mean age of the patients was 70.95 ± 9.80 (range 49-92) years. 31 (56.4%) of the patients were in the non-PG and 24 (43.6%) in the PG group. The PG and non-PG groups were similar in terms of age (p=0.8) and sex (p=1.000). The duration of follow-up in the PG group was significantly shorter (p=0.049).

According to the WHO classification, the non-PG group had a significantly higher percentage of patients with RCUD, while the PG group had a significantly higher percentage of patients with RAEB-2 (overall comparison, p=0.049). The FAB classification also showed significant difference between groups. The non-PG group had a higher proportion of RA patients, while the PG group had a higher proportion of RAEB patients (p=0.008). Mean hemoglobin level (p=0.004), monocyte count (p=0.017), and platelet count (p=0.011) were significantly lower in the PG group, while these patients had significantly higher mean ferritin levels (p<0.001). BM blast percentage was significantly higher among patients in the PG group (p=0.008). BM dysplasia in three cell lines was found to be significantly more common in the PG group (75.0%) compared to the non-PG group (45.2%) (p=0.043). The two groups were similar in terms of BM cellularity (p=0.26) and BM fibrosis grade (p=0.167). Patients in the PG group were found to have required significantly more transfusions (p<0.001). Median IPSS (p=0.004), IPSS-R (p=0.001), WPSS (p<0.001), MDACC (p=0.002) scores were found to be significantly higher in PG. The percentage of patients classified as having high (and very high) risks according to IPSS, IPSS-R, WPSS and MDACC scores was significantly higher in the PG group compared to the non-PG group; however, while comparisons for IPSS (p=0.027), IPSS-R (p=0.024) and WPSS (p=0.013) demonstrated significant difference between groups, the MDACC results were statistically similar (p=0.067) (Table 1).

Evaluation of various parameters with regard to their performance to predict progression (ROC analysis) yielded the following significant results: IPSS with ≥intermediate-2 cut-off (AUC: 0.728, 95%CI: 0.592-0.864; p=0.004), IPSS-R with ≥high cut-off (AUC: 0.748, 95%CI: 0.618-0.878; p=0.002), WPSS with ≥high cut-off (AUC: 0.761, 95%CI: 0.628-0.894; p=0.001), MDACC with ≥intermediate-2 cut-off (AUC: 0.702, 95%CI: 0.562-0.841; p=0.011). In particular, WPSS with ≥ high cut-off had 81.8% sensitivity and 83.3% negative predictive value (NPV) (Table 2, Figure 1).

Next, we performed multiple logistic regression analysis to determine the best predictive factors associated with progression. All parameters demonstrating significant difference in univariate analyses and previously suggested risk factors were included in the model. Patients with high ECOG-PS score (≥2) were found to have a 6.939-fold higher risk of progression than other patients (OR: 6.939, 95%CI: 1.527-31.526; p=0.012). Patients with high or very high WPSS were found to have a 10.115-fold higher risk of progression than other patients (OR: 10.115, 95%CI: 2.293-44.614; p=0.002) (Table 3, Figure 2, Figure 3). These results indicated that the ECOG-PS and WPSS combination was the best combination that could be used to predict progression. Other variables included in the model, age (p=0.733), sex (p=0.634), fibrosis grade (p=0.099), cytogenetics (p=0.484), dysplasia (p=0.513), IPSS (p=0.554), IPSS-R (p=0.354), and MDACC (p=0.974), were found to be non-significant.

Discussion

About two-thirds of patients with MDS die from bleeding, recurrent infections, and severe anemia due to progressive BM failure. Progression to AML is also associated with an extremely poor outcome and short survival [20]. Therefore, in our study, we identified BM failure and/or conversion to AML and/or death as the progression criteria of MD. We then aimed to identify various predictors that may be most associated with progression. We found that MDS progression could be associated with being classified as having RAEB-2 (WHO classification) and RAEB

Table 1. Summary of patient characteristics with regard to progression

		Progression		
	Total (n=55)	No (n=31)	Yes (n=24)	p
Age	70.95 ± 9.80	70.65 ± 9.06	71.33 ± 10.86	0.8
Sex				
Male	35 (63.6%)	20 (64.5%)	15 (62.5%)	1.000
Female	20 (36.4%)	11 (35.5%)	9 (37.5%)	
Comorbidity	31 (56.4%)	17 (54.8%)	14 (58.3%)	1.000
Diabetes mellitus	6 (10.9%)	5 (16.1%)	1 (4.2%)	0.216
Hypertension	10 (18.2%)	4 (12.9%)	6 (25.0%)	0.304
Ischemic heart disease	9 (16.4%)	4 (12.9%)	5 (20.8%)	0.48
COPD	4 (7.3%)	2 (6.5%)	2 (8.3%)	1.000
Other	7 (12.7%)	4 (12.9%)	3 (12.5%)	1.000
Malignancy	7 (12.7%)	3 (9.7%)	4 (16.7%)	0.69
Type of MDS, WHO				
RCUD	5 (9.1%)	5 (16.1%)	0 (0.0%)	0.049
RCMD	15 (27.3%)	11 (35.5%)	4 (16.7%)	
RARS	4 (7.3%)	3 (9.7%)	1 (4.2%)	
Isolated del(5q)	4 (7.3%)	3 (9.7%)	1 (4.2%)	
RAEB-1	7 (12.7%)	2 (6.5%)	5 (20.8%)	
RAEB-2	17 (30.9%)	6 (19.4%)	11 (45.8%)	
MDS/MPN	3 (5.5%)	1 (3.2%)	2 (8.3%)	
Type of MDS, FAB				
RA	22 (40.0%)	18 (58.1%)	4 (16.7%)	0.008
RARS	5 (9.1%)	4 (12.9%)	1 (4.2%)	
RAEB	23 (41.8%)	7 (22.6%)	16 (66.7%)	
RAEB-T	2 (3.6%)	1 (3.2%)	1 (4.2%)	
CMML	3 (5.5%)	1 (3.2%)	2 (8.3%)	
ECOG performance status				
0	15 (27.3%)	9 (29.0%)	6 (25.0%)	0.085
1	22 (40.0%)	16 (51.6%)	6 (25.0%)	
2	16 (29.1%)	5 (16.1%)	11 (45.8%)	
3	2 (3.6%)	1 (3.2%)	1 (4.2%)	
Hemoglobin (gr/dL)	9.17 ± 2.27	9.92 ± 1.94	8.20 ± 2.34	0.004
MCV (fL)	96.69 ± 13.71	95.17 ± 15.31	98.66 ± 11.32	0.354
WBC (/μl)	3300 (2360-5440)	3420 (2800-6060)	3125 (2075-5150)	0.175
Neutrophil (/μl)	1460 (900-2370)	1750 (1000-3000)	1295 (580-2030)	0.082
Lymphocyte (/μl)	1600 (1040-2340)	1400 (1090-2390)	1760 (1005-2260)	0.95
Monocyte (/μl)	330 (130-580)	380 (200-690)	185 (65-435)	0.017
Platelet (*10^3/μl)	107 (68-188)	141 (84-230)	87.5 (37-133)	0.011
LDH (IU/L)	233 (177-367)	228 (177-383)	234 (175.5-347)	0.96
Ferritin (ng/mL)	525 (143-1258)	160 (87-668)	1155 (412-1801)	<0.001
Bone marrow blast (%)	4 (2-12)	3 (2-7)	8 (3.5-14.5)	0.008
Bone marrow cellularity				
Hypercellular	46 (83.6%)	27 (87.1%)	19 (79.2%)	0.261
Normocellular	7 (12.7%)	4 (12.9%)	3 (12.5%)	
Hypocellular	2 (3.6%)	0 (0.0%)	2 (8.3%)	
Dysplasia (in … cell line(s))				
1	9 (16.4%)	8 (25.8%)	1 (4.2%)	0.043
2	14 (25.5%)	9 (29.0%)	5 (20.8%)	
3	32 (58.2%)	14 (45.2%)	18 (75.0%)	
Fibrosis grade				
MF-0	6 (10.9%)	4 (12.9%)	2 (8.3%)	0.167
MF-1	34 (61.8%)	22 (71.0%)	12 (50.0%)	
MF-2	11 (20.0%)	3 (9.7%)	8 (33.3%)	
MF-3	4 (7.3%)	2 (6.5%)	2 (8.3%)	

Cytogenetic				
Good	25 (45.5%)	17 (54.8%)	8 (33.3%)	0.262
Moderate	16 (29.1%)	8 (25.8%)	8 (33.3%)	
Poor	14 (25.5%)	6 (19.4%)	8 (33.3%)	
Transfusion need	30 (54.5%)	10 (32.3%)	20 (83.3%)	<0.001
Chelating agent use	4 (7.3%)	3 (9.7%)	1 (4.2%)	0.624
IPSS	1 (0-2)	0.5 (0-1.5)	1.5 (1-2.5)	0.004
Low	15 (27.3%)	12 (38.7%)	3 (12.5%)	0.027
Intermediate-1	17 (30.9%)	11 (35.5%)	6 (25.0%)	
Intermediate-2	11 (20.0%)	5 (16.1%)	6 (25.0%)	
High	12 (21.8%)	3 (9.7%)	9 (37.5%)	
IPSS-R	4 (2-6.5)	3 (2-5)	6 (3.75-7.25)	0.001
Very low	5 (9.1%)	5 (16.1%)	0 (0.0%)	0.024
Low	15 (27.3%)	11 (35.5%)	4 (16.7%)	
Intermediate	9 (16.4%)	6 (19.4%)	3 (12.5%)	
High	10 (18.2%)	4 (12.9%)	6 (25.0%)	
Very high	16 (29.1%)	5 (16.1%)	11 (45.8%)	
WPSS	3 (1-4)	1.5 (1-3)	4 (3-5)	<0.001
Very low	7 (13.5%)	6 (20.0%)	1 (4.5%)	0.013
Low	10 (19.2%)	9 (30.0%)	1 (4.5%)	
Intermediate	7 (13.5%)	5 (16.7%)	2 (9.1%)	
High	16 (30.8%)	6 (20.0%)	10 (45.5%)	
Very high	12 (23.1%)	4 (13.3%)	8 (36.4%)	
MDACC	6 (4-8)	5 (3-8)	8 (6-10)	0.002
Low	15 (27.3%)	12 (38.7%)	3 (12.5%)	0.067
Intermediate-1	15 (27.3%)	9 (29.0%)	6 (25.0%)	
Intermediate-2	12 (21.8%)	6 (19.4%)	6 (25.0%)	
High	13 (23.6%)	4 (12.9%)	9 (37.5%)	
Chemotherapy	3 (5.5%)	1 (3.2%)	2 (8.3%)	0.575
Follow-up time, month	22 (8-33)	26 (10-38)	12.5 (6.5-28)	0.049
AML transformation	12 (21.8%)	-	12 (50.0%)	-
Mortality	16 (29.1%)	-	16 (66.7%)	-

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

COPD: Chronic obstructive pulmonary disease, MDS: myelodysplastic syndromes, WHO: World Health Organization, RCUD: Refractory cytopenia with unilineage dysplasia, RCMD: Refractory cytopenia with multilineage dysplasia, RARS: Refractory anemia with ringed sideroblasts, RAEB: Refractory anemia with excess of blasts, MPN: Myeloproliferative neoplasms, FAB: French-American-British, RA: Refractory anemia, RARS: Refractory anemia with ringed sideroblasts, RAEB-T: Refractory anemia with excess of blasts in transformation, CMML: Chronic myelomonocytic leucaemia, ECOG: Eastern Cooperative Oncology Group, MCV: Mean corpuscular volume, WBC: White blood cell, LDH: Lactate dehydrogenase, MF: Myelofibrosis, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-revised, WPSS: WHO classification-based Prognostic Scoring System, MDACC: MD Anderson Cancer Center, AML: Acute myeloid leukemia

(FAB classification). In addition, we observed that the likelihood of progression appeared to increase in the presence of higher risk category in IPSS, IPSS-R, and WPSS. As a result of multiple logistic regression analysis, we found that having an ECOG-PS score of ≥2 and a WPSS classification of ≥high were the only factors independently associated with progression.

The prognosis of MDS patients, with respect to OS and risk of transformation to AML, is primarily defined by the IPSS and the IPSS-R scores [2,21]. IPSS-R has been shown to have improved accuracy over IPSS. In this study, IPSS(-R) scores were not found to be strongly associated with prognostic prediction, especially relative to ECOG-PS and WPSS. Median OS for high-risk MDS patients (IPSS: intermediate-2 and high-risk; IPSS-R: intermediate [with >3.5 points], high or very-high-risk score) ranges from a few months to 1.2 years [21]. The recent study by Papageorgiou et al. showed that IPSS or IPSS-R independently predicted shortened LFS and

Table 2. Performance of the variables to predict progression

	Cut-off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95.0% CI)	p
ECOG-PS	≥ 2	50.0%	80.6%	67.3%	66.7%	67.6%	0.621 (0.466-0.776)	0.127
Fibrosis grade	≥ MF-2	41.7%	83.9%	65.5%	66.7%	65.0%	0.624 (0.472-0.776)	0.118
Cytogenetic	Moderate & Poor	66.7%	54.8%	60.0%	53.3%	68.0%	0.618 (0.468-0.769)	0.135
IPSS	≥ Intermediate-2	62.5%	74.2%	69.1%	65.2%	71.9%	0.728 (0.592-0.864)	0.004
IPSS-R	≥ High	70.8%	71.0%	70.9%	65.4%	75.9%	0.748 (0.618-0.878)	0.002
WPSS	≥ High	81.8%	66.7%	73.1%	64.3%	83.3%	0.761 (0.628-0.894)	0.001
MDACC	≥ Intermediate-2	62.5%	67.7%	65.5%	60.0%	70.0%	0.702 (0.562-0.841)	0.011

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, ECOG: Eastern Cooperative Oncology Group, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-revised, WPSS: WHO classification-based Prognostic Scoring System, MDACC: MD Anderson Cancer Center

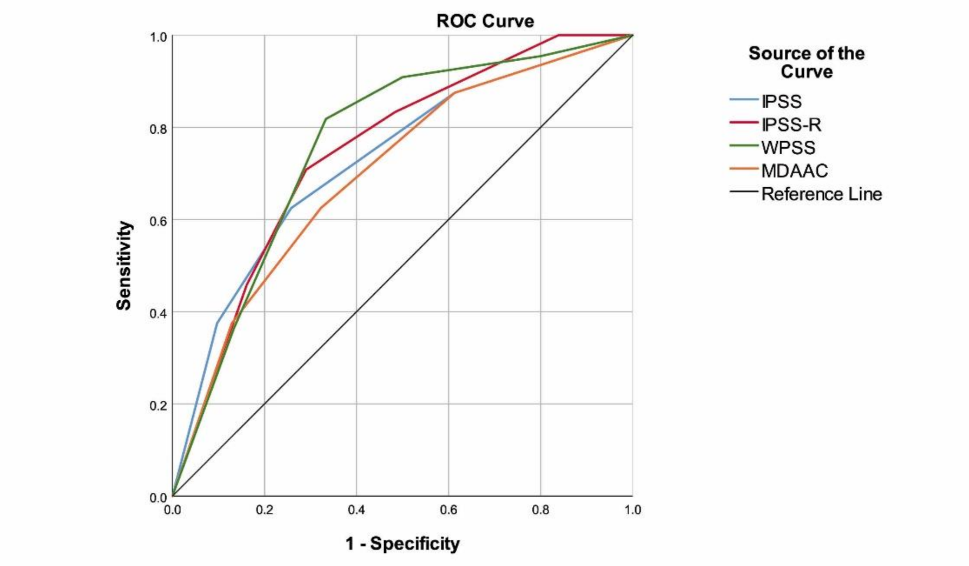

Figure 1. ROC curve of the risk scores to predict progression

Table 3. The best predictive factors of the progression, multiple logistic regression analysis

	β coefficient	Standard Error	p	Exp(β)	95% CI for Exp(β)	
ECOG-PS, ≥ 2	1.937	0.772	0.012	6.939	1.527	31.526
WPSS, ≥ High	2.314	0.757	0.002	10.115	2.293	44.614
Constant	-2.335	0.703	0.001	0.097		

Dependent variable: Progression; Nagelkerke R^2=0.430

CI: Confidence Interval, ECOG: Eastern Cooperative Oncology Group, WPSS: WHO classification-based Prognostic Scoring System

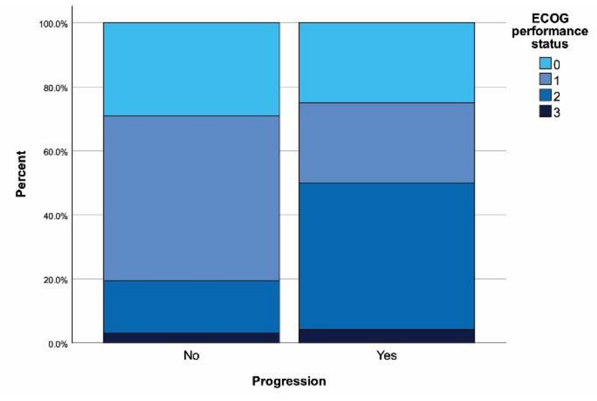

Figure 2. ECOG performance status score with regard to progression

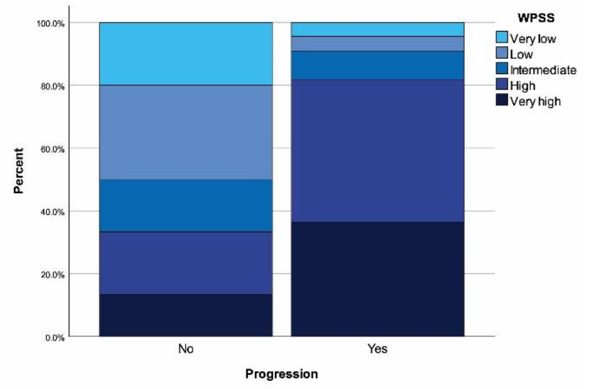

Figure 3. WPSS risk groups with regard to progression

OS [21]. Apart from these two, the other 2 classification systems developed and accepted as prognostic determinants are WPSS and MDACC models [16,22]. We believe the outcomes of our study may be associated with the fact that WPSS performs a dynamic risk assessment and has prognostic value not only at the time of diagnosis but also at other times [23]. Porta and colleagues studied OS and AML conversion time in 5326 MDS patients with respect to IPSS-R and WPSS classes. They found that according to, median OS was 121, 67, 35, 20, and 9 months in very low, low, intermediate, high and very high risk IPSS-R classes, respectively. Also, after excluding the “very low risk” group, median time for 25% of patients to develop AML was found to be 188, 34, 17 and 9 months, respectively. They also showed that according to WPSS classes median OS was 98, 76, 44, 21 and 9 months in very low, low, intermediate, high and very high risk, respectively, while median times for 25% of patients to develop AML (except very low) were 174, 72, 18 and 8 months, respectively. They found the prognostic power of the WPSS was comparable to that of IPSS-R [22]. Comparing the IPSS and WPSS outcomes, it appears that the relatively steep decline regarding length of OS and time until AML conversion from the “intermediate” to the “high risk” groups of the WPSS may have had a role in establishment of statistical significance in the present study. The multivariable analysis results of our study support the relationship of the WPSS system with MDS progression. In our study, RAEB-2 was found to be significantly associated with progression and WHO-RAEB-2 significantly increased the WPSS score. Taken together, these provide support for the importance of blast percentage in determining prognosis, as this parameter is the primary parameter that distinguishes RAEB-2 from other WHO subclasses. However, before drawing direct conclusions regarding this matter, the non-homogeneous distribution of patient characteristics in MDS and the limited patient counts in several subgroups must be considered.

The MDACC is another prognostic system that assesses treated and untreated MDS patients, as well as patients with proliferative CMML and treatment-associated MDS [16,23]. Notwithstanding its reliable performance and wide inclusion criteria, the relative complexity of this model has limited its use in routine clinical practice [23]. The studies by Komrokji et al. and Nazha et al. also supported the prognostic value of MDACC in MDS [24,25]. Although we did not find an independent relationship between MDACC and MDS progression, ECOG-PS (which is included in the MDACC) was independently associated with MDS progression, further supporting the utility of MDACC in prognostic assessment while also showing the need for further data to improve patient risk stratification in MDS. When we evaluated ECOG-PS's prognostic value as a separate parameter, it was found that half of the patients with progression had an ECOG-PS score of 2 or higher. Perhaps more importantly, 80% of the non-PG group had an ECOG-PS score of <2. Similar to our study, the logistic regression analysis performed in one study showed that having a poor ECOG-PS (score ≥2) was an independent predictor of shortened LFS and OS, independent of IPSS-R risk class [21]. This relationships was also supported by another study in which an ECOG-PS score of 2 or higher was independently associated with shorter survival [26].

The FAB and WHO classifications are two widely accepted models in the pathological classification of MDS. The WHO classification was revised in 2016 [27,28], but since we used data obtained between 1999 and 2012 in our study, we classified patients according to the WHO 2008 classification. In a comprehensive study involving 5326 patients, OS for the types defined according to the WHO classification were as follows: median OS was 99 months for RCUD, RARS, and del5q (considered a single category), 66 months for RCMD, 28 months for RAEB-1, and 18 months for RAEB-2. The median time that surpassed until 25% of patients developed AML was 123 months for RCMD, 23 months for RAEB-1, and 9 months for RAEB-2 [22]. In the study by Ohyashiki et al., the conversion of RAEB-1 to AML was reported at a frequency of 37.5%, while the conversion rate of RAEB-2 to AML was 50% [29]. A recent study from Japan reported that MDS patients with high ferritin levels were significantly more likely to have RARS according to the FAB classification and were significantly less likely to have RA when compared to those with low ferritin levels [10]. Considering that high ferritin level is associated with worse survival in MDS, the ferritin elevation in these groups could be a factor contributing to survival [30]. We found that patients with RAEB-2 (WHO classification) and patients with RAEB (FAB classification) were significantly more likely to be in the PG group rather than the non-PG group. Furthermore, patients with RCUD (WHO classification) and patients with RA (FAB classification) were significantly more common in the PG group than in the non-PG group. We can say that these results are relatively consistent with the results of previous studies. Undoubtedly, the combination of the excess blast percentage with the presence of dysplasia in one or more cell lines has an important role in this relationship.

The limitations of our study can be listed as follows: the fact that it was a single-center study and the small number of participants limits the generalizability of the results. The retrospective analysis limited both the addition of new data and the use of the revised version of the WHO classification (2016) and comparison with other studies in this respect. In addition, since some patients had been diagnosed prior to access to advanced methods, we could not examine the effects of molecular genetics on the clinical course of MDS. The heterogeneity of the patient population is true for all studies evaluating patients with MDS, and therefore, is unavoidable; however, our data were further limited by the heterogeneous distribution of patients into prognostic subgroups. This may have influenced the statistical analyses.

Multivariable analysis showed that having an ECOG-PS score of ≥2 and being classified with ≥high risk according to the WPSS were independent predictors of MDS progression. Compared to the non-PG group, patients with progression had lower hemoglobin, monocyte, and platelet values, while BM blast percentage, transfusion need and ferritin levels were higher. In addition, the presence of dysplasia in more than one cell line was also found to be associated with progression. The development of different systems to predict the progression of MDS disorders, possibly with inclusion of genetic studies, will be beneficial to increase the accuracy of available classification systems, to determine the most appropriate and early treatment regimens, and ultimately, to improve survival.

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Corresponding author e-mail: gulturke@yahoo.com.tr

Orcid ID:
Emine Gültürk: 0000-0003-2836-6162

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Original Article

Opioid Administration for Mucositis-Related-Pain Using Patient Controlled Analgesia (PCA) Method is Associated with the Development of Early Posttransplant Complications

Mukozit İlişkili Ağrı için Hasta Kontrollü Analjezi Yöntemi Eşliğinde Uygulanan Opioid Tedavisinin Erken Dönem Nakil Komplikasyonları ile İlişkisi

Kübra Haşimoğlu Gürün[1], Zeynep Arzu Yeğin[2], Didem Akçalı[3], Zübeyde Nur Özkurt[2], Oktay Tertemiz[3], Ferda Can[2], Asena Dikyar[2], Suzan Berkiten[2]

[1]Gazi University Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey
[2]Gazi University Faculty of Medicine, Department of Hematology, Ankara, Turkey
[3]Gazi University Faculty of Medicine, Department of Anesthesiology, Ankara, Turkey

ABSTRACT

Introduction: Mucositis is one of the major complications of allogeneic hematopoietic stem cell transplantation with myeloablative conditioning. Several measures have been developed to improve pain palliation and quality of life in transplant recipients. This study was performed to evaluate the association of opioid administration using patient controlled analgesia (PCA) method with early posttranplant complications.

Materials and Methods: Medical records of 452 patients [median age: 35(15-67) years, male/female: 285/167] were retrospectively reviewed.

Results: PCA was used in 157 patients (34.7%) for median 9(1-24) days. The proportion of patients who received myeloablative conditioning regimen was significantly higher in PCA+ group ($p<0.001$). Severe mucositis was more common in patients who required PCA administration ($p<0.001$). Total body irradiation ($p<0.001$) and methotreaxate prophylaxis ($p<0.001$) were more frequently used in PCA+ patients. Hypoxia, bleeding, sinusoidal obstruction syndrome, invasive fungal infections, neurotoxicity, hepatotoxicity and nephrotoxicity were significantly more common in PCA+ patients. Duration of hospitalization was significantly longer in PCA+ group ($p<0.001$).

Discussion: Opioid administration with PCA, which was more frequently used in patients who had myeloablative conditioning and mucositis, was found to be associated with the development of early posttransplant complications.

Keywords: Patient Controlled Analgesia; Myeloablative Conditioning; Mucositis; Allogeneic Hematopoietic Stem Cell Transplantation; Pain Palliation

ÖZET

Giriş: Mukozit, myeloablatif hazırlama rejimiyle allojeneik kök hücre nakli yapılan hastalarda gelişebilen önemli komplikasyonlardan biridir. Kök hücre nakil alıcılarında ağrı palyasyonu sağlamak ve yaşam kalitesini artırmak için farklı yöntemler geliştirilmiştir. Bu çalışmanın amacı, hasta kontrollü analjezi (HKA) yöntemi eşliğinde uygulanan opioid tedavisinin erken dönem nakil komplikasyonlarıyla ilişkisini araştırmaktır.

Gereç ve yöntemler: Toplam 452 hastanın [ortanca yaş: 35(15-67) yıl, erkek/kadın: 285/167] verileri geriye dönük olarak incelendi.

Bulgular: Hasta kontrollü analjezi 157 hastada (%34.7) ortanca 9(1-24) gün süreyle uygulandı. HKA+ grupta myeloablatif rejim uygulanan hasta sayısı anlamlı yüksekti ($p<0.001$). HKA gereksinimi olan hastalarda ağır mukozit gelişiminin daha sık olduğu gözlendi ($p<0.001$). Tüm beden ışınlaması ($p<0.001$) ve metotreksat kullanımı ($p<0.001$) HKA+ grupta daha sıktı. Hipoksi, kanama, sinuzoidal obstrüksiyon sendromu, invaziv fungal enfeksiyonlar, nörotoksisite, hepatotoksisite ve nefrotoksisite

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HKA+ grupta daha sık görüldü. Hastanede kalış süresi HKA+ grupta anlamlı uzun saptandı (p<0.001). **Tartışma:** Bu çalışmada, myeloablatif hazırlama rejimi uygulanan ve ağır mukozit gelişen hastalarda daha sık kullanılan HKA eşliğinde opioid uygulamasının erken dönem nakil komplikasyonlarıyla ilişkili olduğu gösterildi.

Anahtar kelimeler: Hasta Kontrollü Analjezi; Myeloablatif Hazırlama Rejimi; Mukozit; Allojeneik Kök Hücre Nakli; Ağrı Palyasyonu

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHCT) is considered as a curative modality in the treatment of various hematological disorders. Despite favorable improvement in patient care and supportive measures, unacceptable morbidity and mortality rates remain a major problem in high risk patients. Although chronic graft versus host disease (GvHD) and relapse seem to be responsible for the long-term adverse outcomes, early posttransplant complications including mucositis, infection, acute GvHD and sinusoidal obstruction syndrome (SOS) may cause significant toxicity which may result in prolonged hospitalization and impaired quality of life [1-3].

Among a variety of transplant related factors which may increase the risk of periengraftment complications, the prominent role of conditioning regimen intensity should be pronounced in the development of severe mucositis and other complications due to endothelial dysfunction. Myeloablative conditioning (MAC) which contains high dose chemotherapy and/or radiotherapy has an adverse impact on rapidly dividing cells and may cause severe mucositis in the early posttransplant course. Approximately 75% of alloHCT recipients develop oral mucositis in the preengraftment phase of transplantation. The severity of mucositis is associated with the intensity of conditioning regimen as well as immunosuppressive medications which are used for GvHD prophylaxis such as methotrexate [4-7]. Oral nutrition may be impaired in these patients as a result of mucositis associated pain. Bacterial translocation and catheter related infections may develop in patients who require parenteral support because of oral nutrition impairment. Therefore, pain palliation including topical local anesthetics and systemic opioid analgesics is indispensable to maintain normal gastrointestinal function in order to accelerate the healing process of mucosal barriers and improve quality of life [7-9].

Patient controlled analgesia (PCA) is a pain relief method which enables self administration of the analgesic substance via intravenous bolus and/or infusion using a specific pump which is programmed by an expert, preferably by an anesthesiologist. Maximum drug dose, dose ranges and infusion rates can be individualized by this procedure. The total amount of opioid substance was shown to be significantly reduced in patients who receive PCA [8,10].

To our knowledge, the role of opioid administration via PCA method in the development of transplant complications has not been previously studied. Therefore, this retrospective study is performed to evaluate the effect of opioid use with PCA in the early posttransplant course and to clarify its possible association with transplant related complications and hospital stay.

Materials and Methods

Patients

A total of 452 patients [median age: 35(15-67) years, male/female:285/167] who underwent alloHCT between 2003 and 2018 were included in this study. Medical records of the patients were analyzed retrospectively. Demographic and clinical characteristics of the patients were recorded. Transplant risk assessments including European Society for Blood and Marrow Transplantation (EBMT) score and Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) were evaluated [11,12]. National Cancer Institute Common Toxicity Criteria (version 4) was used for toxicity assessments. Patient and transplant characteristics are represented in Table 1.

Pain Management and PCA Schedule

Pain scores of the transplant recipients, which range from 0 to 10 points (pts), were determined by numeric rating scale (NRS) [9,13]. Daily pain status of all patients was questioned and recorded by transplant nurses. Tramadol infusion with PCA was started when the pain score was greater than 3 pts. Tramadol was mixed with normal saline at a concentration of 5 mg/mL. Lockout time was identified as 30 minutes while 4-hour infusion limit was indicated to be 200 mL. Initial dose arrangements were 20 mg and 5 mg/mL for bolus and infusion rates, respectively. All steps of the setting, including basal and subsequent modifications, were adjusted by an anesthesiologist. In patients with a permanent pain score greater than 5 pts, which was considered as refractory to appropriate dose increments, intravenous morphine and/or transdermal fentanyl patch were used to support PCA infusion. Antiemetic drugs such as serotonin 5-HT3 antagonists or metoclopramide were used for PCA induced nausea and vomiting. PCA infusion was stopped in case of severe side effects including dizziness, confusion and hypoxemia.

Transplant Protocols

The criteria of the Centre for International Blood and Marrow Transplant Research (CIBMTR) was used for the classification of conditioning intensity [14]. Myeloablative conditioning regimens consisted total body irradiation (TBI) (1200 cGy)/ cyclophosphamide (120 mg/kg) or busulfex (12.8 mg/kg)/cyclophosphamide (120 mg/kg), whereas fludarabine (150 mg/m^2)/melphalan (140 mg/m^2) and TBI (400 cGy)/fludarabine (150 mg/m^2) were designated as reduced intensity conditioning (RIC) regimens. Cyclosporine A / methotrexate and cyclosporine A / mycofenolate mofetil combinations were used for GvHD prophylaxis in MAC and RIC transplants respectively.

Supportive Care

Standards for antibacterial and antifungal prophylaxis, febrile neutropenia, invasive fungal infections (IFI) and cytomegalovirus reactivation were assessed based on the European Conference on Infections in Leukemia (ECIL) and Infectious Diseases Society of America (IDSA) guidelines [15-17]. The diagnosis and grading of SOS was identified according to the EBMT guidelines [18].

Statistical Analysis

Categorical and continuous variables were represented as frequency (percentage) and median (range) respectively. Kolmogorov-Smirnov and Shapiro Wilk tests were performed for normality analysis with $p>0.05$ taken as evidence of normality. Parametric and non-parametric tests were used in case of normal and abnormal distributions. Continuous variables were compared using Student T-test, Mann Whitney U and Kruskal Wallis tests. Chi-square test was used for the comparison of categorical variables. Correlation analysis was performed using Pearson and Spearman tests. Kaplan-Meier method was used for survival analysis and log rank test for the comparisons of Kaplan-Meier curves. Cox proportional hazards regression model with the calculation of HRs and 95% confidence intervals (CI) was used for univariate and multivariate analysis in order to determine statistically significant prognostic factors. IBM SPSS Statistics Version 22.0 (IBM Corp, Armonk, NY, USA) programme was used for statistical analysis. All P values were two-sided and $P<0.05$ was considered as statistically significant.

Ethical Standards

The study was approved by the institutional review board of Gazi University Faculty of Medicine (Date: 11.06.2018; Number: 449) All procedures in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Table 1. Patient and Transplant Characteristics

Age (years) [median (range)]	35 (15-67)
Gender (male/female) [n(%)]	285 (63.1) / 167 (36.9)
Diagnosis [n(%)]	
Acute myeloid leukemia	169 (37.4)
Acute lymphoblastic leukemia	109 (24.1)
Myelodysplastic syndrome	29 (6.4)
Non Hodgkin lymphoma	32 (7.1)
Hodgkin lymphoma	19 (4.2)
Multiple myeloma	25 (5.6)
Chronic lymphocytic leukemia	2 (0.4)
Chronic myeloid leukemia	14 (3.1)
Primary myelofibrosis	10 (2.2)
Aplastic anemia	34 (7.5)
Paroxysmal nocturnal hemoglobinuria	5 (1.1)
Thalassemia major	4 (0.9)
Pretransplant Disease Status (n=378) [n(%)]	
Complete remission	262 (69.3)
Partial remission	33 (8.7)
Progressive disease / Relapse	66 (17.5)
Primary refractory	15 (4)
Stable disease	2 (0.5)
ECOG Performance Status [median (range)]	1 (0-4)
HCT-CI [median (range)]	1 (0-6)
EBMT Score [median (range)]	3 (0-7)
HLA Compatibility [n(%)]	
Matched sibling	365 (80.8)
Mismatched related	14 (3.1)
Unrelated	71 (15.7)
Haploidentical	2 (0.4)
Graft Source [n(%)]	
Peripheral blood	429 (94.9)
Bone marrow	23 (5.1)
Conditioning Regimen [n(%)]	
Myeloablative	276 (61.1)
Reduced intensity	176 (38.9)
Total Body Irradiation [n(%)]	109 (24.1)
GvHD Prophylaxis [n(%)]	
Cyclosporine A–methotreaxate	379 (83.8)
Cyclosporine A–mycophenolate mofetil	73 (16.2)
Infused $CD34^+$ Cell Count ($x10^6$/kg) [median (range)]	4.2 (0.3-9.5)
Neutrophil Engrafment (days) [median (range)]	17 (7-43)
Platelet Engraftment (days) [median (range)]	15 (0-89)
Total Parenteral Nutrition [n(%)]	194 (42.9)
Duration of parenteral nutrition (days) [median (range)]	10 (2-46)
Sinusoidal Obstruction Syndrome [n(%)]	97 (21.5)
Grade [median (range)]	2 (1-3)
Thrombotic Microangiopathy [n(%)]	4 (0.9)
Duration of Febrile Neutropenia (days) [median (range)]	3 (0-52)
Septic Shock [n(%)]	35 (7.7)
Invasive Fungal Infection [n(%)]	116 (25.7)
Mechanical Ventilation [n(%)]	52 (11.5)
Pain Score [median (range)]	6 (0-10)
PCA Administration [n(%)]	157 (34.7)
Duration of PCA (days) [median (range)]	9 (1-24)
Duration of Hospitalization (days) [median (range)]	31 (9-130)

EBMT European Society for Blood and Marrow Transplantation; ECOG Eastern Cooperative Oncology Group; GvHD Graft versus Host Disease; HCT-CI Hematopoietic Cell Transplantation Comorbidity Index; PCA Patient Controlled Analgesia

Results

Median pain score was indicated to be 6(0-10) pts in the whole study population. Patient controlled analgesia was used in 157 patients (34.7%) for median 9(1-24) days. A total of 118 patients (75.2%) were diagnosed as acute leukemia in PCA+ group.

Patient controlled analgesia requirement was observed to be significantly predominant in acute leukemia patients (P<0.001). Furthermore, PCA was more commonly used in patients who received TBI (P<0.001) and cyclosporine A-methotrexate as GvHD prophylaxis (P<0.001). Patients who developed SOS (P<0.001), febrile neutropenia (P<0.001) and IFIs (P<0.001) required significantly more PCA support.

Comparison of PCA+ and PCA- Groups

Based on PCA administration, the study population was seperated into two subgroups, each of which implicates PCA+ (n=157, 34.7%) and PCA- (n=295, 65.3%) patients. Median pain score was significantly higher in PCA+ group compared to PCA- group [8(0-10) vs 4(0-10) pts; P<0.001)]. Patients in PCA+ group were found to be younger than PCA- patients [29(16-65) vs 38(15-67) years; P<0.001] which may be associated with the predominance of acute leukemia patients in PCA+ group who were frequently exposed to MAC regimens. Thus, the proportion of patients receiving MAC in PCA+ group was found to be significantly higher compared to PCA- group (79% vs 51.5%, P<0.001). Patient controlled analgesia was administered in 44.9% of the patients who received MAC regimen and 18.9% of the patients who had RIC (P<0.001). Total body irradiation (42.7% vs 14.2%; P<0.001) and methotreaxate prophylaxis (97.5% vs 76.6%; P<0.001) were observed to be more frequently used in PCA+ patients. Neutrophil [17(10-43) vs 16(7-29) days; P<0.001] and platelet engraftments [16.5(0-89) vs 14(0-64) days; P<0.001] occured later in PCA+ group compared to PCA- group. Total parenteral nutrition (TPN) was extensively used in PCA+ patients (76.4% vs 24.8%; P<0.001). Duration of febrile neutropenia was significantly longer [(5(0-52) vs 3(0-28) days; P<0.001] and IFIs were found to be more frequent in PCA+ group [38.2% vs 20%; P<0.001)]. Similarly, incidence of SOS was indicated to be higher in patients who received PCA [36.3% vs 13.6%; P<0.001]. Duration of hospitalization was recorded to be significantly longer in PCA+ patients [32(16-130) vs 29(9-94) days, P<0.001) (Table 2).

Conditioning regimen and transplant related toxicities including hypoxia (p=0.032), bleeding (P<0.001), neurotoxicity (P=0.003), hepatotoxicity (P=0.001) and nephrotoxicity (P=0.033) were observed to be more common in PCA+ patients. Table 3 represents the comparison of toxicity profiles between two groups.

Subgroup Analysis Based on Pain Status

The study cohort was further divided into two distinct subgroups based on the severity of pain, such as “mild-to-moderate” and “severe”. Maximum pain score ≥7 pts was classified as “severe” pain, whereas pain score <7 pts was referred to “mild-to-moderate” pain. Acute leukemia diagnosis (P<0.001), MAC (P=0.005) and TBI administration (P<0.001) were more frequently observed in the severe-pain group.

Survival Analysis and Prognostic Factors

Probability of overall survival (OS) was estimated to be 35.5% in the whole population at the end of 539(1-5435) days of follow-up. Probability of OS was not different between PCA+ and PCA- groups (33.2% vs 37.7%) (P>0.05) (Figure 1).

Factors which had a significant impact on OS in univariate analysis are represented in Table 4. Eastern Cooperative Oncology Group (ECOG) performance status [P<0.001; HR: 3.869 (95% CI: 1.849-8.098)], EBMT risk score [P=0.022; HR: 1.222 (95% CI: 1.029-1.451)], duration of febrile neutropenia [P=0.005; HR: 1.110 (95% CI: 1.032-1.193)], hypoxia [P=0.031; HR: 1.372 (95% CI: 1.029-1.830)] and nephrotoxicity [P<0.001; HR: 2.494 (95% CI: 1.566-3.972)] were indicated to be significant prognostic factors in multivariate analysis.

Table 2. Distribution of Comparative Variables among PCA^+ and PCA^- Groups

	PCA^+ Group n=157	PCA^- Group n=295	*P* Value
Age (years) [median (range)]	29 (16-65)	38 (15-67)	<0.001
Neutrophil Engraftment (days) [median (range)]	17(10-43)	16 (7-29)	<0.001
Platelet Engraftment (days) [median (range)]	16.5 (0-89)	14 (0-64)	<0.001
Red Blood Cell Transfusion (units) [median (range)]	4 (0-50)	3 (0-33)	0.005
Platelet Transfusion (units) [median (range)]	6 (0-75)	4 (0-63)	<0.001
Duration of Febrile Neutropenia (days) [median (range)]	5(0-52)	3(0-28)	<0.001
Duration of Hospitalization (days) [median (range)]	32 (16-130)	29 (9-94)	<0.001
Maximum Pain Score (points) [median (range)]	8 (0-10)	4 (0-10)	<0.001
Myeloablative Conditioning Regimen [n(%)]	124 (79)	152 (51.5)	<0.001
Total Body Irradiation [n(%)]	67 (42.7)	42 (14.2)	<0.001
Methotrexate Administration [n(%)]	153 (97.5)	226 (76.6)	<0.001
Sinusoidal Obstruction Syndrome [n(%)]	57 (36.3)	40 (13.6)	<0.001
Total Parenteral Nutrition [n(%)] Duration of parenteral nutrition (days) [median (range)]	120 (76.4) 11 (2-46)	73 (24.8) 8 (2-32)	<0.001 0.031
Invasive Fungal Infection [n(%)]	60 (38.2)	59 (20)	<0.001

Table 3: Comparison of Toxicity Profiles between PCA^+ and PCA^- Groups Based on NCI Common Toxicity Criteria

	PCA^+ Group (n=157)	PCA^- Group (n=295)	*P* Value
Mucositis [median (range)]	4 (0-4)	1 (0-4)	<0.001
Febrile Neutropenia [median (range)]	2 (0-4)	2 (0-4)	<0.001
Infection [median (range)]	3 (0-4)	3 (0-4)	<0.001
Nausea [median (range)]	1 (0-3)	0 (0-3)	0.01
Vomiting [median (range)]	2 (0-4)	1 (0-4)	0.01
Diarrhea [median (range)]	1 (0-4)	0 (0-4)	<0.001
Constipation [median (range)]	0 (0-4)	0 (0-3)	0.001
Hypoxia [median (range)]	0 (0-4)	0 (0-4)	0.03
Bleeding [median (range)]	0 (0-4)	0 (0-2)	<0.001
Neurotoxicity [median (range)]	0 (0-3)	0 (0-3)	0.003
Hepatotoxicity [median (range)]	1 (0-4)	0 (0-3)	0.001
Nephrotoxicity [median (range)]	0 (0-4)	0 (0-4)	0.03

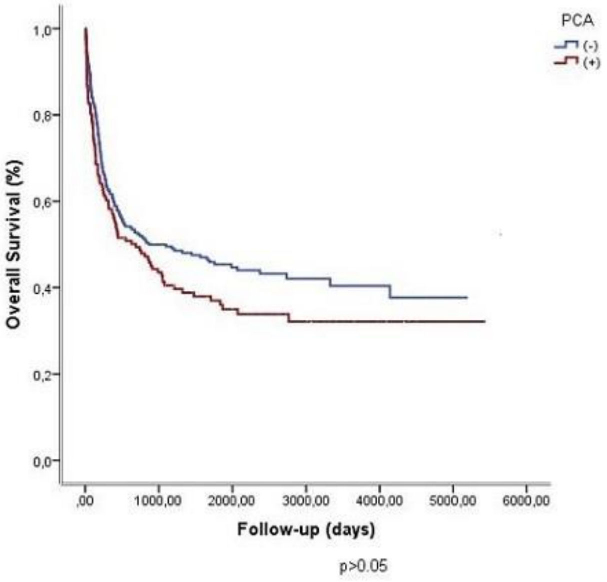

Figure 1. Probability of Overall Survival in PCA^+ and PCA^- Groups (33.2% vs 37.7%) (p>0.05)

Table 4. Prognostic Risk Factors for Survival in Univariate Analysis

Risk Factors	*P* Value	Hazard Ratio	95% Confidence Interval
Pretransplant disease status	<0.001	1.44	1.28-1.62
ECOG performance status	<0.001	2.57	2.01-3.3
EBMT score	<0.001	1.26	1.12-1.43
Mismatched donor	0.02	1.46	1.05-2.02
Pretransplant CRP	<0.001	1.00	1.00-1.01
Pretransplant ferritin	<0.001	1.00	1.00-1.00
ATG for GvHD prophylaxis	0.03	0.6	0.39-0.94
Sinusoidal obstruction syndrome	<0.001	2.15	1.64-2.83
Defibrotide treatment for SOS	<0.001	1.46	1.27-1.69
Thrombotic microangiopathy	0.04	2.78	1.03-7.49
Infused CD34$^+$ cell count	0.04	0.89	0.81-0.99
Red blood cell transfusion	<0.001	1.04	1.02-1.05
Platelet transfusion	<0.001	1.02	1.01-1.03
Total parenteral nutrition	<0.001	1.82	1.43-2.33
Mucositis	<0.001	1.16	1.07-1.27
Febrile neutropenia	0.002	1.29	1.10-1.51
Duration of Febrile Neutropenia	<0.001	1.04	1.02-1.05
Infection	<0.001	1.26	1.12-1.43
Invasive fungal infection	<0.001	1.52	1.27-1.82
Diarrhea	0.02	1.13	1.02-1.26
Hypoxia	<0.001	1.57	1.45-1.71
Bleeding	0.002	1.38	1.12-1.70
Pscycological toxicity	<0.001	1.42	1.18-1.71
Neurotoxicity	0.02	1.46	1.06-2.02
Hepatotoxicity	<0.001	1.4	1.24-1.59
Nephrotoxicity	<0.001	1.72	1.55-1.92

ATG Anti-thymocyte Globulin; CRP C Reactive Protein; ECOG Eastern Cooperative Oncology Group; EBMT European Society for Blood and Marrow Transplantation; GvHD Graft versus Host Disease; SOS Sinusoidal Obstruction Syndrome

Discussion

In this study, the potential role and tolerability of opioid administration for mucositis-related-pain were investigated in a retrospective cohort of alloHCT recipients. Intensive conditioning, TBI administration and methotrexate use were shown to potentiate opioid requirement. Febrile neutropenia, IFIs and SOS were found to be more common in patients who received opioids with PCA. Discharge from hospital was delayed in the same group of patients. Early complications including hypoxemia, neurotoxicity, hepatotoxicity and nephrotoxicity were more frequently observed in PCA+ patients. Opioid administration with PCA did not represent a significant impact on OS.

Conditioning regimen is one of the most important factors for the development of mucositis in the early course of alloHCT. The intensity of the preparative regimen has a direct impact on epithelial cell damage [5-7]. Eduardo et al showed that myeloablative doses of busulfan may result in more frequent and long lasting mucositis [19]. Current study confirms and underlines the association of the conditioning regimen with the severity of mucositis and mucositis associated pain. As mucositis was more severe in patients who received MAC regimen, opioid and TPN requirement were more frequent in the same group of patients as expected. The frequency and grade of mucositis were found to be higher in patients who received methotrexate for GvHD prophylaxis. Leucovorine, which was not routinely used in our patients, was shown to shorten the duration of mucositis, neutrophil engraftment and hospital stay in previous reports [4,20]. Methotrexate may also prolong the healing process of mucositis in these patients [4,6,7,21]. In our study, patients who received methotrexate represented an increased requirement for opioid support which was potentially attributed to severe mucositis. Therefore, less toxic regimens for conditioning and GvHD prophylaxis may help to reduce the frequency and severity of mucositis, as well as opioid requirement.

Total body irradiation has a significant role in early transplant related complications including mucositis [6,21-23]. In a study by Anand et al, the incidence and severity of mucositis were reduced in patients who received low dose TBI. In addition, TPN and opioid analgesics were more frequently used in patients with severe mucositis. Duration of hospitalization was significantly longer in the same group of patients [21]. In our study, opioid administration was more common in patients who were treated with TBI, independent from the dosing schedule. Similarly, the duration of TPN was significantly longer in PCA+ group. As maintenance of enteral nutrition is essential for the prevention of TPN related complications, appropriate and effective pain palliation can be lifesaving in these circumstances [4,7,21,23].

The association of age and mucositis was pronounced in several studies indicating that mucositis may be more severe and prolonged in younger patients which is also confirmed in the present study [1,24]. Nevertheless, this association was mainly attributed to the predominant use of MAC regimens in young and fit patients. On the contrary, as RIC regimens are generally preferred in relatively fragile elderly population with comorbidities, early transplant complications due to conditioning toxicity are expected to be lower in this group of patients.

Infections are important causes of non relapse mortality in the early posttransplant course. Delayed engraftment, which was also found to be associated with severe mucositis in the present study, may have a major role in the development of severe infections. Studies have shown that infectious morbidity was higher in patients with severe mucositis in concordance with our results which underline the potential intercourse between neutrophil engraftment and recovery of mucositis. In the present study, SOS was also found to be more frequent in patients who received opioids with PCA. Intensive conditioning regimens may cause a significant tendency for the development of preengraftment complications including mucositis and SOS, since they share a similar etiopathology mainly based on endothelial cell damage [2,3,25,26].

On the other hand, the association of opioid administration and early transplant toxicities including hypoxia, bleeding, neurological, hepatic and renal complications, may be attributed to the underlying conditions and comorbidities which may generate an additional risk for the development of severe toxicities. Nevertheless, transplant physicians should be aware of the potential drug side effects and/or interactions although average opioid dose is considered to be relatively lower and tolerable with PCA than standard methods [2,7,27].

Several studies have shown that hospitalization may be prolonged in patients with severe mucositis [10,25,28]. In a study by McCann et al, the length of hospital stay was found to be associated with a variety of factors including age, poor performance status, severe mucositis and delayed neutrophil engraftment [25]. Vera-Llonch et al demonstrated a significant relationship between the severity of mucositis and the length of hospital stay [28]. In concordance with these previous reports, duration of hospitalization was also found to be significantly longer in PCA+ group in the present study, which may be associated with the higher frequency of transplant related complications in this group, such as prolonged mucositis.

Although there are several reports which represented the prognostic impact of mucositis in transplant candidates, any significant association of mucositis with OS was not shown in the present study [5,29]. Mucositis was indicated to be a significant prognostic factor in univariate analysis, however the significance was not confirmed in multivariate analysis. Despite relatively large cohort of patients included, heterogeneity of the study population may be a potential explanation for the lack of survival effect.

Despite the association of opioid administration with serious posttransplant complications, any significant impact of opioid use on OS was not demonstrated. This fact may draw attention to a potential additive role of opioid administration on transplant complications rather than being the primary underlying cause. Nevertheless, multifactorial nature of the milieu, as well as complex microenvironmental background, should also be taken into account in order to generate a more global and accurate vision for the development of posttransplant toxicities.

Based on the presented results, early and prompt treatment of mucositis and optimal supportive care including maintenance of oral hygiene, local and systemic measures for pain palliation, may prevent consecutive associated complications and improve quality of life in the early posttransplant setting. Reduced intensity conditioning, fractionated and low dose TBI, less toxic regimens for GvHD prophylaxis and integration of new therapeutic approaches which may overcome or compensate drug side effects may not only prevent mucositis and related complications, but also reduce the necessity for further recovery attempts.

In conclusion, opioid administration with PCA may be considered as an easy, safe and humanistic procedure with a tolerable side effect profile compared to its alternatives, particularly in patients who are exposed to intensive regimens and predicted to have a tendency for severe transplant related complications. The intensity of the conditioning should be determined based on a highly selected list of contributing factors including patient, disease and transplant characteristics. In consideration with its potential toxicity profile, pain palliation with PCA remains to be a privileged attempt to improve patient’s quality of life in the early posttransplant course.

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Corresponding author e-mail: zeyneparzuyegin@gmail.com

Orcid ID:
Kübra Haşimoğlu Gürün 0000-0002-0110-4325
Zeynep Arzu Yeğin 0000-0002-0212-9663
Didem Akçalı 0000-0003-3590-5531
Zübeyde Nur Özkurt 0000-0001-9834-6058
Oktay Tertemiz 0000-0002-6131-1756
Ferda Can 0000-0002-9899-1441
Asena Dikyar 0000-0002-9108-876X
Suzan Berkiten 0000-0001-7226-4636

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Original Article

Relationship Between Staging FDG PET/CT Findings and Distribution of Metastatic Sites in Metastatic Breast Cancer

Metastatik Meme Kanserinde Evreleme FDG PET/BT Bulgularının Metastatik Bölge Dağılımı ile İlişkisi

Bedriye Büşra Demirel, Seda Gülbahar Ateş, Hüseyin Emre Tosun, Süleyman Aksu, Gülin Uçmak

Ankara Oncology Research and Training Hospital, Department of Nuclear Medicine, Ankara, Turkey

ABSTRACT

Introduction: We aimed to investigate the relationship between staging FGD PET/CT findings and metastasis distribution and histopathological features of primary tumor in patients with metastatic breast cancer at diagnosis time.

Materials and Methods: Eighty patients with breast cancer who underwent F-18 FDG PET/CT for staging were included. The patients with newly diagnosed metastatic disease were included. Age and histopathological features of the primary tumor were recorded. The distant metastases sites, the numbers of metastasis and metastatic axillary/non-axillary lymph nodes were reviewed from PET/CT. The maximum standardized uptake(SUVmax) values were measured.

Results: All patients(n:80,mean age 58.0±14.4) had invasive breast carcinoma. Age was significantly related to the presence of lung metastases(p=0.006, mean ages 54y vs 64y).Only liver metastasis had a significant relationship with primary tumor SUVmax values and tumor molecular profile. The patients with HR+/HER2- (7/60 patients, 11.7%) had relatively less liver metastasis than with the other subtypes (9/20patients, 45%). There were significant associations between SUVmax of axillary lymph node(p=0.02), primary tumor(p=0.001), liver metastasis(p=0.02) and tumor subtypes. The numbers of distant metastasis were related with the numbers of axillary lymph node metastasis(p=0.02) and the highest SUVmax of distant metastasis(p=0.001).

Discussion: Accurate detection of distant metastases in breast cancer at the time of diagnosis is of great importance in terms of treatment planning and prognosis of the disease. FDG PET/CT is a very reliable modality in determining distant metastasis and their distribution, and as a result of our study, we suggest that PET/CT findings can predict factors with prognostic importance.

Keywords: breast cancer, metastasis, 18f fluorodeoxyglucose positron-emission tomography, cancer staging

ÖZET

Giriş: Tanı anında metastatik meme kanserinde evreleme FDG PET/BT bulgularının metastaz dağılımları ve tümör histopatolojik özellikleri ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Meme kanseri tanısıyla bölümümüzde evreleme FDG PET/BT görüntülemesi yapılan 80 hasta çalışmaya dahil edildi. Daha önce tedavi almamış hastalar çalışmaya alındı. Yaş, primer tümörün histopatolojik özellikleri geriye dönük olarak kaydedildi. Uzak metastaz alanları, metastaz odak sayıları, aksilla-aksilla dışı metastatik lenf nodlarıi PET/BT görüntülerinden tarandı. Standart maksimum tutulum (SUVmaks) değerleri hesaplandı.

Bulgular: Tüm hastalar (n:80, ort. Yaş 58.0±14.4) invaziv meme kanseri tanılı idi. Hasta yaşı akciğer metastazı ile ilişkiliydi (p=0.006, ort yaşlar 54, 64). Uzak metastaz alanlarından sadece karaciğer metastazının primer tümör SUVmaks değeri ve tümör moleküler profili ile ilişkisi olduğu gösterildi. Karaciğer metastaz sıklığı HR+/HER2- olan hastalarda (7/60, %11.7) diğer tümör subtipleri (9/20, %45) olanlara göre daha düşüktü. Primer tümör (p=0.001), aksilla lenf nodu(p=0.02) ve karaciğer metastaz(p=0.02) SUVmaks değerleri ile tümör subtipleri arasında anlamlı ilişki gözlendi. Uzak

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metastaz alan sayısı ile metastatik aksiller lenf nodu sayısı (p=0.02) ve en yüksek uzak metastaz SUVmaks değeri (p=0.001) arasında anlamlı ilişki gözlendi.

Tartışma: Meme kanserinde tanı anında metastaz varlığının doğru olarak saptanmasının tedavi planı ve hastalığın seyri açısından önemi büyüktür. FDG PET/BT uzak metastazı ve hatta dağılımını belirlemede oldukça güvenilir bir modalite olup, çalışamamız sonunda FDG PET/BT bulgularının prognostik öneme sahip faktörleri öngörebileceğini düşünmekteyiz.

Anahtar kelimeler: meme kanseri, metastaz, f18 florodeoksiglukoz positron-emisyon tomografi, kanser evreleme

Introduction

Breast cancer is the most commonly diagnosed cancer accounting for 29% of all newly diagnosed cancers and the major cause for the death of women worldwide [1,2]. About 6% of breast cancer patients have metastatic disease at presentation [3]. The five-year relative survival rate of patients diagnosed with distant metastasis is significantly less than that of patients with early-stage disease at the time of diagnosis [4].The median five-year survival of metastatic breast cancer patients is only 33.8% [5].Despite advances in the current treatments for metastatic breast cancer that based on a strategy of systemic chemotherapy, endocrine or HER2-targeted therapy (depending on estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor type-2 [HER2]status), and palliative therapies, there are no specific standard-of-care therapeutic strategies indicated for patients with organ-specific metastases [6,7].

Precise evaluation of disease extent is quite essential for metastatic breast cancer patients before determining treatment strategy.18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography(PET/CT) has been widely used in various malignant diseases for initial stage, disease extent assessment, therapy response assessment, metastasis detection and prognosis prediction[8].FDG-PET/CT has shown high accuracy in detecting distant metastases and also, it allows on a single “whole-body” examination to assess for locoregional as well as distant metastases with a high positive predictive value [9,10].The maximum standardized uptake (SUVmax) value of 18F-FDG is useful for diagnosing high-grade malignancy and predicting the prognosis in breast cancer patients. It was reported that SUVmax and the HR status were useful for predicting malignancy grades and prognosis of patients with breast cancer [11].

We aimed to investigate whether pretreatment FDG PET/CT findings are related to metastatic sites distribution and histopathological features of the primary tumor, and whether SUVmax values may be associated with primary tumor molecular profile for breast cancer patients with metastatic disease at presentation.

Material and Methods

Eighty patients with breast cancer who underwent F-18 FDG PET/CT for staging in our department were included in the retrospective study. The inclusion criteria were newly diagnosed metastatic breast cancer that are not previously treated for metastatic disease and at least one visible lesion as metastatic with positive FDG uptake. Patients with prior excisional biopsy of breast, patients without distant metastasis and patients with second primary malign disease were excluded from the study.

This study adheres to the ethical principles of the Declaration of Helsinki and was approved by the ethics committee of our institution (2022-09/168).

Age and histopathological features of the primary tumor such as grade, hormone receptor (HR), human epidermal growth factor receptor type-2 (HER2) status and Ki-67 index were recorded from the institution patient information system, retrospectively.

PET/CT Acquisition and Imaging Analysis

Patients were imaged on an integrated PET/CT scanner (Siemens Biograph 6-True Point PET/CT systems). Patients were fasted for at least 6 hours prior to injection of 90µCi/kg 18F-FDG by using automatic infusion system (Intego PET Infusion System). The blood glucose levels were less than 150 mg/dl in all patients at the time of the FDG injection. Unenhanced CT images were acquired for attenuation correction from the vertex of the skull to distal thigh using 3 mm slice thickness and calculated effective mAs due to patient weight. The PET and CT images were reviewed on a workstation (Syngovia, Siemens Medical Solutions) in all standard planes along with maximum-intensity-projection images and were visually and quantitatively by two specialists experienced in interpreting PET/CT scans.

According to PET/CT findings; The sites of distant metastasis, the numbers of metastatic site, the numbers of metastatic axillary lymph node, the presence of retropectoral, internal mammarian and supraclavicular lymph nodes, T and N stages were recorded. The size of primary tumor and the size of enlarged axillary lymph node were measured. The maximum standardized uptake (SUVmax) values of primary tumor, axillary and non-axillary lymph nodes, each site of distant metastasis were measured by drawing of region of interest (ROI). To provide the most accurate measurement of SUV, voxels were created large enough to maintain tumor inside the boundaries.

Statistical Analysis

The statistical analysis was performed using commercial software (SPSS 21.0, IBM SPSS Statistics for Windows, Version 21.0. Armonk NY: IBM Corp.). The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using frequencies for the ordinal/nominal variables and medians, minimum, and maximum values for the non-normally distributed variables. Kruskal-Wallis tests were conducted to compare the parameters and tumor molecular profiles, and metastatic sites distribution. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. The Chi-square test or exact method, where appropriate, was used to compare the proportions in different groups. An overall 5% type-1 error level was used to infer statistical significance.

Results

Patient characteristics are listed in Table 1.

The mean age of patients was 58.0±14.4 with a range of 23-90 years. All patients had invasive carcinoma.

Axillary lymph node metastasis was observed in 75 (93.8%) patients, followed by retro-pectoral lymph node metastasis in 58 (72.5%) patients.

Bone metastasis was seen as the most common distant metastasis site with a rate of 83.8% (n:67), followed by mediastinal lymph node (43.8%), lung (33.8%), and liver metastasis (20.0%), respectively.

The numbers of distant metastasis were>10 in 45 (56.2%) patients, and 5-10 in 15 (18.8%) patients and <5 in 20 (25%) patients.

We did not observe significant difference between the presence of bone metastasis and primary tumor SUVmax (p=0.55) and axillary lymph node SUVmax (p=0.75), the number of metastatic axillary lymph node (p=0.1). There was significant association between bone metastasis and the presence of retropectoral lymph node metastasis (p=0.03).Fifty-two (89.7%) of 58 patients with retropectoral lymph node metastasis had bone metastases.

We found that the patients with liver metastasis had a higher primary tumor size (median 33.0 mm vs 52.5 mm p=0.04), primary tumor SUVmax (median 10.1 vs 15.8 p=0.012), and Ki-67 index (median 30% vs 40% p=0.004) (Table 2). There was statistically significant difference between the presence of liver metastasis and the status of PR (p<0.001), ER (p=0.003), and HER2

Table 1. Patient Characteristics

Characteristics			
Age, years (mean)			58.0±1.6
Primary tumor size (mm) (median)			34 (9-134)
Primary tumor	Grade (N, %)	1	4 (5.2%)
		2	42 (54.5%)
		3	31 (40.3%)
	ER (N, %)	Positive	70 (87.5%)
		Negative	10 (12.5%)
	PR (N, %)	Positive	64 (80%)
		Negative	16 (20%)
	HER2 (N, %)	Positive	15 (18.8%)
		Negative	65 (81.3%)
	HR+/HER2- (N, %)		60 (75%)
	HR+/HER2+ (N, %)		10 (12.5%)
	HR-/HER2+ (N, %)		5 (6.3%)
	HR-/HER2- (N, %)		5 (6.3%)
	Ki-67 (%) (median)		30 (5-90)
Number of axillary metastatic lymph nodes (median)			6 (1-20)
Size of axillary metastatic lymph nodes (mm) (median)			13 (2-45)
Number of local metastatic lymph nodes (N, %)	Axillar lymph node		75 (93.8%)
	Inter-pectoral lymph node		27 (33.8%)
	Retro-pectoral lymph node		58 (72.5%)
	Internal mammarian lymph node		14 (17.5%)
	Infra-clavicular lymph node		14 (17.5%)
	Supra-clavicular lymph node		19 (23.8%)
T Stage (N, %)	T1		6 (7.5%)
	T2		27 (33.8%)
	T3		4 (5%)
	T4		43 (53.8%)
N Stage (N, %)	N0		5 (6.3%)
	N1		40 (50%)
	N2		6 (7.5%)
	N3		29 (36.3%)
Number of distant metastases (N, %)	<5		20 (25%)
	5-10		15 (18.8%)
	>10		45 (56.2%)
Sites of distant metastases (N, %)	Contralateral axillar and/cervical lymph node node		20 (25%)
	Mediastinal lymph node		35 (43.8%)
	Abdominal lymph node		10 (12.5%)
	Lung		27 (33.8%)
	Liver		16 (20%)
	Bone		67 (83.8%)
	Others (soft tissue, adrenal, pleura)		6 (7.5%)

ER, estrogene receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor type-2.

Table 2. Association between primary tumor SUVmax, histopathological features of primary tumor and the presence of liver metastasis

	Liver metastasis		P value
	Negative	Positive	
Primary tumor size (mm)	39.7±21.7 33.0 (9.0-98.0)	57.2±33.1 52.5 (21.0-134.0)	p=0.04*
Primary tumor SUVmax	10.8±5.4 10.1 (1.09-33.3)	15.6±6.9 15.8 (5.6-27.2)	p=0.01*
Ki-67 index (%)	33.1±19.0 30.0 (5.0-90.0)	48.1±19.0 40.0 (25.0-80.0)	p=0.004*

*p value <0.05 was regarded as significant

(p=0.04) receptors and the presence of abdominal lymph node metastasis (p=0.003). The patients with HR+/HER2- (7 of 60 patients, 11.7%) had relatively less liver metastasis than with the other molecular profiles (9 of 20 patients, 45%). Also, it was demonstrated that there were significant associations between axillary lymph node SUVmax (p=0.02), primary tumor SUVmax (p=0.001), liver metastasis SUVmax (p=0.02) and tumor molecular profiles (Table 3). In the statistical sub-analysis, the primary tumor SUVmax of the patients with HR+/HER2- were significantly lower than patients with HR+/HER2+ (p=0.007), and patients with HR-/HER2+ or triple negative (p=0.006). Moreover, liver metastasis SUVmax values of patients with HR-/HER2+ or triple negative were higher than patients with HR+/HER2- (p=0.008).

As a result of the study, it was shown that the presence of lung metastases was significantly related to the patient age (p=0.006, mean ages 54.5 y vs 64.5 y). Moreover, there was a significant association between lung metastasis and mediastinal lymph node metastasis (p=0.02).

We observed that the numbers of distant metastasis related with the numbers of axillary lymph node metastasis (p=0.02) and the highest SUVmax of distant metastasis (p=0.001). In the statistical sub-analysis, in the patients with <5 distant metastases the highest SUVmax of distant metastasis was significantly lower than in the patients with >10 distant metastases (p<0.001, median 8.9 vs 13.9).

Discussion

FDGPET/CT has proven to be an effective imaging modality for detecting distant metastases in the initial staging of breast cancer [10,12]. In our study, we investigated the association of initial staging PET/CT findings and tumor histopathological features with metastatic sites distributions in newly diagnosed breast cancer patients with distant metastasis.

As stated in previous studies, PET/CT is more sensitive and more specific than conventional imaging modalities such as contrast-enhancement CT or bone scan to detect lytic or mixed bone metastases, or bone marrow involvement [13,14]; and by careful reading of the CT-scan data PET/CT can help to detect osteoblastic metastases because of variable FDG uptake [15]. Most recently, a National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) database analysis indicated that specifically, the incidence of bone metastasis is highest inluminal subtypes. Furthermore, the study

Table 3. Association between tumor molecular subtypes and SUVmax

		SUVmax	
Primary tumor	HR+/HER2-	(10.5±5.8) 9.6 (1.1-33.3)	p=0.001*
	HR+/HER2+	(14.5±3.4) 15.5 (10.0-20.2)	
	HER2+ or triple negative	16.6±6.5 15.8 (7.6-27.2)	
Axillary lymph node metastasis	HR+/HER2-	8.5±5.6 7.2 (1.3-29.0)	p=0.02*
	HR+/HER2+	13.0±5.2 12.7 (6.3-21.0)	
	HER2+ or triple negative	12.0±5.9 13.2 (4.5-22.1)	
Liver metastasis	HR+/HER2-	8.0±2.4 8.0 (4.4-12.3)	p=0.02*
	HR+/HER2+	11.3±1.1 11.9 (10.1-12.0)	
	HER2+ or triple negative	13.7±4.5 12.3 (9.5-21.0)	

HR, Hormone receptor; HER2, human epidermal growth factor receptor type-2
*p<0.05 was regarded as significant

revealed that all breast cancers regardless of subtype, were prone to metastasize to bone over other locations [16]. A recent study which examined HER2+ patient data deposited within the SEER database, uncovered that breast cancers which are HR+/HER2+ are significantly more likely to metastasize to the bone when compared to HR−/HER2+ disease, and that patients with HR−/HER2+ disease have a worse overall prognosis than those with HR+, HER2+ malignancy [16]. At the current study, bone metastasis was the most common distant metastasis detected by PET/CT. We did not find association with bone metastasis and findings derived from PET/CT and tumor histopathological features. We observed that bone metastasis is more common in those with only the presence of retropectoral lymph node metastasis.

We defined that lung metastasis as the third most common distant metastasis site is associated with the presence of second most common site mediastinal lymph node metastasis and advanced age. The mean age of patients without lung metastases was 54 years, while the mean age of patients with lung metastases was 64 years. To the results of studies, triple-negative and basal-like disease is more likely than other types of breast cancer to metastasize to the lungs [18], and patients with triple negative, especially basal-like type, primarily presented with lung metastasis. However, there was no difference in the total probability of lung metastasis across all subtypes [16]. We also did not find any relationship between lung metastasis and primary tumor histopathological features and PET/CT findings (such as primary tumor SUVmax, axillary lymph node SUVmax) in our study. The reason for this result may be due to the fact that the number of triple negative patients is less than the patients with HR+/HER2-.

Prognosis is poor in breast cancer with liver metastasis, with median survival time being 2 to 3 years [19]. In the analysis based on SEER database, it was reported that 1.4% of breast cancer patients assessed harbored liver metastasis at the time of diagnosis, and that the presence of liver metastasis significantly reduced patient overall survival compared to patients without liver metastasis (HR 1.94 [1.86, 2.02]) [20]. In the present study, liver metastasis was the fourth most common distant metastasis site and it is the only distant metastasis site found to be associated with PET/CT findings and tumor molecular profile. Liver metastasis was associated with hormone [progesterone (PR) and estrogen (ER)] status and HER2. Patients with HR+/HER2- had less liver metastasis than HR+/HER2+, HR-/HER2+ and triple negative subtypes. Patients with liver metastasis had higher primary tumor size, higher primary tumor SUVmax and higher Ki-67 index.

In a prospective study which was performed with luminal type breast cancer patients with newly diagnosed metastases, baseline (maximum one of SUVmax of metastatic lesions) SUVmax was found significantly related to the number of metastatic sites and presence of visceral metastasis but could not effectively differentiate patients with luminal A from luminal B subtype. Baseline SUVmax as determined on PET//CT was predictive of both progression-free survival and overall survival. In multivariate analysis, the baseline SUVmax, relapse-free interval, and number of metastatic sites were independent prognostic factors for progression-free survival. For overall survival, the significant predictors were only baseline SUVmax and relapse-free interval [21].

In a recent study, the authors suggested that SUVmax of metastatic site would be useful biomarker of molecular subtypes in patients with metastatic breast cancer while yet with unknown HR and HER2 status and SUVmax also an independent prognostic factor on overall survival [22]. In our study, we demonstrated the association with the presence of synchronal liver metastasis and high SUVmax of primary tumor, and also the relation with primary tumor subtypes and primary tumor SUVmax, axillary lymph node SUVmax, liver metastasis SUVmax values. It was observed that SUVmax values of primary tumor, axillary lymph node and also liver metastasis were significantly lower in HR+/HER2- subtype compared to other subtypes. Although there is no survival data in our study as a limitation, we think that defining on staging PET/CT that liver metastasis is more common in patients with high primary tumor SUVmax, regardless of tumor subtypes, may be an important prognostic indicator and may predict the tumor subtype in patients whose tumor histopathological characteristics are not clearly known.

It is known that high SUVmax values are an indicator of tumor aggressiveness in many malignancies including breast cancer and the number of metastatic axillary lymph nodes is predicting poor prognosis in breast cancer [11,23,24]. In compatibility with this knowledge, in this study, we defined that the numbers of distant metastasis is related with the number of metastatic axillary lymph nodes and the highest SUVmax of distant metastasis. The highest SUVmax of distant metastasis was significantly elevated in the patients with >10 distant metastasis sites than in patient with <5 distant metastasis sites. To our results, we predict that further prospective studies can support the thesis that higher distant metastasis SUVmax value may be a worse prognostic indicator.

Primary tumors of breast cancer have high structural and molecular heterogeneity and may present with minor components of differing tumor cell types, in example, cells with differing molecular profiles [25]. To the authors, when a cancer spreads to other tissues, the metastases can be of a different type to the primary cancer, and sometimes the metastases are even different to each other [26,27]. This may be due to heterogeneity in the primary tumor that comprises more than one cell clone [26]. This heterogeneity of metastatic breast cancer has stimulated the development of new treatment approaches such as estrogen- and HER2-receptor targeting therapies. Survival with metastatic breast cancer is improving along with the rapid development of new treatments [28]. In clinical practice, treatment planning of metastatic breast cancer is based on the histopathological molecular profile of the disease dominant cell type [29]. Despite all these treatment improvements, insufficient therapy response in some patients is maybe due to the cellular differences between primary tumor and metastases. Although treatment is based on primary tumor histopathological features, due to heterogeneity of tumor and also metastasis we believe that a more aggressive treatment approach can be initiated in patients with high SUVmax of distant metastasis especially with high SUVmax of liver metastasis in order to increase the treatment response. The limitation of our study is that it is a retrospective study without patient follow-up information. More prospective studies with larger series and with follow-up data may be required to support our suggestions.

In conclusion, accurate detection of distant metastases in breast cancer at the time of diagnosis is of great importance in terms of treatment planning and prognosis of the disease. FDG PET/CT is a very reliable modality due to superiority in determining distant metastasis and their distribution, and it can lead to alter treatment approach in newly diagnosed metastatic breast cancer patients. As a result of our study, we suggest that PET/CT findings can predict factors with prognostic importance in breast cancer patients with metastasis at time of diagnosis.

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Corresponding author e-mail: demirelbbusra@hotmail.com

Orcid ID:
Bedriye Büşra Demirel 0000-0002-6494-062X
Seda Gülbahar Ateş 0000-0003-0422-0863
Hüseyin Emre Tosun 0000-0002-0169-6316
Süleyman Aksu 0000-0002-7146-393X
Gülin Uçmak 0000-0002-0268-4747

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Original Article

Investigation of BRCA2 Gene K3326X Variant in Patients with Breast and Ovarian Cancer by Next-Generation Sequencing Technique

Yeni Nesil Dizileme Tekniği ile BRCA2 Geninde K3326X Varyantı Tespit Edilen Meme ve Over Kanseri Hastalarının İncelenmesi

Neslihan Düzkale[1], Cengiz Karaçin[2], Serap Yörübulut[3], Haktan Bağış Erdem[4],
Özlem Öz[5], Mustafa Altınbaş[6]

[1]Dışkapı Yıldırım Beyazit Training and Research Hospital, Department of Medical Genetics, Ankara, Türkiye
[2]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Oncology, Ankara, Türkiye
[3]Kırıkkale University Faculty of Science and Letters, Department of Statistics, Kirikkale, Türkiye
[4]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Genetics, Ankara, Türkiye
[5]Harran University Faculty of Medicine, Department of Medical Genetics, Sanliurfa, Türkiye
[6]Dışkapı Yıldırım Beyazit Training and Research Hospital, Department of Medical Oncology, Ankara, Türkiye

ABSTRACT

Introduction: The BRCA2 gene is a tumor suppressor gene involved in the repair of double-stranded DNA damage by homologous recombination. Until now, many cancer-related variants of the BRCA2 gene have been reported. There are conflicting publications in studies of the possible effect of the K3326X variant of this gene in cancer. This study investigates the K3326X BRCA2 gene variant and its role in the cancer pathogenesis of Turkish patients diagnosed with breast and ovarian cancer.

Materials and methods: In the study, 1957 patients with cancer diagnosis for BRCA1 and BRCA2 genetic analysis and 432 healthy individuals without a history of cancer were included. The K3326X variant was investigated using the next-generation sequencing method from the genomic DNA sample obtained from the individuals.

Results: K3326X variant was detected in 54 of 1957 (2.75%) cancer patients. For the non-cancerous group, 11 of 432 (2.5%) patients were carrying the K3326X variant. When both groups were compared in terms of K3326X variant carriage, a statistically significant result could not be obtained for the individuals (p=0.934).

Discussion: BRCA2 K3326X variant did not have a significant role in cancer etiopathogenesis. As a result, the variant whose clinical significance is not still been fully understood, was investigated for the first time for Turkish population. Our results suggest that the variant could be a benign variant.

Keywords: BRCA2, Breast cancer, Ovarian cancer, K3326X

ÖZET

Giriş: BRCA2 geni, homolog rekombinasyon ile çift sarmallı DNA hasarının onarımında yer alan bir tümör baskılayıcı gendir. Şimdiye kadar, BRCA2 geninin kanserle ilgili birçok varyantı rapor edilmiştir. Bu genin K3326X varyantının kanserdeki olası etkisine ilişkin çalışmalarda çelişkili yayınlar bulunmaktadır. Bu çalışmada meme ve yumurtalık kanseri tanısı almış Türk hastaların K3326X BRCA2 gen varyantı ve kanser patogenezindeki rolü araştırılmıştır.

Gereç ve yöntemler: Çalışmaya BRCA1 ve BRCA2 genetik analizi için kanser tanısı konan 1957 hasta ve kanser öyküsü olmayan 432 sağlıklı birey dahil edildi. Bireylerden elde edilen genomik DNA örneğinden yeni nesil dizileme yöntemi kullanılarak K3326X varyantı araştırıldı.

Bulgular: 1957 kanser hastasının 54'ünde (%2.75) K3326X varyantı tespit edildi. Kanserli olmayan grup için 432 hastanın 11'i (%2,5) K3326X varyantını taşıyordu. Her iki grup K3326X varyant

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taşıyıcılığı açısından karşılaştırıldığında, bireyler için istatistiksel olarak anlamlı bir sonuç elde edilemedi (p=0,934).
Tartışma: Çalışmamızda BRCA2 K3326X varyantının kanser etyopatogenezine anlamlı etkisi tespit edilememiştir. Sonuç olarak, klinik önemi henüz tam olarak anlaşılamayan bu varyant, ilk kez Türk popülasyonu için araştırılmıştır. Sonuçlarımız, varyantın benign bir varyant olabileceğini düşündürmektedir.

Anahtar kelimeler: BRCA2, Meme kanseri, Over kanseri, K3326X

Introduction

BRCA2 gene is one of the important tumor suppressor genes that play a role in maintaining genomic stability in breast cancer. This gene was determined as Fanconi anemia (FA), complementation group D1 (FANCD1), which helps to repair DNA double-strand breaks by its homologous recombination mechanism. This powerful tumor suppressor gene is responsible for the formation of the BRCA2 protein, which is actively involved with some other proteins in many processes such as cell cycle and DNA replication control, telomere hemostasis, and maintenance of genomic integrity [1]. BRCA2 is one of the genes responsible for hereditary breast and ovarian cancer syndrome (HBOC), and its germline disease-related variants cause susceptibility to certain types of cancer such as; breast, ovarian, and prostate in the individual, and show intermediate penetrance (20–50%) in terms of cancer [2]. Meta-analysis results have shown that in carriers of pathogenic variants of the BRCA2 gene, the mean cumulative risk increase in female sex up to age 70 is 38-84% for breast cancer and 16.5 -27% for ovarian cancer. Male BRCA2 pathogenic variant carriers were estimated to have breast cancer risk by 6.8%, and lifetime risk of prostate cancer is 20% up to the age of 70 [3].

In many studies in the literature, it has been reported that disease-related variant carriers of BRCA2 in both sexes also increase the risk of some other types of cancer such as pancreatic cancer, gastric cancer, and malignant melanoma [4]. According to the universal mutation database (UMD), 3454 different variants of the BRCA2 gene have been reported until today, the clinical significance of the majority of them is still unknown [5]. One of these variants, BRCA2 c.9976A>T (K3326X), results in a termination codon at the penultimate exon, predicted to cause a truncation of the last 91 amino acids. There are conflicting publications in the literature regarding the possible effect of this variant on cancer. In this study, the importance of BRCA2 K3326X variant, detected in patients diagnosed with Turkish breast and ovarian cancer, in the etiopathogenesis of the disease, was investigated.

Method

In this retrospective study between January 2018 and January 2020, the K3326X variant was investigated in patients with breast/ovarian cancer whose genetic analysis to detect a genomic change associated with hereditary cancer was performed in Diskapi Yildirim Beyazit Training and Research Hospital Department of Medical Genetics. All of 1957 patients included in the study were older than 18 years of age and were suspected of having BRCA1/2 genes in the etiopathogenesis of their existing cancers. General demographic and clinicopathological characteristics and gene analyses results of the patients were obtained retrospectively from the patient files.

This study was conducted by considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. A written informed consent was obtained from all participants prior to the study and this descriptive case series study was approved by the Harran University Local Ethics Committee (Approval number: HRU/21.08.14).

Peripheral blood samples were obtained from patients and Genomic DNA investigated by the next-generation sequencing method. Analysis of the BRCA1/2 genes was performed on the Illumina MiSeq system (Illumina Inc., San Diego, CA, USA) with the GeneRead QIAact BRCA Advanced DNA UMI Panel (Qiagen, Hilden, Germany). This panel provides 100% coverage for all exons and exon/intron junctions (up to 25 base pairs) of the BRCA1/2 genes. In addition, this panel made possible the analysis of SNVs and Indels. QIAGEN Clinical Insight (QCI™) software was used for the analysis of the data obtained. NM_007294.3 for the BRCA1 gene and NM_000059.3 for the BRCA2 gene, set as reference transcripts. In the study, the detected gene variants were classified based on the criteria in the American College of Medical Genetics and Genomics guideline.[6] In order to investigate the possible effect of the K3326X variant detected in patients with cancer on the etiopathogenesis of cancer, a control group of 432 people without cancer diagnosis were included. The control group consisted of patients with neurological, metabolic, cardiological, nephrological, ophthalmological and musculoskeletal disorders.

Sequence analysis of DNA sample obtained from the peripheral blood of these control group patients was performed using the Next Generation Sequencing (NGS) method using the Hereditary Disease Solution by Sophia Genetics (HDS_v3) on Nextseq Platform (Illumina, USA). HDS_v3 panel contained 569 genes. The raw data of the patients obtained by NGS were analyzed in a web-based bioinformatics program (https://www.sophiagenetics.com/home.html) and according to the reference genome (GRCh37 (h19)). In this group, 11 individuals were found with the K3326X variant in a heterozygous state. This group and the group with cancer patients were compared statistically in terms of the rate of having the K3326X variant.

The software "SPSS for Windows v23.0 (SPSS Inc., Chicago, IL, USA)" was used in the statistical evaluation of all results obtained. "Mean values (±) and standard deviation (SD), ±SD" were presented for scale data and percentage (%) for nominal variables Pearson chi square test. " were used in the study of the relations of the two qualitative variables. When the p-value used for the level of statistical significance was "0.05 or less", which was accepted as a meaningful result.

Results

In this study, K3326X variant was detected in 54 (2.75%) of 1957 cancer patients. Among 54 cancer patients, 52 (96.3%) carried this variant as heterozygous, two of them homozygous (3.7%). Of these 54 cancer cases, two (3.7%) were being followed up with a diagnosis of ovarian cancer and 52 (96.3%) with a diagnosis of breast cancer. The ages of diagnosis of two patients with ovarian cancer were 48 and 56, respectively, and the histopathological subtype of cancer in both patients was detected as serous adenocarcinoma. The mean age at diagnosis of patients with breast cancer was 46.26 ± 9.32 years. Histopathological subtypes of cancer of these patients were mostly determined as invasive ductal carcinoma (IDC) (78.8%) and invasive lobular carcinoma (ILC) (11.5%). Breast cancer subtypes of the other five patients were medullary (1.9%), mucinous (IMC) (1.9%), IDC/ILC (1.9%), IDC/ILC / IMC (1.9%), IDC/IMC (1.9%). It was determined that 77.1% of the tumors of breast cancer patients were estrogen receptor (ER) positive, 73.5% progesterone receptor (PR) positive, and 61.4% had c-erbB-2 (HER2/neu) amplification. 11.1% of these patients were triple negative (TNBC). The mean age at diagnosis of TNBC patients was 48.33 ± 7.11 and the mean age at diagnosis of non-TNBC patients was 46.00 ± 9.59, and no statistically significant difference was found in the mean age at diagnosis of both groups (p = 0.568). Genomic changes of NM_007294.3 (BRCA1): c.5035delC(p.Asn 1678_ Leu1679 insTer) and NM_000059. 3(BRCA2): c.5969delA(p.Asp1990Valfs) were detected in two of the carriers heterozygously. Two patients were diagnosed with HBOC. In the other 52 patients with the K3326X variant, a

Table 1. Relationship between K3326X carrier status and cancer

	The group of patients with cancer (n=1957)		The group of patients without cancer (n=432)		Statistical analysis* Probability
K3326X	n	%	n	%	
Carrier	54	2,8	11	2,5	p=0,934
Non-carrier	1903	97,2	421	97,5	

* Chi-Square Test: Analysis of Contingency Tables

causal variant was not found in BRCA1 and BRCA2 genes. There were 432 patients in the non-cancerous group, of which 11 carried the K3326X variant. The group which included cancer patients, and other group were compared in terms of the frequency of K3326X variant carriage, and no statistically significant difference was found between the groups (p = 0.934) (Table I).

Discussion

Amino acids subjected to truncation caused by the K3326X variant in the BRCA2 gene have functional importance due to the C-terminus region where they are located. In deletions of this region, it has been observed that BRCA2 colocalization does not occur with FANCD2 protein that plays a role in the repair of DNA damage, and regulation of the checkpoint of the cycle after injury [7, 8]. Various studies investigating the cellular and biochemical effects of this variant on cancer cell lines have been reported in the literature. As a result of some studies, it has been shown that the K3326X variant has no effect on BRCA2 function, while some studies have yielded opposite results [9-11]. In the study of, Morimatsu et al; the importance of this region in mouse cells with deletion of the region containing the last 188 amino acids at the COOH terminal of the BRCA2 gene was investigated. It has been observed that the cell cycle progression rate of these cells and wild type cells are similar. However, it has been observed that cells with deletion age faster than wild ones and are more radiosensitive. As a result, it has been shown that BRCA2 deletion can accelerate cell proliferation and induce cancer through defective DNA repair.[11] These studies on BRCA2 K3326X variant have conflicting results. Sergey et al., designed an assay using mouse embryonic stem cells and bacterial artificial chromosomes to investigate the functional significance of mutations in BRCA2. In their study, they showed that the K3326X genomic modification had no effect on BRCA2 gene functions and that it was a neutral variant [9]. In another study, Wu et 190 al. investigated the functional importance and cancer relationship of various VUSs in the BRCA2 gene, and found that the K3326X variant did not cause a change in BRCA2 function at a level that would cause cancer susceptibility. In their study using three independent assays evaluating homologous recombination, cell survival, and centrosome regulation, they showed that this variant did not affect the function of the BRCA2 gene in any of the assays [10].

Various researchers have investigated the importance of this variant in cancer susceptibility in many malignancies, especially breast and ovarian cancer, and different results have been obtained. The K3326X variant, which was first described by Mazoyer in the literature, was detected at approximately 1% in both the 462 control and 513 breast cancer patients has suggested to be a polymorphic variant [12]. While the same variant was detected in the control population by Wagner et al [13], it was found by Bergthorsson et al in a patient with breast cancer and was evaluated as a polymorphism [14]. As a result of a study conducted by Offit et al. with patients followed up for Fanconi Anemia (FA), they concluded that the BRCA2 K3326X allele could not be evaluated pathogenic [15]. Reid et al; claimed that this variant was not pathogenic, as it did not show segregation with the disease in some cancer families and its incidence in the population was the same as that of breast cancer patients [16].

In some studies, researchers claimed that the K3326X variant, considered a polymorphism, may be a risk factor. Martin et al found this variant at a higher prevalence in patients with familial pancreatic cancer than in healthy controls. The researchers have claimed that this variant has a detrimental effect and leads to an increased risk of pancreatic cancer [17]. Michailidou et al., in a meta-analysis based on GWAS (genome-wide association studies) they performed in 2013, suggested that this variant may cause a small increase in the risk of breast cancer in the individual [18]. In another GWAS conducted by the same researcher in 2015, breast cancer-related common variants located in 79 different loci were investigated and it was found that the K3326X variant could increase the risk of breast cancer by 1.26-fold [19]. In addition to these studies, we have suggested that this variant may cause an increase in the risk of some cancer types other than breast and ovarian cancer.

Howlett et al have argued that if the BRCA2 K3326X variant is compound heterozygous, it may cause FA [20]. Wang et al suggested that the BRCA2 K3326X sequence variant may have a direct effect on lung cancer development [21]. Akbari et al. detected the K3326X variant at a higher rate in 220 patients diagnosed with esophageal squamous cell carcinoma compared to healthy controls, and suggested that this variant may be a risk factor for the disease [22]. In a case diagnosed with bilateral breast cancer and melanoma, variants Q563X in the BRCA1 gene and K3326X in the BRCA2 gene were defined as double heterozygous by Palmirotta et al. It has been emphasized that the presence of a second variant with K3326X induces to have an earlier onset of the neoplasia to develop, and this variant has a strong penetrance modifier role [23]. One of the most comprehensive studies on this variant is the study by Meeks et al in 2016 involving approximately 77000 patients and 84000 controls diagnosed with breast, ovarian and prostate cancer. The researchers found a statistically significant relationship between the K3326X variant and all invasive breast cancer cases in this study, especially cases with triple-negative breast cancer and estrogen receptor negative breast cancer. In patients with lobular breast cancer, there was no significant relationship between this variant and the disease. In the same study, a strong association was observed between this variant and the disease in cases with serous ovarian cancer, but not in non-serous ovarian cancer patients. In addition, no significant association was reported between prostate cancer and K3326X. The results of this large study have suggested that the BRCA2 K3326X variant may play a role in the etiopathogenesis of breast and ovarian cancer [24,25]. In another study in the literature, the mean age at diagnosis of breast/ovarian cancer patients carrying the K3326X variant was reported as 43.2 ± 9.6 (range 28-67), and no significant difference was found in mean age at diagnosis with non-carrier patients (45.5 ± 10.6). In the same study, the researchers claimed that this variant has a different clinical significance from the BRCA2 truncating mutations located at the other 5'end, and its effect on breast and/or ovarian cancer development cannot be ignored. Therefore, they were suggested that the K3326X variant should be included in panels of all low penetration susceptibility SNPs [26].

In our study, the mean age at diagnosis of breast cancer patients was found to be 46.26 ± 9.32, similar to the literature. Although breast cancer is frequently diagnosed between the ages of 55-64 in developed countries, it has been reported that the breast cancer patient population in Turkey is between the ages of 45-49 mostly [27].

Breast cancer is a disease that can occur with the effect of many environmental, individual and genetic risk factors, and the age of onset may vary geographically and ethnically. The age at onset of breast cancer is significantly younger in patients with BRCA1/2 pathogenic variants compared to 250 patients without BRCA1/2 [28]. For this reason, National Comprehensive Cancer Network (NCCN) guidelines include the age factor, in the testing criteria for hereditary breast and ovarian cancer [29].

Up to 70% of breast cancers are hormone-dependent, and they are usually ER-positive. TNBC is detected only in 10-20% of invasive breast cancers [30]. In some studies, it has been shown that BRCA1-associated tumors, usually TNBC and BRCA2 mutation carriers, tend to develop mostly ER-positive breast cancer. In addition, in some publications, it was reported that patients with the same causal variant of BRCA1 were diagnosed with breast cancer at a younger age compared to others [31]. In our study, no significant difference was observed between the ages of cancer diagnosis between patients with variant carriers, those with TNBC, and non-TNBCs (p = 0.568).

In the Genome Aggregation Database (GnomAD), it is stated that the frequency of this variant allele is approximately 1 in 151. The allelic frequency of BRCA2 K3326X variant has been reported as 1 in 845 in the African population, 1 in 251 in Ashkenazi Jewish, 1 in 379 in Latinos, 1 in 100 in Europeans, and 1 in 144 in South Asian population [32]. In this study, we investigated the frequency of BRCA2 K3326X variant carriage in cancer and non-cancerous patients who were genetically analyzed in our own laboratory, and we have found that this variant does not play an important role in the etiopathogenesis of breast/ovarian cancer.

Conclusion

We have examined the role of the K3326X variant, which has been investigated many times in the literature and whose clinical significance is not fully understood in the etiopathogenesis of the breast and ovaries in the Turkish population. Our results have provided evidence in favor that BRCA2 K3326X variant may be a benign variant. In order to determine the possible mechanism of action of this variant in cancer, comprehensive studies are needed in different populations.

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Corresponding author e-mail: neslihanduzkale@gmail.com

Orcid ID:
Neslihan Düzkale 0000-0001-6122-5316
Cengiz Karaçin 0000-0002-7310-9328
Serap Yörübulut 0000-0003-0781-4405
Haktan Bağış Erdem 0000-0002-4391-1387
Özlem Öz 0000-0002-5533-6025
Mustafa Altınbaş 0000-0002-8024-2362

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Original Article

The Efficacy and Safety of CDK 4/6 Inhibitors Plus Endocrine Therapy with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2-Negative Metastatic Breast Cancer Patients

Hormon Reseptörü-Pozitif, İnsan Epidermal Büyüme Faktörü Reseptörü-2-Negatif Metastatik Meme Kanseri Hastalarında CDK 4/6 İnhibitörleri ile Endokrin Tedavisinin Etkinliği ve Güvenliği

Özgür Açıkgöz, Sabin Göktaş Aydın, Ahmet Bilici, Yasin Kutlu, Harun Muğlu, Ebru Karcı, Jamshid Hamdard, Elkhan Mammadov, Ömer Fatih Ölmez, Özcan Yıldız

Department of Medical Oncology, Istanbul Medipol University Hospital, Istanbul, Turkey

ABSTRACT

Introduction: Combining cyclin-dependent kinases 4/6 inhibitors with endocrine therapy are indicated as first or second-line treatment for hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.We aimed to investigate the efficacy and safety of adding CDKIs to endocrine therapy in patients whose tumors might have differing degrees of endocrine sensitivity.

Materials and methods: Totally, 99 patients with HR+, HER2-, ABC who received CDK4/6 inhibitor and hormonotherapy were included.Clinicopathological features of patients and progression-free survival (PFS) and overall survival (OS) outcomes were analyzed.The toxicity, combine drugs and the factors that may predict survival were also evaluated.

Results: This study with a median age of 51 years (range;31-80).The molecular subtypes of the patients were as follows; 51 patients (51.5%) were in the luminal A group, and 48 patients (48.5%) were in the luminal B HER2- group. Before CDK 4/6 inhibitor therapy, visceral and non-visceral metastasis were seen in 48 and 46 patients, respectively.At the median follow-up time of 13.7 months (range:3-48 months), the median OS was 38.5 months, the median PFS was 5.2 months. Univariate analysis demonstrated that the choice of CDK 4/6 agent was significantly associated with PFS. 6-months PFS rate with ribociclib was 42.3%, in palbociclib, it was 63.6%, in abemaciclib it was NA (not aplicable) (p=0.01).Univariate analysis revealed that the luminal type of tumor (p=0.002), advanced stage disease at the initial diagnosis ($p<0.001$), and presence of visceral metastasis (p=0.006) were significant factors for OS.

Discussion: In this study we demonstrated that there is a survival benefit for all three agents and there is a significant difference especially between first and second-line usage.

Keywords: breast neoplasm, cyclin-dependent kinases, survival, safety

ÖZET

Giriş: Sikline bağımlı kinaz 4/6 inhibitörlerinin endokrin terapi ile birleştirilmesi, hormon reseptörü pozitif, HER2 negatif ilerlemiş veya metastatik meme kanseri için birinci veya ikinci basamak tedavi olarak endikedir. Tümörleri farklı derecelerde endokrin duyarlılığa sahip olabilecek hastalarda endokrin tedaviye CDKI'lerin eklenmesinin etkinliğini ve güvenliğini araştırmayı amaçladık.

Gereç ve yöntemler: CDK4/6 inhibitörü ve hormon tedavisi alan HR+, HER2-, ABC'li toplam 99 hasta dahil edildi. Hastaların klinikopatolojik özellikleri ve progresyonsuz (PFS) ve genel sağkalım (OS) sonuçları analiz edildi. Toksisite, kombine ilaçlar ve sağkalımı öngörebilecek faktörler de değerlendirildi.

Bulgular: Ortanca yaşı 51 (31-80) olan bu çalışmada hastaların moleküler alt tipleri şöyleydi; 51 hasta (%51,5) lümen A grubunda, 48 hasta (%48,5) lüminal B HER2-grubunda.CDK 4/6 inhibitör tedavisi

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öncesi sırasıyla 48 ve 46 hastada visseral ve visseral olmayan metastaz görüldü. Medyan 13,7 aylık takip süresinde (dağılım:3-48 ay) , medyan OS 38,5 aydı, medyan PFS 5.2 aydı. Tek değişkenli analiz, CDK 4/6 ajanı seçiminin PFS ile önemli ölçüde ilişkili olduğunu gösterdi. Ribosiklib ile 6 aylık PFS oranı %42,3, palbosiklib ile %63,6, abemaciclib ile NA idi (p=0,01). Tek değişkenli analiz tümörün lüminal tipi (p=0,002), ilk tanı anındaki ileri evre hastalık (p<0,001) ve visseral metastaz varlığının (p=0,006) OS için anlamlı faktörler olduğunu ortaya koydu.

Tartışma: Bu çalışmada, her üç ajan için de sağkalım yararı olduğunu ve özellikle birinci ve ikinci basamak kullanım arasında anlamlı bir fark olduğunu gösterdik.

Anahtar kelimeler: meme kanseri, siklin bağımlı kinazlar, sağkalım, güvenlik

Introduction

Hormone receptor (HR) positive, human epidermal growth factor receptor-2 (HER2)-negative advanced breast cancer (ABC) constitutes approximately 70% of all metastatic breast cancer (MBC) [1,2]. Although effective results are obtained with various endocrine treatment options, resistance to treatment develops after a certain period of time and disease progression is observed. Many molecular resistance mechanisms have been defined, and in recent years, the effectiveness of various treatment combinations in overcoming resistance through these mechanisms has been proven and it has been demonstrated that they show significant survival advantages [1,2]. For this purpose, agents such as aromatase inhibitors (AI), gonadotropin-releasing hormone analogues and cyclin-dependent kinase (CDK) 4/6 inhibitors, the efficacy of which has been proven by recent studies, in patients with HR+, HER2-, ABC, according to menopausal status. It is used alone or in combination as the main components of treatment [1,3-6].

CDK4/6 inhibitors are rapidly transforming this treatment landscape for these patients. There are currently three CDK4/6 inhibitors that have been approved by the US Food and Drug Administration (FDA): palbociclib, ribociclib, and abemaciclib. All three CDK 4/6 inhibitors have been studied in combination with a non-steroidal aromatase inhibitor in the first-line setting. They have shown similar progression-free survival (PFS) contribution, but only ribociclib and abemaciclib provided overall survival (OS) benefit [4-6]. Moreover, they have also been studied in combination with the selective estrogen-receptor degrader fulvestrant in the first and second-line setting (7-9). PALOMA-3 with palbociclib, MONELESSA-3 with ribociclib, and MONARCH-2 with abemaciclib are all three conducted phase III studies. although there are some key study population differences between the phase III trials, these combination studies demonstrated significant improvement in PFS which is primary end point of them [7-9].

The aim of our study was to provide a real-life analysis of the efficacy and safety of CDK 4/6 inhibitors and combination patterns reported in HR+, HER2- for patients with ABC in the first and second-line setting.

Patients and Methods

In this study, a total of 99 patients with HR+, HER2-, ABC who were treated between 2018 and 2022 were retrospectively analyzed. Our study was conducted in accordance with the Declaration of Helsinki. The Local Ethics Committee of Istanbul Medipol University approved the study on January 2023 with E-10840098-772.02-269 decision number.

The data include demographic characteristics of patients, menopausal status, histo-pathology, stage of diagnosis, visceral metastasis, molecular characteristics of breast cancer, as well as adjuvant chemotherapy or endocrine therapy for operated patients. The CDK4/6 inhibitor used as treatment, combined drugs, side effects and toxicity secondary to treatment, objective response rate (ORR), OS and PFS were evaluated and recorded. Eastern Cooperative Oncology Group (ECOG) performance score (PS) was used for the detection of performance status [10].

The response to treatment of all three CDK4-6 was assessed by thorax CT scan and abdomino-pelvic CT scan. It was evaluated with the Response Evaluation Criteria in Tumors (RECIST) version 1.1. A complete response (CR) was defined as the disappearance of all measurable disease, a partial response (PR) represented a decrease of at least 30% of the tumor volume and stable disease (SD) defined small changes that do not meet above criteria without actual progression of disease. Progressive disease (PD) was defined as more than 20% increase in tumor volume or any new sites of disease.

Statistical analysis

IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp IBM Corp. Released 2011) was used for statistical analysis. Parameters were described with their median values. Response rates and toxicity profiles according to CDK 4-6 inhibitor treatment choice were compared using the chi-squared test and Fisher's exact test. OS was defined as the time from diagnosis to the date of the patient's death. PFS was defined as the time from the diagnosis of advanced-stage disease to progression. Survival analysis and curves were established using the Kaplan-Meier method and compared with the long-rank test. Univariate analyses were carried out to assess the significant prognostic factors on survival. These significant prognostic factors were further analyzed by multivariate Cox regression in order to determine independent prognostic factors on survival. The 95% confidence interval [CI] was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests, and p values less than or equal to 0.05 were accepted to be statistically significant.

Results

Fifty-three of the patients were premenopausal, and 46 were postmenopausal with a median age of 51 years (range; 31-80). Disease recurrence <12 months after adjuvant treatment occurred in 25 patients. Before CDK 4/6 inhibitor therapy, visceral and non-visceral metastasis were seen in 48 and 46 patients, respectively. 47.5% of patients were treated with CDK 4/6 inhibitor in the first-line setting, 49.5% were in the second-line, and 3% were in the later-line setting. The rate of treatment-related toxicity was 64.7%, and grade 3 or higher toxicity was 26.3%. The CDK 4/6 agent dose was adjusted in 33 patients concerning toxicity. No treatment-related death or discontinuation to CDK 4/6 inhibitor agent was observed. (Table 1)

CR was observed in 22 (34.9%) patients with ribociclib, 7 (23.3%) with palbociclib, and 1 (20%) with abemaciclib. ORR in ribociclib, palbociclib and abemaciclib groups were 66.7%, 63.3%, 100% respectively. The best response did not significantly differ between CDK 4/6 inhibitor agents. Any grade of toxicity and grade 3 or higher toxicity were detected in 47 (74.6%), 22 (73.3%), 5 (100%) and 20(31.7%), 15 (50.0%), 1(20%) in groups, respectively. There was no significant difference between toxicity rates. However, hematological toxicity rates were significantly higher in patients treated with palbociclib and ribociclib compared with abemaciclib (89.8% and 81.0% vs 20%) ($p<0.001$). The diarrhea rates were significantly higher in patients treated with abemaciclib ($p<0.001$). (Table 2)

At the median follow-up time of 13.7 months (range: 3-48 months), the median OS was 38.5 months and the median PFS was 5.2 months. Univariate analysis demonstrated that the choice of CDK 4/6 agent was significantly associated with PFS. 6-months PFS rate with ribociclib was 42.3%, in palbociclib, it was 63.6%, in abemaciclib, it was NA ($p=0.01$). (Figure 1) Age, disease recurrence <12 months after adjuvant therapy, menopausal status, ECOG PS, history of curative surgery, the treatment line of CDK 4/6 inhibitor therapy and luminal type of disease had no significant impact on PFS. In patients with non-visceral metastasis, the median PFS was 5.2 months with ribociclib; 12.2 months with palbociclib; not reached in abemaciclib ($p=0.06$). In patients with visceral metastasis,

Table 1. Patient and tumor characteristics

Characteristics	N=99	%
Age	median 51(range 31-80)	
Menopausal status		
Premenopausal	53	53.5
Postmenopausal	46	46.5
Advance Stage Disease at initial diagnosis	55	56.1
History of		
Curative surgery	54	54.5
Adjuvant endocrine treatment	52	52.5
Luminal A disease	51	51.5
Luminal B disease	48	48.5
Disease recurrence < 12 months after adjuvant treatment	25	25.3
Metastatic site		
Non-visceral metastasis	46	46.5
Visceral metastasis	48	48.5
CDK 4-6 inhibitor		
1st line	47	47.5
2nd line	49	49.5
≥ 3rd line	3	3
Choice of CDK 4-6 inhibitor		
Ribociclib	63	63.6
Palbociclib	30	30.3
Abemaciclib	6	6.1
Choice of antiestrogen treatment		
Letrozole	54	54.5
Fulvestrant	45	45.5
Any Grade of toxicity with CDK 4-6 inh.	64	64.7
Grade 3 or higher toxicity	26	26.3
Dose adjustment due to toxicity	33	(33.3)

*CDK: cyclin-dependent kinases

Table 2: Response rates and toxicity profile according to the choice of CDK 4-6 inhibitor treatment

Characteristics	Ribociclib N (%)	Palbociclib N(%)	Abemaciclib N(%)	P
RECIST 1.1				
Complete response	22 (34.9)	7 (23.3)	1 (20.0)	
Partially response	20 (31.7)	12 (40.0)	4 (80.0)	
Stable Disease	3 (4.8)	3 (10.0)	0	0.4
Progressive Disease	18 (28.6)	8 (26.7)	0	
ORR	42 (66.7)	19 (63.3)	5 (100)	0.2
Any grade of toxicity	47 (74.6)	22 (73.3)	5 (100)	0.4
Grade ≥3 toxicity	20 (31.7)	15 (50.0)	1 (20.0)	0.1
Toxicity				
Hematological toxicity	35 (89.8)	17 (81.0)	1 (20.0)	
Liver toxicity	2 (5.1)	1 (4.8)	0	<0.001*
Cardiac toxicity	1 (2.6)	0	1 (20.0)	
Diarrhea	0	1 (4.8)	3 (60.0)	
Other	1 (2.6)	2 (9.5)	0	
Toxicity-related dose adjustment	22 (50.0)	12 (57.1)	1 (20.0)	0.24

ORR: Objective response rate
* p values <0.05 was regarded statistically significant."

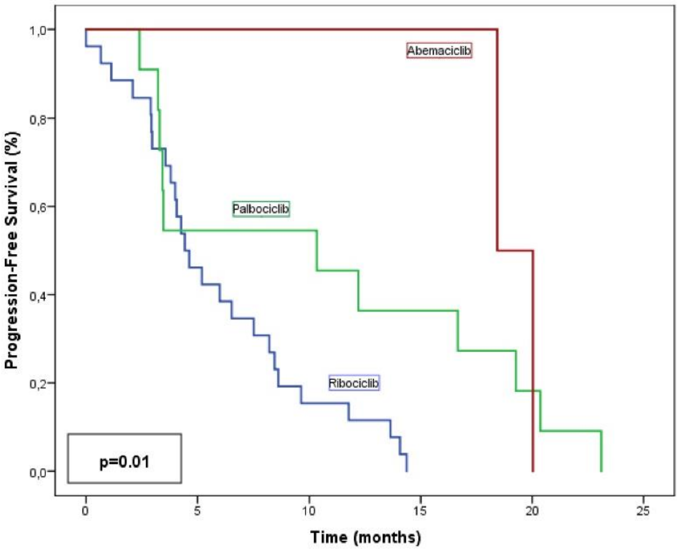

Figure 1. PFS according to CDK

Table 3. Prognostic factors for overall and progression-free survival

	PFS		OS	
Factor	Univariate analysis (p)	Multivariate analysis p (HR 95%CI)	Univariate analysis (p)	Multivariate analysis p (HR 95%CI)
Age (median 51 years)	0.9		0.8	
Performance status 0/1 vs. 2	0.2		0.3	
Menopausal status Premenopausal vs postmenopausal	0.2	0.7	0.1	
Advanced stage at initial diagnosis Yes vs. no	<0.001	0.9	0.5	0.7
Metastatic site (visceral vs. non-visceral)	0.006	0.03 (14.2; 1.25-16.6)	0.7	0.5
History of curative surgery Present vs. absent	0.9		0.7	0.5
Luminal A vs Luminal B	0.002	0.09	0.5	0.4
CDK 4-6 inhibitor in 1st line vs. later lines	0.002	0.05 (13,5; 1.02-17.7)	0.1	0.3
Choice of CDK 4-6 inhibitor agent	0.3	0.1	0.01	0.02 (0.2; 0.06-0.80)
Disease recurrence < 12 months after adjuvant treatment Yes vs. no	0.6	0.2	0.4	0.6

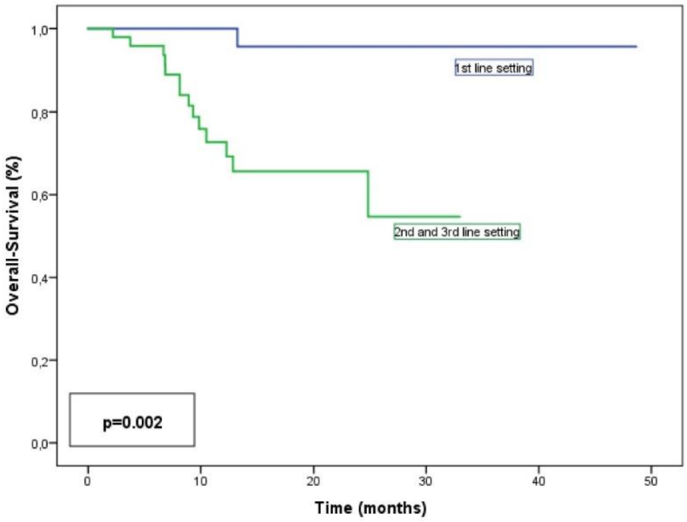

Figure 2. OS acording to CDK line

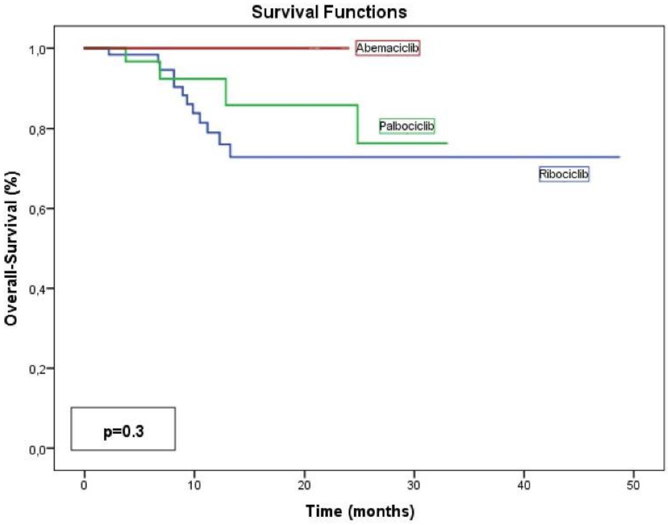

Figure 3. OS according to CDK

median PFS was 4.2 months with ribociclib, 3.3 months with palbociclib, and 18.4 months with abemaciclib (p=0.1). (Table 3)

The choice of CDK 4/6 inhibitor in first-line and later-line setting had a significant impact on PFS (p=0.002). 24-months OS rates were 95.7% vs 64.5%, respectively. (Figure 2)

Univariate analysis revealed that the luminal type of tumor (p=0.002), advanced stage disease at the initial diagnosis (p<0.001), and the presence of visceral metastasis (p=0.006) were significant factors for OS. There was no significant correlation between OS and CDK 4/6 inhibitor agent, disease recurrence <12 months after adjuvant therapy, menopausal status, EGOG PS and history of curative surgery. 24-months OS rate with ribociclib was 72.9%, in palbociclib it was 85.9%, in abemaciclib it was NR. (Figure 3)

Multivariate analysis was performed to identify independent prognostic factors for survival. It demonstrated that the choice of CDK 4/6 inhibitor agent was a significant independent prognostic factor for PFS (p=0.02, HR:0.2 95% CI 0.06-0.80). On the other hand, metastatic site of disease (visceral vs non-visceral) and the line of CDK 4/6 inhibitor therapy (first-line vs later-lines) were independent prognostic factors for OS (p=0.03, HR:14.295% CI; 1.25-16.6; p=0.05, HR:13.5 95% CI 1.02-17.7, respectively).

Discussion

The development of CDK 4/6 inhibitors such as abemaciclib, palbociclib and ribociclib has changed the therapeutic approach in patients with HR+, HER2- MBC. The combination of these drugs with aromatase inhibitor and fulvestrant has been approved by all health authorities. Although there is no clinical study comparing all three agents, there are meta-analyzes in the literature where they are indirectly compared [11]. In this study, we evaluated the efficacy differences between the addition of each of the three CDK 4/6 inhibitors to the endocrine treatment according to PFS, OS, toxicity, and visceral involvement in patients with HR+, HER2-, ABC, treated and followed-up in our center. CDK 4/6 inhibitors were used in combination with NSAI (anastrozole/letrozole) in the first-line and received FDA approval. Phase III studies were conducted for PALOMA-2 for palbociclib, MONELESSA-2 for ribociclib, and MONARCH-3 for abemaciclib, all showing PFS contribution [4-6]. In conclusion, the choice of CDK 4/6 inhibitor agents in HR+, HER2-, ABC depends on several factors such as patient preference, comorbidities and disease burden. Although there is a difference in survivals between agents, it is not sufficient to influence our choice of treatment. Despite our limitations, in this study we demonstrated that there is a survival benefit for all three agents and there is a significant difference especially between first and second-line usage. In the future, studies including real-life analysis are needed in which all three CDK 4/6 inhibitors with more patients are compared in both first- and second-line setting.

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Corresponding author e-mail: ozgur_acikgoz@yahoo.com

Orcid ID:
Özgür Açıkgöz 0000-0003-2715-4002
Sabin Göktaş Aydın 0000-0002-0077-6971
Ahmet Bilici 0000-0002-0443-6966
Yasin Kutlu 0000-0003-2184-634X
Harun Muglu 0000-0001-9584-0827
Ebru Karcı 0000-0001-8802-6376
Jamshid Hamdard 0000-0002-5823-1704
Elkhan Mammadov 0000-0002-3386-1427
Ömer Fatih Ölmez 0000-0001-7934-7039
Özcan Yıldız 0000-0003-2342-073X

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Original Article

Investigation of Clinical and Histopathological Features in Invasive Lobular Breast Cancers

Memede Lobüler Kanserlerin Klinik ve Histopatolojik Özelliklerinin İncelenmesi

Giray Gökhan Akgül[1], Ebru Esen[1], Müjdat Turan[2], Şevket Barış Morkavuk[1], Simay Akyüz[2],
Yasin Gülap[2], Pelin Seçken[3], Mehmet Ali Gülçelik[1]

[1]University of Health Sciences, Gülhane Research and Training Hospital,
Department of Surgical Oncology, Ankara
[2]University of Health Sciences, Gülhane Research and Training Hospital,
Department of General Surgery, Ankara
[3]University of Health Sciences, Gülhane Research and Training Hospital,
Department of Pathology, Ankara

ABSTRACT

Introduction: Analyze the clinical and immunohistopathological characteristics of lobular breast cancers, which are one of the more common subtypes of breast cancer among a wide range, which are important in terms of diagnosis, treatment, and monitoring.

Methods: Our study was conducted retrospectively. Patients diagnosed with and treated for breast cancer between January 2019 and August 2022 were included in the study after obtaining the necessary ethics committee permissions.

Results: Patients included in the study were between 28 and 81 years of age, and the median age was 53.04. While 26 (35.6%) of the patients were premenopausal, 47 (64.4%) were postmenopausal. The number of patients with unilateral characteristics was 71 (97.3%). The number of patients with bilateral ILC was 2 (2.7%). There were 38 patients with tumors (44.3%) in the upper outer quadrant (UOQ). Patients with tumors in the UOQ were followed by 11 patients with tumors in the lower outer quadrant (LOQ) and 8 patients in the central location (15.1% and 11%). Among the patients, 42 (57.5%) had undergone breast-conserving surgery and 31 (42%) had undergone mastectomy. Sentinel lymph node biopsy (SLNB) was performed in 51 (69.9%) of the patients.

Discussion and Conclusion: Although invasive lobular carcinoma has histopathologically bilateral and multicentric features, it is a disease that can be treated surgically not only with mastectomy but also with breast-conserving surgery, similar to invasive lobular carcinomas.

Keywords: Lobular carcinoma, immunohistopathological feature, mastectomy, breast conserving surgery

ÖZET

Giriş ve Amaç: Meme kanserinin en sık görülen alt tiplerinden biri olan lobüler meme kanserlerinin; tanı, tedavi ve takip açısından önem taşıyacak, klinik ve immünohistopatolojik özelliklerini analiz etmektir.

Yöntem ve Gereçler: Araştırma retrospektif olarak yapılmıştır. Ocak 2019 – Ağustos 2022 tarihleri arasında meme kanseri tanısı alan ve tedavisi yapılan hastalar çalışmaya dahil edilmiştir.

Bulgular: Çalışmaya dahil edilen hastaların yaşları 28-81 (yıl) aralığında olup medyan yaş 53,04'tü. Hastaların 26'sı (%35,6) premenapozal iken 47'si (%64,4) postmenapozaldır. Unilateral özellikteki hasta sayısı 71'dir (%97.3). Bilateral invaziv lobüler karsinomlu hasta sayısı 2'dir (%2,7). 38 hasta ile en sık üst dış kadran lokalizasyonunda tümörlü hasta bulunmaktadır (%44,3). Üst dış kadranı sırası 11 hasta alt dış kadran ve 8 hasta ile santral lokalizyon da tümörlü hastalar takip etmektedir (%15,1 ve %11). Hastaların 42'sine (%57,5) meme koruyucu cerrahi, 31'ine (%42)mastektomi uygulandı.

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Hastaların 51'ine (%69,9) sentinal lenf nodu biyopsisi uygulandı. Aksiller diseksiyon uygulanan hasta sayısı 22'dir (%30,1).

Tartışma ve Sonuç: İnvaziv lobüler karsinom histopatolojik olarak bilateral ve multisentrik özelliklere sahip olsa da cerrahi olarak invaziv lobüler karsinomlar ile benzer şekilde sadece mastektomi değil meme koruyucu cerrahiyle de tedavi edilebilen bir hastalıktır

Anahtar Kelimeler: Lobüler karsinom, immünohistopatolojik özellik, mastektomi, meme koruyucu cerrahi

Introduction

Breast cancer is the most common cancer among women. It is the second most important cause of death due to cancer in women after lung cancer [1]. The incidence of breast cancer has increased in recent decades, especially in the younger age group. Despite the increase in the incidence and improvements in the treatment modalities of breast cancer, which is diagnosed early due to the developments in all screening and imaging methods, the mortality rate of the disease continues to be important and frightening. Conventional treatment methods for breast cancer include surgery, chemotherapy, radiotherapy and hormone therapy. Despite the developments in all treatment methods, especially chemotherapy, the need for new treatment modalities has increased due to the inability to achieve the expected survival rates in some subgroups. Patients with breast cancer have different prognoses after diagnosis, and there are differences in the disease biology in terms of progression and metastasis pathways; therefore, breast cancer has been classified, and different morphological variants have been defined. The final tumor classification of the WHO published in 2019 includes many variants of breast cancer, including a total of 44 major types and minor subtypes [2]. Nevertheless, some concerns have been raised about the biological significance of the identified variants. Despite the fact that many variants have been defined, they have not yet led to any changes in the clinical diagnosis, treatment, or follow-up practices of the disease.

Breast cancer is a heterogeneous disease. Invasive breast cancers are currently classified as the no special type of ductal carcinoma and special subtypes. Breast cancers of special subtypes have specific definitions, while the no special type is a general definition that includes carcinomas other than special subtypes. Non-specific type invasive ductal carcinomas (IDC) constitute approximately 60-75% of all breast cancers. Special subtypes account for 20-25% of all tumors and metaplastic, lobular, tubular, papillary, and mucinous tumors represent the most common types within this group [3, 4]. The histopathological features should be revealed effectively and in detail, and pathologic indicators concerning good and bad prognoses should be reviewed to treat patients with breast cancer under optimal conditions [5, 6].

Invasive lobular carcinomas (ILC) account for 15% of all breast cancers in women [7]. It is the most common group among special subtypes and has clinical and histopathological differences in terms of disease biology, with varied treatment and surgical options for the disease [8, 9]. The IDC usually emerges as a separate, palpable mass. In contrast, ILC is not well palpable and is often diagnosed late with multifocal, multicentric, or contralateral involvement [10]. Therefore, ILC develops differently, requiring different treatment modalities and prognoses [11].

In this study, we aimed to analyze the clinical and immunohistopathological characteristics of lobular breast cancers, which are one of the more common subtypes of breast cancer among a wide range, which are important in terms of diagnosis, treatment, and monitoring.

Materials and Methods

Our study was conducted retrospectively in the General Surgery-Surgical Oncology Clinic of the Gulhane Training and Research

Hospital of the University of Health Sciences. Patients diagnosed with and treated for breast cancer between January 2019 and August 2022 were included in the study after obtaining the necessary ethics committee permissions (Approval number E-50687469-199-210072112, Date 24.02.2023).

The demographic characteristics of patients with invasive lobular carcinoma were primarily recorded as age and menopausal status. The size and location of the disease at the time of diagnosis, its laterality, and the quadrants where the tumor was located were evaluated. The stage of cancer was determined by combining the type of surgery performed on the patients, the number of patients who had undergone sentinel lymph node biopsy and axillary dissection, the total number of lymph nodes removed in sentinel lymph node biopsy and axillary dissection, T(tumor size), N (metastatic lymph node count), and M (distant metastasis) results.

Tumor grades, immunohistochemical distribution of hormone profiles, estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptors (HER2), and Ki67 proliferation index values of the patients were recorded. The status of surgical margins after surgery was examined. All data were recorded and analyzed using the SPSS 25.0 statistical software. Descriptive statistics were performed.

Results

Among the 728 patients diagnosed and treated in our clinic during the period specified, 73 had been diagnosed with ILC. Demographic, clinical, and pathological characteristics of patients with ILC were summarized in Table-1.

Patients included in the study were between 28 and 81 years of age, and the median age was 53.04. While 26 (35.6%) of the patients were premenopausal, 47 (64.4%) were postmenopausal. The number of patients with unilateral characteristics was 71 (97.3%). The number of patients with bilateral ILC was 2 (2.7%). There were 38 patients with tumors (44.3%) in the upper outer quadrant (UOQ). Patients with tumors in the UOQ were followed by 11 patients with tumors in the lower outer quadrant (LOQ) and 8 patients in the central location (15.1% and 11%). Among the patients, 42 (57.5%) had undergone breast-conserving surgery and 31 (42%) had undergone mastectomy. Sentinel lymph node biopsy (SLNB) was performed in 51 (69.9%) of the patients. The number of lymph nodes removed in a sentinel lymph node biopsy was in the range of two and 12. The mean number of lymph nodes excised was 3.82 ± 1.42. The number of patients who had undergone axillary dissection was 22 (30.1%). The number of lymph nodes removed in axillary dissection was between eight and 25. The mean number of lymph nodes dissected was 14.82 ± 4.79. The distribution range for the number of metastatic lymph nodes was 1-5. The mean number was 2.86 ± 1.39.

Histologically, 62 (84.9%) of the patients with ILC had isolated lobular carcinoma, while 11 (15.1%) had mixed lobular carcinoma. Among the patients, 73 (100%) had ER, 67 (91.8%) had positive PR, and all had negative HER2. Ki-67 was evaluated in 67 of the patients. The distribution range for Ki-67 was 1.0-80.0 and the median Ki-67 proliferation index value was 20%. The tumor sizes were observed below 2 cm (T1) in 47.9%, between 2 and 5cm (T2) in 42.5%, and above 5 cm (T3) in 9.6% of the patients. In pathological staging, the number of patients without lymph node metastasis (N0) was 46 (63%), the number of patients with lymph node metastasis between 1 and 3 (N1) was 17 (23.3%), and the number of patients with lymph node metastasis between 4 and 9 (N2) was 10 (13.7%). There were 3 patients with histological grade 1 (4.1%), 65 patients with histological grade 2 (89%), and five patients with histological grade 3 (6.8%).

In invasive breast carcinoma, the membranous positivity of E-cadherin immunohistochemically is typical in NST. Tumor cells with cytological loss of cohesion, generally forming scattered or "single file" aligned linear cords in a fibrous stroma or concentric placement around normal ducts,

Table 1. Demographic and Clinico-pathological Characteristics of the Patients

Age, years, mean ± SD, distribution	53,04±11,68 (28-81)
Side, n(%)	
Right	34 (%46,6)
Left	37 (%50,7)
Bilateral	2 (%2,7)
Tumor Localization, n(%)	
UOQ	38 (%44,3)
UİQ	6 (%55,6)
LOQ	11 (%15,1)
LİQ	5 (%6,8)
Central	8 (%11)
UOQ+Central	3 (%4,1)
Multifocal	2 (%2,7)
Tumor Type, n(%)	
İsolated Lobular Carcinoma	62 (%84,9)
Mixed Lobular Carcinoma	11 (%15,1)
Operation, n(%)	
Breast Conserving Surgery	42 (%57,5)
Mastectomy	31 (%42,5)
Axillary İnterference, n(%)	
SLNB	51 (%69,9)
ALND	22 (%30,1)
SLNB Lymph Node Dissection, number, mean±SD, distribution	3,82±1,42 (2-12)
ALND Lymph Node Dissection, number, mean±SD, distribution	14,82±4,79 (8-25)
ALND Lymph Node metastasis, number, mean±SD, distribution	2,86±1,39 (1-5)
N Stage, n(%)	
N0	46 (%63)
N1	17 (%23,3)
N2	10 (%13,7)
T Stage, n(%)	
T1	35 (%47,9)
T2	31 (%42,5)
T3	7 (%9,6)
Ki 67,percent, mean±SD, distribution	16,86±14,92 (1-70)
Nottingham grade, number, mean±SD, distribution	6,51±0,71 (5-8)
Histological grade, number, mean±SD, distribution	
Grade 1	3 (%4,1)
Grade 2	65 (%89)
Grade 3	5 (%6,8)
Menopause Status, n(%)	
Premenopausal	26 (%35,6)
Postmenopausal	47 (%64,4)

UOQ: Upper Outer Quadrant UİQ: Upper İnner Quadrant LOQ: Lower Outer Quadrant LİQ: Lower İnner Quadrant SLNB: Sentinel lymph node biopsy ALND: Axillary lymph node dissection

are common in ILC (Figure 1 and 2). The tumor consists of uniform cells with round or ovoid nuclei, narrow cytoplasm, low mitotic activity, and usually mild pleomorphism. Intracytoplasmic lumen formations or central mucoid inclusions can be observed in neoplastic cells. In ILC, the loss of E-cadherin protein causes a discohesive appearance in cells. Therefore, immunohistochemical loss of E-cadherin expression is observed in approximately 85% of cases. Nevertheless, E-cadherin expression can be observed in approximately 15% of the cases. In such cases, it is recommended to refer to the morphology (Figure 3).

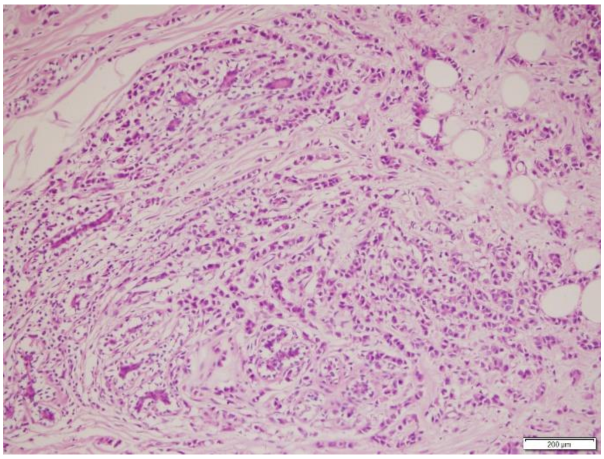

Figure 1. invasive lobular carcinoma, classical type

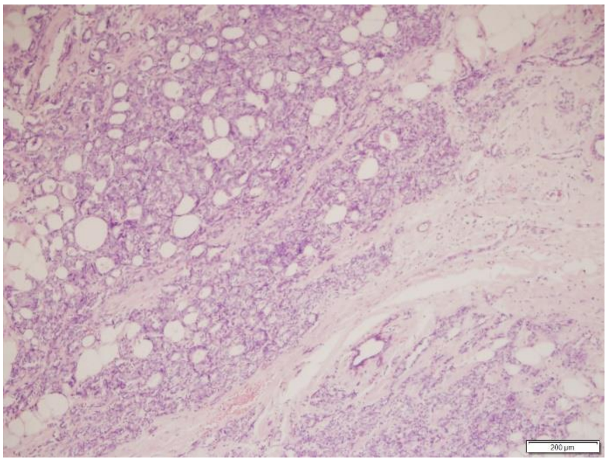

Figure 2. invasive breast carcinoma,NST

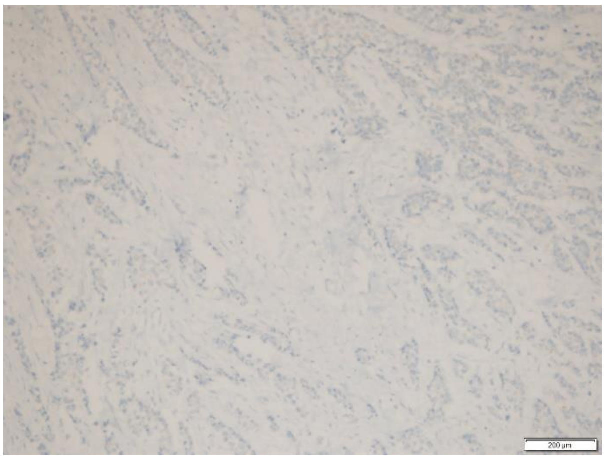

Figure 3: Immunohistochemical loss of e-cadherin in invasive lobular carcinoma

Discussion

Invasive lobular carcinoma is the second most common type of invasive breast cancer after IDC. ILC has unique clinical, pathological, and radiographic features, suggesting a separate clinical entity; however, it is treated with the same treatment paradigms as IDC. There is limited information about the specific treatment of ILC, including the response to standard therapy. In this study, 10.2% of the patients treated for breast cancer were determined to be of the ILC histological type, and this rate was found to be consistent with the literature.

Generally, women with ILC are slightly older compared to women with ICD at the time of diagnosis. The mean age of 53.04 was found to be compatible with the public health cancer statistics data of Turkey and the study conducted by Ozmen V (mean age 51.6) [12]. In the study of Enrico Orvieto et al., 36.8% of the patients were premenopausal and 63.2% were postmenopausal. Similar to the literature, 35.6% were premenopausal and 64.4% were postmenopausal in our study [13, 14].

ILC generally involves normal tissues without the intense desmoplastic response that usually accompanies IDC. The mass in the breast is not always a pronounced clinical feature, and sometimes it is difficult to distinguish it from the dense normal breast parenchyma. More than one-third is determined by asymmetric density, poorly defined opacity, and structural distortion in mammography. Microcalcifications screened on mammography are common symptoms of ductal carcinomas and are rarely detected in ILC. In ultrasonography (USG), the ILC appears as a heterogeneous hypoechoic mass with irregular margins and a posterior acoustic shadow. Some studies have demonstrated that USG has a higher sensitivity compared to mammography in detecting ILC and has the advantage of evaluating the presence of axillary lymph node metastasis. On the other hand, sensitivity in detecting ILC varies in the studies between 57-81% for mammography and 68-87% for

USG [15]. In the diagnosis of ILC and ICD, digital breast tomosynthesis and contrast-enhanced digital mammography are more sensitive compared to standard mammography [16, 17, 18]. USG is preferred as a complementary imaging method to standard mammography [19]. Greater multifocality and multicentricity in ILC is one of the factors causing the decrease in sensitivity in standard mammography compared to ICD. For all these reasons, breast magnetic resonance imaging (MRI) is recommended for all patients with ILC, unlike ICD. USG and breast MRI are recommended for both pre-operative evaluation and postoperative follow-up [19, 20].

Whether the prognosis in the ILC of the breast is different from the IDC is still a matter of discussion. Despite the controversy, factors affecting prognosis and treatment protocols are generally similar for both histological types. Nevertheless, ILC has been reported to be more frequently associated with factors such as advanced age at the time of diagnosis, large tumor size, multicentricity, multifocality, bilateralism, hormone receptor positivity, and HER2 negativity [11, 15].

ILC is almost always ER-positive and PR-positive. Excessive expression and/or amplification of HER2 is rare (3-13%). However, HER2 overexpression and/or amplification develop in a subset of pleomorphic ILCs. While 90-95% of patients with ILC have luminal A, this rate is 50% in ICD. Six studies analyzed ER, PR, and HER2 in detail and found that ICD was associated with triple-negative and HER2 with molecular subtypes, while ICL was associated with the luminal A subgroup. In this study, the ER receptor was positive in all patients, while 67 (91.8%) were PR positive and all were Cerb-B2 negative. These rates were consistent with the literature.

In terms of the location of the disease, ILC is more often multifocal. ILC is considered to have higher rates of bilateral disease; however, Pestalozzi et al. calculated similar rates of bilateral disease for IDC and ILC [22]. In our study, only two (2.7%) of the patients were bilateral.

Some studies in the literature observed the highest tumor size frequency in the T1 stage compared to the American Joint Committee on Cancer (AJCC) TNM staging criteria, while some studies observed it more frequently in the T2 stage. The percentage of T1 patients was found to be higher in our study, [21, 23, 24, 25, 26, 27]. In the literature, N0 has been demonstrated as the most common stage in terms of lymph node involvement, and it was followed by N1, N2, and N3, respectively. Pathological lymphatic stages were defined as pN0 by 50%, pN1 by 28%, pN2 by 15%, and pN3 by 7% [23, 24]. In our study, the lymph node status was pN0 by 63%, pN1 by 23.3%, and pN2 by 13.7%. In terms of distant metastasis, metastasis to bone and liver is frequent in both ILC and ICD. Unlike in ILC, the areas with greater metastatic spread are the abdominal cavity and the leptomeninges. Metastasis to the lung and central nervous system is less common compared to ICD [28, 29, 30, 31].

The general surgical treatment approach for breast cancer includes breast-conserving surgery (BCS) or mastectomy and systemic treatment depending on tumor characteristics such as tumor size, grade, lymph node, hormonal, and growth receptor status. One of the important points for the surgical treatment of invasive lobular cancer is the ability to choose the appropriate method among the BCS or mastectomy options due to the high rates of multifocality, multicentricity, and bilaterality. Fodor et al. investigated the long-term outcomes of BCS and mastectomy in ILC. For 15 years, they observed 235 patients with early-stage ILC who were prospectively treated with mastectomy or BCS. They found similar results for mastectomy and BCS in 15 years. Distant metastatic-free survival (62% vs. 70%; P= .2017), breast cancer-specific survival (62% vs. 70%; P= .1728), and regional recurrence-free survival (84% vs. 77%); P= .0644). Interestingly, better overall survival (OS) was observed in the BCS group compared to the mastectomy group (63% vs.

49% P= .0122) [32]. The fact that ILC is more multifocal and multicentric compared to IDC does not imply any contraindications for BCS. According to our patient data, 57.5% of the patients had undergone BCS, while 42.5% had undergone mastectomy. Our standard treatment policy is not based on the type of tumor histology. In their study, Biglia et al. concluded that a second surgery (conservative rejection/mastectomy) was necessary for a significantly higher percentage of patients with ILC to achieve negative limits. In general, there was no difference in the total number of mastectomies performed for ILC and IDC. In the multivariate analysis, only multifocality and tumor size (not histological type, grading, age, ER, and HER-2 status) were found to be independent predictors for re-excision or doubling the risk. In the first surgical approach, no significant difference was observed between the IDC and ILC groups, and BCS was the preferred treatment for most patients [21]. Recent studies have reported mastectomy rates ranging from 22% to 52% in patients with ILC (compared to 14% to 46% in patients with ICD). A positive surgical margin rate between 17% and 65% has been reported in patients with ILC undergoing BCS [33]. Similar to ICD, no improvement was observed in patients with ILC in terms of long-term survival after mastectomy compared to BCS with clear margins and the combination of radiotherapy [34].

Compared to the patients with ICD, patients with ILC appear to benefit less from neoadjuvant chemotherapy (NACT) administered to facilitate BCS and shrink the tumor. Low proliferation rate and high ER expression make ILC less susceptible to chemotherapy, as reflected by low pathological complete response (pCR) rates [36, 36, 37, 38]. There are conflicting results as to whether these low pCR rates can be attributed to differences in ER expression. Lips et al. found no difference between patients with ICD and ILC in response to chemotherapy [39]. Nevertheless, other studies have shown that the rate of pCR is still lower in patients with ILC when comparing ILC and ICD with a similar receptor status [40]. Although pCR appears to be a good prognostic factor for most breast cancers, this may not be the case for ILC, as low pCR rates do not lead to significantly worse outcomes in patients with ILC compared to ICD. Most patients with ILC still require mastectomy after NACT due to the lack of response to NACT [37, 41, 42].

Several studies have reported a higher nodal stage at diagnosis and a higher number of positive lymph nodes during surgery in ILC compared to ICD, leading to a higher rate of axillary lymph node dissection [22, 43, 44]. Since this is no longer seen in multivariate analysis, it can be attributed to larger tumor sizes and other misleading factors [45]. After sentinel lymph node biopsy, there is a 38% nodal positivity rate in node-negative patients, which highlights the challenges of clinical nodal evaluation in ILC [46].

Although ILC accounts for only a small percentage of invasive cancers, the pathogenesis, diagnosis, and clinical course of ILC have unique aspects and deserve special attention. Current analyses have demonstrated that the histology of ILC provides less benefit compared to NACT and tumors with ductal morphology. Despite the challenges in terms of radiological diagnosis and localization, BCS is preferred as an important treatment option for ILCs. While research on breast cancer is quite extensive, research on ILC is more limited. Further research is needed in this area, including providing an overview of ILC and treatment considerations that focus on early-stage treatment, particularly in the neoadjuvant setting.

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Corresponding author e-mail: girayakgul@hotmail.com

Orcid ID:
Gökhan Giray Akgül 0000-0002-0592-7521
Ebru Esen 0000-0003-3019-0872
Müjdat Turan 0000-0002-7854-4855
Sevket Barış Morkavuk 0000-0003-0441-0333
Simay Akyüz 0000-0002-0464-8934
Yasin Gülap 0000-0002-8983-3089
Pelin Seçken 0009-0007-5751-7907
Mehmet Ali Gülçelik 0000-0002-8967-7303

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Original Article

Comparison of Adjuvant Modified FOLFIRINOX with Other Adjuvant Chemotherapies in Resected Pancreatic Adenocarcinoma: Real-Life Data

Rezeke Edilmiş Pankreas Adenokarsinomda Adjuvan Modifiye FOLFİRİNOX'un Diğer Adjuvan Kemoterapilerle Karşılaştırılması: Gerçek Yaşam Verisi

Cihan Erol[1], Emre Hafızoğlu[2], Musa Barış Aykan[3], Deniz Can Güven[4], Bengü Dursun[5], Mutlu Hızal[2], Seda Kahraman[1], Didem Şener Dede[1], Muhammed Bülent Akıncı[1], Nuri Karadurmuş[3], Yüksel Ürün[5], Efnan Algın[2], Şuayib Yalçın[4], Bülent Yalçın[1], Mehmet Ali Nahit Şendur[1]

[1]Department of Medical Oncology, Faculty of Medicine,
Ankara Yıldırım Beyazıt University, Ankara, Turkey
[2]Department of Medical Oncology, Ankara City Hospital, Ankara, Turkey
[3]Department of Medical Oncology, Gülhane Education and Research Hospital, Ankara, Turkey
[4]Department of Medical Oncology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[5]Department of Medical Oncology, Faculty of Medicine, Ankara University, Ankara, Turkey

ABSTRACT

Background: Pancreatic cancer is among the cancers with the worst prognosis and therefore adjuvant treatment is very important for reducing mortality. The aim of this study is to compare the gold standard mFolfirinox regimen with other treatment regimens in the adjuvant treatment of pancreatic cancer in real-world practice.

Materials and methods: Patients who underwent pancreatic cancer resection and received at least one dose of adjuvant chemotherapy were included in the study as two groups, mFolfirinox and Others (at a ratio of 1:2). The primary endpoint was disease-free survival (DFS). Secondary endpoints were determined as overall survival (OS), predictive factors, and safety.

Results: Data of 166 patients were collected from five oncology centers. With a median follow-up of 30.3 months (24.6-35.9), the estimated median DFS was detected 17.9 months (95% CI, 10.3-25.6) in the mFolfirinox group and 12.5 months (95% CI, 9.7-15.3) in the others group (p = 0.088). The estimated median OS was 30.7 months (95% CI, 15.7-45.7) in the mFolfirinox group and 22 months (95% CI, 16-27.9) in the others group (p=0.464). Better ECOG performance status, tumor location outside the head and ampulla, stage 1 and 2B, not receiving adjuvant chemoradiotherapy (CRT), and perineural invasion provide a disease-free survival advantage in favor of mFolfirinox.

Conclusion: In the adjuvant treatment of resected pancreatic cancer, the mFolfirinox regimen provided a statistically insignificant, but clinically significant DFS and OS benefit.

Keywords: Pancreatic adenocarcinoma, modified folfirinox, adjuvant chemotherapy, real-life experience

ÖZET

Amaç: Pankreas kanseri prognozu en kötü olan kanserler arasında yer alır ve bu nedenle adjuvan tedavi mortaliteyi azaltmak için çok önemlidir. Bu çalışmanın amacı, gerçek dünya pratiğinde pankreas kanserinin adjuvan tedavisinde altın standart mFolfirinox rejimini diğer tedavi rejimleriyle karşılaştırmaktır.

Gereç ve yöntem: Pankreas kanseri rezeksiyonu yapılan ve en az bir doz adjuvan kemoterapi alan hastalar mFolfirinox ve Diğerleri (1:2 oranında) olmak üzere iki grup olarak çalışmaya alındı. Birincil sonlanım noktası hastalıksız sağkalımdı (DFS). İkincil sonlanım noktaları, genel sağkalım (OS), prediktif faktörler ve güvenlik olarak belirlendi.

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Bulgular: Beş onkoloji merkezinden 166 hastanın verileri toplandı. Ortanca 30,3 aylık (24,6-35,9) takipte, tahmini ortanca DFS, mFolfirinox grubunda 17,9 ay (%95 GA, 10,3-25,6) ve diğerleri grubunda 12,5 ay (%95 GA, 9,7-15,3) olarak saptandı (p = 0.088). Tahmini ortanca OS, mFolfirinox grubunda 30,7 ay (%95 GA, 15,7-45,7), diğerleri grubunda 22 aydı (%95 GA, 16-27,9) (p=0,464). Daha iyi ECOG performans durumu, tümörün baş ve ampulla dışında yerleşimi, evre 1 ve 2B, adjuvan kemoradyoterapi (CRT) almama ve perinöral invazyon, mFolfirinox lehine hastalıksız sağkalım avantajı sağladı.
Sonuç: Rezeke edilmiş pankreas kanserinin adjuvan tedavisinde, mFolfirinox rejimi istatistiksel olarak önemsiz, ancak klinik olarak anlamlı bir DFS ve OS faydası sağladı.

Anahtar Kelimeler: Pankreas adenokarsinomu, modifiye folfirinox, adjuvan kemoterapi, gerçek yaşam deneyimi

Introduction

Pancreatic cancer is among the cancers with the worst prognosis and has an important place among cancer-related deaths [1, 2]. Minimal survival improvement has been achieved in the last few decades [3]. Although surgery is the only option for cure, 5-year survival rates are around 10% with surgery alone [4]. This low survival rate with surgery alone has led to the development of adjuvant treatment strategies. Gemcitabine was used in adjuvant therapy, which is an important drug in the treatment of metastatic pancreatic cancer, and in the landmark study phase-III CONKO-1, there was a significant improvement in median disease-free survival (DFS) with gemcitabine compared to surgery alone (13.4 months vs. 6.7 months $p<0.001$) [4]. With this study, gemcitabine remained the standard adjuvant therapy for a long time. The ESPAC-4 trial compared gemcitabine with the combination of gemcitabine and capecitabine in adjuvant therapy following the CONKO-1 trial. Median survival was 28 months to 25.5 months, with moderate significance in favor of combination therapy ($p = 0.032$) [5]. In the APACT trial which was recently presented, the adjuvant gemcitabine plus nab-paclitaxel study did not meet the primary endpoint of independently assessed DFS gemcitabine [6]. The combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (Folfirinox regimen) resulted in longer overall survival than gemcitabine when administered as first-line treatment in patients with metastatic pancreatic cancer [7]. Based on these results, the PRODIGE-24 phase III study was planned to investigate the efficacy of gemcitabine versus Folfirinox regimen in adjuvant treatment after pancreatic cancer resection [8]. In this study, the median disease-free survival was 21.6 months versus 12.8 months in favor of Folfirinox regimen, and the median survival was 54.4 months versus 35 months, respectively. Despite its apparent clinical efficacy, the Folfirinox chemotherapy regimen had high treatment toxicity. In this study, the efficacy was achieved by considering more toxicity. Because of this toxicity, the dose of irinotecan was reduced by removing the bolus 5-Fluorouracil, and this modified form (mFolfirinox) has become the gold standard for adjuvant therapy in patients with good performance in pancreatic adenocarcinoma. However, in real-life, patients are not treated with strict rules as in clinical trials [9]. There are many patient groups that were not included in the clinical trial. Therefore, real-life data are important to shed light on the treatment of these patient groups and also to confirm the results of clinical trials. We planned this retrospective real-life study to compare the gold standard mFolfirinox regimen with other treatment regimens in adjuvant treatment of pancreatic cancer.

Materials and Methods

Patients and design

This is a multi-center retrospective study. Study data were obtained retrospectively from patient files and hospital records. Ethical approval was obtained from the ethics committee of Ankara City Hospital, with the date of 08.06.2022 and number E2-22-1969, before starting study. The study was conducted in accordance with ethical rules, the Declaration of Helsinki and good clinical practice guidelines.

In our study, patient data were obtained from five high-volume tertiary oncology centers. Patients who underwent pancreatic cancer resection and received at least one dose of adjuvant chemotherapy were included in the study. All patients aged 18 years and older were included in the study. Patients who underwent R2 resection were allowed. Patients who received chemoradiotherapy in adjuvant treatment were also included in the study. The study was based on the comparison of two groups of patients, mFolfirinox and Others. In the study, which included patients at a ratio of 1:2, respectively, clinical, pathological and treatment information of the patients were collected. Data that are thought to be predictive factors were examined. The neutrophil to lymphocyte ratio (NLR), one of these factors, was calculated by dividing the neutrophil count by the lymphocyte count in complete blood count. The primary endpoint was disease-free survival. Secondary endpoints were determined as overall survival (OS), predictive factors, and safety. DFS was defined as the time from initiation of adjuvant treatment to recurrence/metastasis or death. OS was defined as the time from initiation of adjuvant treatment to death. The data of the patients who were not followed up were not used in the DFS analysis. The survival results of these patients were confirmed by checking the system of the Ministry of Health. Adverse events have been evaluated according to The Common Terminology Criteria for Adverse Events (CTCAE).

Statistical analysis

Statistical analysis was carried out using the IBM SPSS Statistics Version 25 program (SPSS Inc., Chicago, IL, USA). A median value and minimum-maximum values were used to determine continuous variables. Categorical variables were shown as numbers and percentages. The difference between the ages of the patients was evaluated with independent t-test, the difference of histologies and surgical margins between groups with the Fisher's exact test, and the differences of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) values between groups were evaluated with the Mann-Whitney U test. Differences between groups other than these were evaluated with the chi-square test. Survival was univariately analyzed by the Kaplan–Meier method with a log-rank test for the comparison of subgroups.

Results

Data of 166 patients were collected from 5 oncology centers at a ratio of 1:2 (mFolfirinox vs. others). The vast majority of patients in the others group received gemcitabine-based therapies as adjuvant treatment. 35.7% of patients (n= 40) were treated with gemcitabine plus capecitabine, 57.1% of patients (n = 64) were treated with single-agent gemcitabine, and 7.2% of patients (n = 8) were treated with other chemotherapy regimens. The median age at diagnosis of the patients was 57 (18-71) years and 63 (34-75) years for the mFolfirinox group and others group, respectively. The ≥ 65-year-old rate was 13% in the mFolfirinox group and 45% in the others group. There was no difference between the baseline characteristics of the patients, except for age, ECOG (Eastern cooperative oncology group) performance scores, whether or not they received adjuvant chemoradiotherapy, and postoperative CEA/CA19-9 values (Table 1).

Treatment and efficacy

The median duration of treatment was median 23.6 weeks (2 to 39.3) in the mFolfirinox group and 18.9 weeks (1 to 43.4) in the others group (p = 0.06). With a median follow-up of 30.3 months (24.6-35.9), 70% (n = 98) of all patients had an event for DFS, and 57.2% (n = 95) of patients died. The estimated median DFS was detected 17.9 months (95% CI, 10.3-25.6) in the mFolfirinox group and 12.5 months (95% CI, 9.7-15.3) in the others group (p = 0.088) (Figure 1). The estimated median OS was 30.7 months (95% CI, 15.7-45.7) in the mFolfirinox group and 22 months (95% CI, 16-27.9) in the others group (p = 0.464) (Figure 1). DFS rates at 12 months were

Table 1. Patient characteristics

	mFolfirinox group n= 54		Others group N=112		p value
Median age – years, *(range)*	57 (18 – 71)		63 (34 – 75)		< 0.001
≥ 65 years – n, (%)	7	*(13)*	49	*(45)*	< 0.001
Histology – n, (%)					0.55
Adenocarcinoma	54	*(100)*	109	*(97)*	
Other			3	*(3)*	
Stage – n, (%)					0.10
1	8	*(15)*	19	*(17)*	
2A	4	*(7)*	18	*(16)*	
2B	23	*(43)*	56	*(50)*	
3	17	*(32)*	19	*(17)*	
Missing	2	*(4)*			
Surgical margins – n, (%)					0.25
R0	41	*(76)*	88	*(79)*	
R1	10	*(19)*	18	*(16)*	
R2	0	*(0)*	6	*(5)*	
Missing	3	*(6)*			
Tumor location – n, (%)					0.15
Head	33	*(61)*	73	*(65)*	
Ampulla	14	*(26)*	16	*(14)*	
Other	7	*(13)*	22	*(21)*	
Lymphovascular invasion – n, (%)	36	*(67)*	72	*(64)*	0.81
Perineural invasion – n, (%)	46	*(85)*	93	*(83)*	0.61
ECOG performance status – n, (%)					0.002
0 - 1	48	*(89)*	87	*(78)*	
2	4	*(7)*	25	*(22)*	
Missing	2	*(4)*			
Adjuvant CRT – n, (%)					0.001
No	38	*(70)*	49	*(44)*	
Yes	16	*(30)*	63	*(56)*	
Median CEA – ng/mL,*(range)*	1.6 *(0.5-35.6)*		2.5 *(0.2-1123)*		0.002
Median CA19-9 – U/mL, (*range)*	32 *(1-3303)*		65 *(0.6-42010)*		0.004

mFolfirinox = Modified folfirinox, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, CEA = Carcinoembryonic antigen, CA19-9 = Carbohydrate antigen 19-9.

51.9% (n=27) and 53.4% (n=47) in the mFolfirinox group and in the others group (p = 0.502), respectively.

Predictive factors

In subgroup analysis, better ECOG performance status, tumor location outside the head and ampulla, stage 1 and 2B, not receiving adjuvant chemoradiotherapy (CRT), and perineural invasion provide a disease-free survival advantage in favor of mFolfirinox. In addition, in moderately differentiated histology and the NLR value being higher than the median value, a significant p value was found at the border. No difference was found between the groups in other subgroups (Table 2). In the overall survival analysis of the subgroups, no difference was found between mFolfirinox and other treatments in any group (Table 3).

Safety

Dose delay and dose reduction requirements were 67.9% (n=36) and 58.5% (n=31) in the mFolfirinox group, compared with 15.4% (n=16) and 12.6% (n = 13) in the others group, respectively (dose delay p<0.001, dose reduction p<0.001). Adverse events of any degree were seen in 92.3% in the mFolfirinox group, while 39.4% in the others group (p<0.001). Grade 3 or 4 adverse events were reported 51.9% in the mFolfirinox group, compared with 10.6% in the others group (p<0.001). The most common grade 3-4 adverse events in the mFolfirinox group were neutropenia (38.5%) and anemia (15.4%),

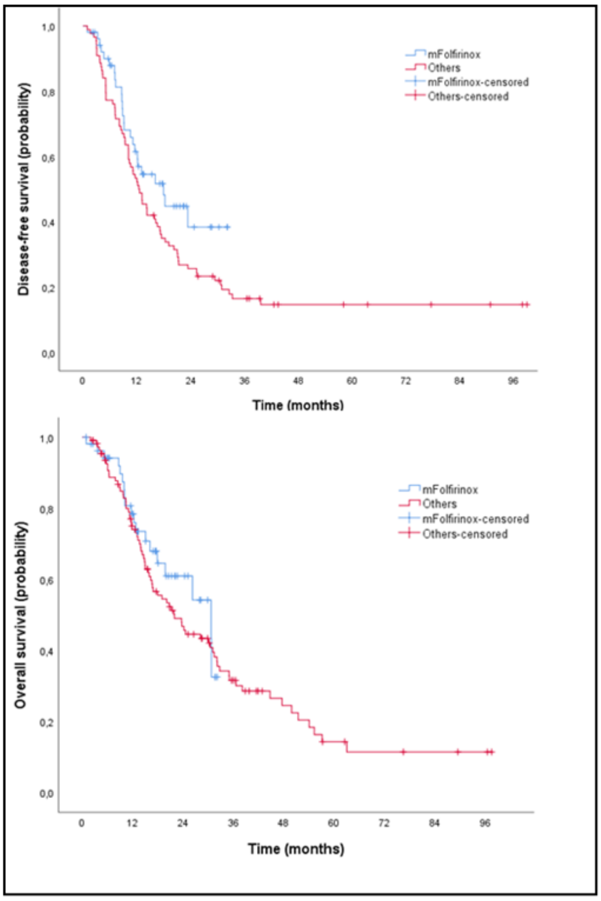

Figure 1. Kaplan-meier curves for disease-free survival and overall survival

compared with neutropenia (8.7%), anemia (3.8%) in the others group. One patient died in the mFolfirinox group due to treatment toxicity.

Discussion

The prognosis of pancreatic cancer is poor due to late diagnosis and aggressive nature [2, 10, 11]. Surgery remains the only curative treatment in resectable tumors. In addition to surgery, the cure rate is increased with adjuvant treatment [3, 12, 13]. Many clinical studies have investigated the results of various adjuvant treatment regimens [14]. However, the optimal multidisciplinary treatment strategy was controversial until the PRODIGE-24 phase 3 study, published in December 2018 [8]. Although there are still controversial points, with this study the mFolfirinox regimen became the gold standard in the adjuvant treatment of pancreatic cancer. In the adjuvant treatment of resected pancreatic cancer in our study, we found a clinically significant difference with the mFolfirinox regimen in median DFS of 17.9 months vs. 12.5 months compared to the other treatments, although it was not statistically significant. We also found a clinically significant, statistically insignificant difference in favor of mFolfirinox in overall survival of approximately 9 months. The mFolfirinox and other groups were generally well balanced, however, the mFolfirinox group consisted of younger, better ECOG performance scores, less treated with chemoradiotherapy, and had lower median CEA/CA 19-9 levels. The fact that fit patients, not exposed to chemoradiotherapy toxicity and had lower postoperative tumor markers were in the mFolfirinox group may have created a potential selection bias. However, the median DFS and OS of the others group were similar to both previous phase 3 studies [4, 5, 8, 15, 16] and real-life data [17, 18]. In the 5-year results of the recently published pivotal phase III trial, the median DFS was reported as 21.4 months and the median overall survival was 53.5 months [19]. In our study, DFS and especially OS in the mFolfirinox group were found to be lower than in the phase III pivotal clinical trial. Real-life data on the use of the mFolfirinox regimen in adjuvant treatment are very limited. In a small number of real-life studies, we see that very few patients use the mFolfirinox regimen for adjuvant treatment [20]. In our study, it is not surprising that the outcomes of patients in clinical practice were worse than in clinical trial. In the PRODIGE-24 study, all patients had an ECOG performance score of 0-1, while in our mFolfirinox group, 7% of patients had an ECOG performance score of 2. In addition, patients with stage III or CA 19-9 levels above 180 were excluded from the PRODIGE-24 study. In our study, 32% of the patients were stage III, and there were patients with high CA 19-9 levels. And we know that poor performance score, advanced stage and high CA 19-9 levels are associated with poor prognosis [17]. For this reasons, we can say that the differences in outcomes between mFolfirinox and the others group are not only

Table 2. Effects of treatments on disease-free survival in subgroup analysis

	mFolfirinox group	Others group	p value
	Median DFS (95% CI), months		
Age			
< 65 years	18.3 (6.7 to 29.8)	13.2 (11.2 to 15.1)	0.127
≥ 65 years	17.6 (13.2 to 22)	11.2 (6.5 to 15.7)	0.208
ECOG performance status			
0 - 1	23.3 (1 to 32.2)	13.2 (10.9 to 15.4)	0.023
2	8.6 (0.6 to 16.5)	11.6 (7.3 to 15.9)	0.908
Tumor grade			
Well differentiated	*	17.5 (4.6 to 30.3)	0.18
Moderately differentiated	18.3 (12 to 24.5)	12.4 (9.1 to 15.9)	0.055
Poorly differentiated	11.1 (8.1 to 14.2)	10.1 (6.7 to 13.4)	0.856
Tumor location			
Head	12.2 (5.1 to 19.1)	12.4 (8.9 to 15.9)	0.728
Ampulla	*	23.3 (7.5 to 39.2)	0.226
Other	*	10.3 (8.2 to 12.5)	0.045
Stage			
1	*	*	0.036
2A	*	14.2 (10.6 to 17.9)	0.512
2B	*	11.2 (8.6 to 13.8)	0.007
3	10.6 (7.7 to 13.5)	8.7 (3.5 to 13.9)	0.741
Surgical margins			
R0	23.3 (14.7 to 31.9)	14.2 (10.3 to 18.1)	0.082
R1	*	7.1 (2.8 to 11.4)	0.111
R2	N/A	8.1 (0.04 to 16.1)	N/A
Adjuvant CRT			
No	23.3 (*)	13.2 (9.1 to 17.3)	0.03
Yes	17.9 (8.9 to 26.9)	11.1 (7.8 to 14.5)	0.481
Body mass index			
< 18.5	11.5 (0.1 to 27.4)	12.2 (6.9 to 17.4)	0.364
18.5 - 24.9	16.1 (7.9 to 24.2)	13.1 (5.5 to 20.9)	0.545
≥ 25	*	12.6 (8.3 to 16.9)	0.104
Smoking history			
No	13.1 (6.6 to 19.4)	12 (5.9 to 18)	0.442
Yes	23.3 (7 to 39.6)	12.5 (10.3 to 14.6)	0.107
NLR			
≤ median	13.1 (5.4 to 20.7)	12 (7.9 to 16.1)	0.511
> median	23.3 (11.1 to 35.5)	13.2 (10.1 to 16.3)	0.06
Postoperative CA19-9 level			
≤ ULN**	*	17.1 (5.8 to 28.5)	0.129
> ULN	12.1 (6.6 to 17.8)	12.1 (9.8 to 14.5)	0.213
Lymphovascular invasion			
No	*	17.5 (5.6 to 29.4)	0.09
Yes	17.9 (6.5 to 29.3)	12 (9.7 to 14.3)	0.156
Perineural invasion			
No	*	39.6 (23.1 to 56.1)	0.466
Yes	17.9 (9 to 26.8)	11.6 (9.7 to 13.5)	0.016

*mFolfirinox = Modified folfirinox, DFS = Disease-free survival, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, NLR = Neutrophil to lymphocyte ratio, CA19-9 = Carbohydrate antigen 19-9, ULN = Upper limits of normal. * Statistical value could not be calculated due to the small number of patients. **The ULN is 30 U/mL.*

Table 3. Effects of treatments on overall survival in subgroup analysis

	mFolfirinox group	Others group	p value
	Median OS (95% CI), months		
Age			
< 65 years	30.7 (15.5 to 45.9)	20.7 (13 to 28.5)	0.28
≥ 65 years	*	23.7 (10.8 to 36.6)	0.627
ECOG performance status			
0 - 1	30.7 (16.6 to 44.7)	24.2 (14.3 to 34.1)	0.6
2	10.1 (*)	16.3 (10.8 to 21.6)	0.916
Tumor grade			
Well differentiated	*	44.7 (12.1 to 77.4)	0.494
Moderately differentiated	30.7 (11.9 to 49.5)	21.2 (15.9 to 26.5)	0.235
Poorly differentiated	12.3 (8.7 to 15.9)	14 (8.4 to 19.6)	0.284
Tumor location			
Head	26.3 (11 to 41.5)	20.7 (15.4 to 26.1)	0.506
Ampulla	*	36.6 (14.2 to 59)	0.249
Other	*	23.7 (12.4 to 34.9)	0.216
Stage			
1	*	32.1 (0.6 to 63.6)	0.252
2A	*	*	0.424
2B	30.7 (24.2 to 37.2)	21.2 (13.9 to 28.5)	0.288
3	15.1 (5.8 to 24.3)	12.8 (9.9 to 15.8)	0.936
Surgical margins			
R0	30.8 (18.2 to 43.4)	24.6 (15.1 to 34.1)	0.508
R1	*	23.7 (9.6 to 37.4)	0.847
R2	N/A	9.1 (2.7 to 15.3)	N/A
Adjuvant CRT			
No	30.7 (22.7 to 38.6)	31.1 (26.1 to 36.1)	0.57
Yes	30.1 (17.1 to 44.5)	16.6 (11.7 to 21.6)	0.317
Body mass index			
< 18.5	15.1 (*)	11.7 (*)	0.535
18.5 - 24.9	30.7 (14.4 to 47)	22 (13.3 to 30.6)	0.754
≥ 25	*	31.1 (12.5 to 49.6)	0.394
Smoking history			
No	*	20.1 (11.4 to 28.8)	0.335
Yes	30.7 (19.2 to 42.2)	30.1 (16.8 to 43.4)	0.918
NLR			
≤ median	30.8 (14.7 to 46.8)	23.7 (8.6 to 38.8)	0.929
> median	30.7 (15.1 to 46.2)	16.7 (10.7 to 22.7)	0.154
Postoperative CA19-9 level			
≤ ULN**	30.7 (*)	30.5 (16.3 to 44.7)	0.592
> ULN	26.3 (8.7 to 43.8)	16.7 (10.8 to 22.6)	0.622
Lymphovascular invasion			
No	*	30.1 (21.1 to 39.1)	0.517
Yes	30.7 (10.1 to 51.3)	19 (12.6 to 25.4)	0.626
Perineural invasion			
No	*	63 (35 to 91)	0.937
Yes	30.7 (16.3 to 45.1)	19 (12.4 to 25.6)	0.331

*mFolfirinox = Modified folfirinox, OS = Overall survival, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, NLR = Neutrophil to lymphocyte ratio, CA19-9 = Carbohydrate antigen 19-9, ULN = Upper limits of normal. * Statistical value could not be calculated due to the small number of patients. **The ULN is 30 U/mL.*

due to selection bias, but are the effectiveness of mFolfirinox.

In subgroup analysis, it is predicted DFS advantage with mFolfirinox in the patients with ECOG performance status 0-1, tumors located in the pancreatic body and tail, stage I and IIB tumors, the patients who do not receive adjuvant chemoradiotherapy and tumors with perineural invasion. The efficacy of mFolfirinox in patients with an ECOG performance score of 2 compared to other regimens is not clear, as all patients in the PRODIGE-24 study were patients with an ECOG performance score of 0-1 [8]. Despite the small number of patients, we did not find any difference between treatment regimens in patients with an ECOG performance score of 2 in our study. These results suggest that this regimen should be considered in fit patients.

Chemotherapy is generally avoided in elderly patients [21]. However, elderly patients have been shown to benefit similarly from chemotherapy [22]. While patients ≥ 65 years of age benefited from mFolfirinox treatment in the pivotal trial, we found no difference between treatment regimens in patients ≥ 65 years of age in our real-life study. Based on these results, it may be a good option to consider less toxic regimens for elderly patients.

The use of adjuvant CRT, in the era of mFolfirinox, is controversial. It can generally be used in patients with positive surgical margins or lymph nodes. In our study, the outcomes of patients who did not receive adjuvant CRT were numerically higher than the patients who received it. This is the result of increasing treatment toxicity and adversely affecting survival. Also, there is no difference between the treatment regimens.

While we expect mFolfirinox, which is considered to be a more effective treatment, to have better survival in patients with poor prognostic factors (poorly differentiated, stage III, R1 resection, high NLR, postoperative high CA19-9 level, and lymphovascular invasion), unlike the pivotal study, no difference was found with other treatment regimens in our study. This may be due to the different patient population and treatment regimens.

As expected, the safety profile of the mFolfirinox regimen was less favorable than other adjuvant treatments. We found that we obtained this non-significant difference in survival outcomes in favor of mFolfirinox with higher treatment-related adverse events. In the PRODIGE-24 study, grade 3-4 adverse events were seen in 75.9% of patients, this rate was 51.9% in our study. Adverse events were lower than in the clinical trial, but slightly higher than in real-life data. In a retrospective study reported from China, dose reduction with mFolfirinox was found to be 41.2%, while in our study it was found to be 67.9% [23]. Toxicity is not only an important problem in the acute period. It may shorten the duration of treatment, leading to early discontinuation of adjuvant therapy. This may adversely affect long-term survival. In a study in which most patients received gemcitabine-based adjuvant treatment, median recurrence-free survival was found to be 22 months in patients who completed adjuvant therapy, and 9 months in patients whose therapy was discontinued early [20]. In our study, almost all patients (92.3%) had adverse events at any grade with mFolfirinox. Most of these were manageable adverse events. However, we would like to emphasize that 2% of patients (one patient) died of treatment-related adverse event in the mFolfirinox group. Therefore, patient selection for the mFolfirinox regimen in the adjuvant treatment of pancreatic cancer is very important. Treatment may be beneficial in patients who can tolerate treatment and experience minimal treatment toxicity.

We would like to highlight a few limitations of our study. The most important limitation is the retrospective nature of our study, and its natural consequences. The uneven distribution between groups and the potential selection bias were the result of this limitation. Second, adverse events may have been underestimated because the data were obtained from hospital records and patient files. Third, there was no granulocyte colonystimulating factor usage information available. Fourth, the treatment information at the time of recurrence of the patients was unknown. And finally, genetic factors (microsatellite instability and Breast cancer gene 1-2) that may affect the prognosis of patients were not known.

In conclusion, in the adjuvant treatment of resected pancreatic cancer, the mFolfirinox regimen provided a statistically insignificant, but clinically significant DFS and OS benefit. The mFolfirinox regimen was found to be more toxic than other adjuvant regimens, and mFolfirinox regimen should be considered in fit patients.

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Corresponding author e-mail: chan_erol@hotmail.com

Orcid ID:
Cihan Erol 0000-0003-3155-8798
Emre Hafızoğlu 0000-0001-6291-851X
Musa Barış Aykan 0000-0001-7538-9119
Deniz Can Güven 0000-0002-6924-9467
Bengü Dursun 0000-0002-1433-8446
Mutlu Hızal 0000-0001-5147-4431
Seda Kahraman 0000-0002-5328-6554
Didem Şener Dede 0000-0002-9756-5942
Muhammed Bülent Akıncı 0000-0001-7575-9925
Nuri Karadurmuş 0000-0003-3291-8062
Yüksel Ürün 0000-0002-9152-9887
Efnan Algın 0000-0002-8917-9267
Şuayib Yalçın 0000-0001-7850-6798
Bülent Yalçın 0000-0002-4431-8948
Mehmet Ali Nahit Şendur 0000-0001-7021-6139

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Case Report

Granulosa Cell Tumor of the Ovary in a Patient with Adjuvant Tamoxifen Use for Breast Cancer: An Extremely Rare Case Report

Meme Kanseri Tedavisinde Adjuvan Tamoksifen Kullanan Bir Hastada Ovaryan Granüloza Hücreli Tümör: Oldukça Nadir Görülen Bir Vaka

Hatice Tülüce Atlım[1], Yusuf İlhan[2], Anıl Alpsoy[3], Sema Sezgin Göksu[4], Gülgün Erdoğan[3],
Ali Murat Tatlı[4], Hasan Şenol Coşkun[5]

[1]Department of Internal Medicine, Akdeniz University, Antalya, Turkey
[2]Department of Medical Oncology, Tatvan State Hospital, Bitlis, Turkey
[3]Department of Pathology, Akdeniz University, Antalya
[4]Department of Medical Oncology, Akdeniz University, Antalya, Turkey
[5]Akdeniz Sağlık Vakfı Yaşam Hospital, Department of Medical Oncology, Antalya

ABSTRACT

Tamoxifen use can cause gynecologic tumors like uterine sarcomas. However, the relationship between tamoxifen use and adult granulosa cell tumors (AGCTs) is uncertain. Here we report a case of AGCT in a 57-year old patient with antecedent tamoxifen use for hormone-receptor positive breast cancer. After 22 months of tamoxifen use, the patient had diagnosed with a stage 1a granulosa tumor. To our knowledge, there are only four cases previously published about the relationship between the development of granulosa cell tumors and the use of tamoxifen. It is very difficult to say that there is a certain relationship between tamoxifen use and AGCT because of the rarity of the condition.

Keywords: Breast cancer, granulosa cell tumor, tamoxifen

ÖZET

Tamoksifen kullanımı uterin sarkomlar gibi jinekolojik tümörlere yol açabilir. Ancak tamoksifen kullanımının yetişkin granüloza hücreli tümör (AGCT) etiyolojisindeki yeri kesin değildir. Biz burada, hormon pozitif meme kanseri nedeniyle adjuvan tamoksifen tedavisi almakta olan 57 yaşındaki bir hastada gelişmiş olan AGCT vakasını bildirmek istiyoruz. Hastamız evre 1a AGCT tanısı aldığında 22 aydır tamoksifen kullanmaktaydı. Bildiğimiz kadarıyla, tamoksifen kullanımı altında gelişen AGCT' ler ile ilgili daha önce yayımlanmış 4 adet vaka bildirimi mevcuttur. Bu tip vakalarının çok nadir olması nedeniyle AGCT gelişimini tamoksifen kullanımı ile ilişkilendirmenin oldukça zor olduğunu söylemek isteriz.

Anahtar kelimeler: Meme kanseri, granüloza hücreli tümör, tamoksifen

Introduction

Breast cancer is the most common cancer type among women worldwide. Selective estrogen receptor modulators are widely used for treating hormone receptor-positive breast cancer. One of their mechanisms of action is that; it competes with estradiol for estrogen receptors. However, their pharmacodynamics are complex. They can also act as a partial estrogen agonist in certain tissues. So,

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sometimes detrimental effects can be developed with these drugs. For example, tamoxifen is known as an important risk factor for endometrial cancer [1].

Ovarian sex cord-stromal tumors (SCSTs) are a group of tumors that originates from the sex cord-stromal cells (Leydig, Sertoli and, Granulosa cells). They are less common when compared with epithelial and germinal origin ovarian tumors. According to Surveillance, Epidemiology and End Results United States national database, the incidence of SCSTs was 0.20 per 100,000 women [2]. Recent studies suggest that sex cord-stromal tumors might be associated with certain genetic syndromes like Peutz-Jeghers syndrome, Ollier Disease, Maffucci syndrome, and DICER1 syndrome [3]. However, the etiology of these tumors remains uncertain.

To our knowledge, they are only a few cases formerly reported about the relation of tamoxifen use and adult granulosa cell tumor (AGCT). Here, we report a case of AGCT with antecedent tamoxifen use for breast cancer.

Case Report

A 57-year-old postmenopausal woman with a history of breast cancer presented with abnormal uterine bleeding and an ovarian mass. Two years ago, the patient had undergone breast-conserving surgery due to intramammarian mass. Her pathology report was given as invasive ductal carcinoma, ER-positive, PR-positive, HER2-negative. Positron emission tomography/computed tomography scan had shown no distant metastasis. She had been diagnosed with hormone receptor-positive breast cancer. The patient was evaluated as T1N0M0, stage 1a breast cancer according to the TNM staging system. After breast-conserving surgery, she had received adjuvant radiotherapy. She has been receiving adjuvant tamoxifen for 22 months since her diagnosis. In June 2021, the patient was admitted to the hospital with abnormal uterine bleeding. Ultrasound showed a nodular mass in her left ovary. Therefore, she underwent an adnexal hysterectomy and salpingo-oophorectomy. On gross examination, 30x21x12 mm diameter of the left ovary with an intact capsule was seen. On the cut surface, an 18 mm yellow and nodular mass with a soft surface adjacent to ovarian stroma was observed. Microscopically, at small magnification, a moderately cellular tumor characterized by solid, microfollicular, insular and trabecular patterns localized at the ovarian stroma was observed. At high magnification, tumor cells showed pale to eosinophilic

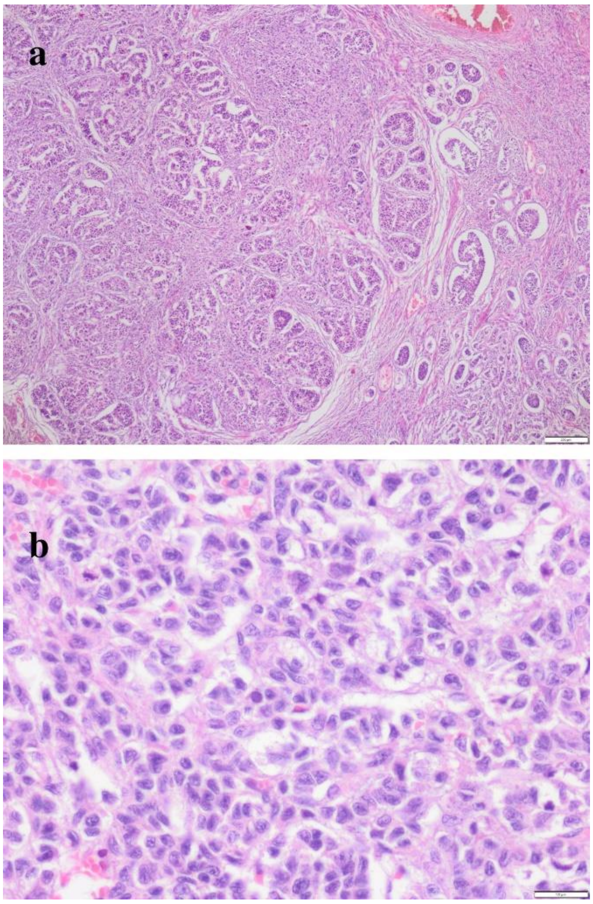

Figure 1a. Trabecular pattern of the tumor can be observed, especially at the right side of the image (HE x40). 1b. Trabecular pattern of the tumor can be observed (HE x100).

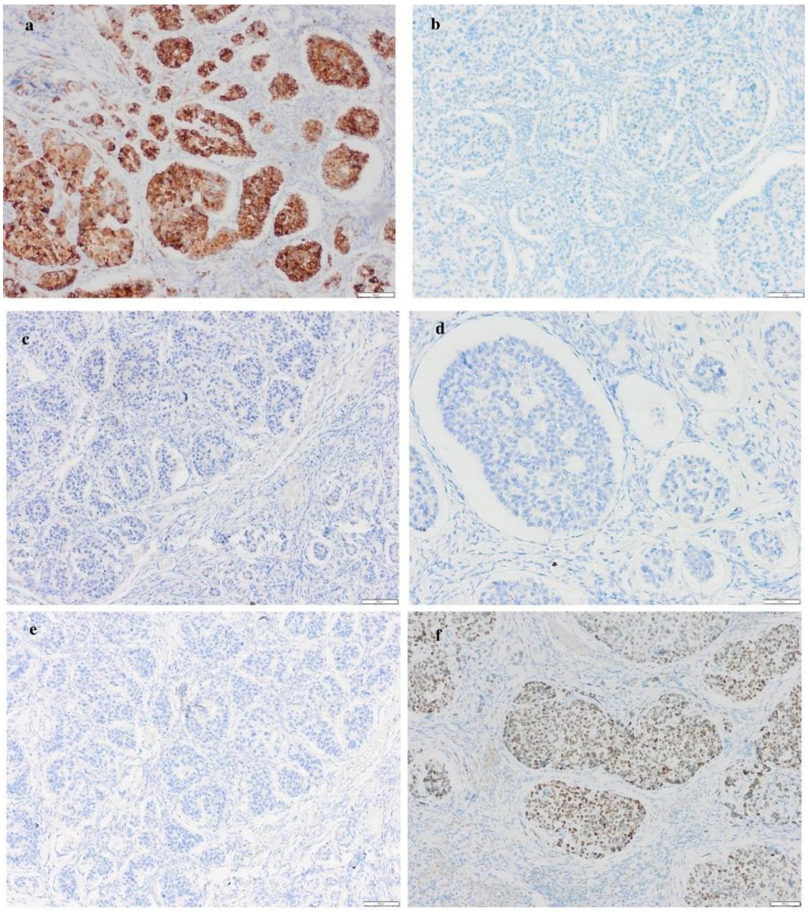

Figure 2a. Tumor cells showed cytoplasmic positivity for Inhibin (x100). b. Tumor cells stained negative for CK7 (x100). c. Tumor cells stained negative for PAX8 (x100). d. Tumor cells stained negative for GCDFP15 (x200).e. Tumor cells stained negative for Mammoglobulin (x100). f. Tumor nuclei stained positive for PR (x100).

cytoplasm and pale, oval nuclei with an irregular border. Some tumor cells had nuclear grooves (Figure 1). On 10 high magnification fields, 13 mitoses were counted. Immunohistochemically tumor cells stained positive for inhibin whereas they stained negative for CK7and PAX8. Since the patient had a breast cancer history differential diagnosis was made with negative staining for GCDFP15, Mammoglobulin, ER, and Cerb B2. PR showed immunopositivity with tumor cells (Figure 2). Inhibin positivity and pale cytoplasm ruled out poorly differentiated adenocarcinoma and small cell carcinoma. A final diagnosis of adult granulosa cell tumor was rendered based on morphology and immunohistochemical stains. The peritoneal washing cytology was negative. The stage of disease was classified as 1A according to FIGO. No adjuvant therapy was suggested. Keeping her on a close follow-up is decided. Tamoxifen therapy is continued since there is no clarity about the relation between tamoxifen use and AGCT. The patient is still in remission for both breast cancer and AGCT. An informed consent form was obtained from the patient.

Discussion

The adult granulosa cell tumor is relatively uncommon cancer type among women cancers [2,4]. Based on a few cases in the literature, it is considered that tamoxifen might play a role in the pathogenesis of AGCT. The studies designed to prove the relationship between tamoxifen use and

Table 1. The clinical and pathological characteristics of the patients

References	Age	Duration of Treatment	FIGO Classification	Mitotic index	ER	PR
Gherman et al.	52	11 months	1c	5	Unknown	Unknown
Arnould et al.	63	4 years	1c	2	-	+
Abhassian et al.	47	5 years	1c	3-5	Unknown	Unknown
Tanaka et al.	58	5 years*	1c	5	-	+
Our current case	57	22 months	1a	13	-	+

*2 years of torefemine use after 5 years of tamoxifen theraphy

uterine sarcomas are first failed due to the rarity of cases [5]. But recently, tamoxifen is known to be a risk factor for uterine sarcomas [1].

To our knowledge, AGCT with antecedent tamoxifen use has been described in only four cases previously. The first case of all was reported by Gherman et al in 1994. It was a 52-old woman with liver disfunction. The authors concluded that the hepatic failure may have resulted in changes in tamoxifen metabolism, therefore AGCT may be developed [6]. The second case was a case of breast carcinoma metastasis within AGCT, reported by Arnould et al in 2002. This time the patient had no signs of hepatic failure [7]. Then in 2010 Abahssain et al reported the third case of AGCT with antecedent tamoxifen use. They presumed that considering worldwide tamoxifen use among women AGCT development might be random [8]. Finally, in 2020, Tanaka et al reported AGCT in a 58-year old female patient with long-term tamoxifen use [9]. We report the fifth case of AGCT in a 57-year old patient after 22 months of tamoxifen use. We also emphasize that the AGCT cases may be incidental. The clinical and pathological characteristics of these patients are summarized in Table 1.

At least in the cases in which we can reach the hormone receptor information, we can see that ER was negative in ovarian GCTs. If tamoxifen acted through only hormone receptors, ER-receptor would have been positive in these GCTs. On the other hand, in 2009 Merglen et al represented that, the risk of death from breast cancer significantly increases in patients with ER-negative breast cancer who were treated with tamoxifen. And they also concluded that, besides its remarkable impact on ER-positive breast cancer, tamoxifen may cause carcinogenesis of ER-negative tumors [10]. Some of the studies demonstrated that tamoxifen's impact on the hormone receptors is not its only mechanism of action. Tamoxifen also can act on growth factor signaling pathways, therefore it can be detrimental effects [11]. Moreover, metabolites like metabolite E and bisphenol derived from tamoxifen can have alternative mechanisms of action for ER-negative cells. For example, Wiebe et al identified metabolite E and bisphenol in tamoxifen resistance MCF-7 human breast tumor implanted in athymic nude mice, as well as tumors from patients with tamoxifen resistance [12]. Due to the multifocal effects of tamoxifen, we think that it may be related to cancers such as AGCT, although it is not certain.

Considering the widespread use of tamoxifen all around the world, among women with breast carcinoma, the development of AGCT seems to be incidental, but these results show the importance of proper surveillance especially for women on tamoxifen and the early diagnosis of gynecological tumors. Our current case and these results show that it is very difficult to say there is a certain relationship between tamoxifen use and AGCT because of the rarity of the condition

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Corresponding author e-mail: dryusufilhan@gmail.com

Orcid ID:
Hatice Tülüce Atlım 0000-0002-6676-2847
Yusuf İlhan 0000-0002-2875-6876
Anıl Alpsoy 0000-0003-4978-7652
Sema Sezgin Göksu 0000-0002-1222-0444
Gülgün Erdoğan 0000-0003-3518-2142
Ali Murat Tatlı 0000-0001-9696-1102
Hasan Şenol Coşkun 0000-0003-2969-7561

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Case Report

A Giant Metastatic Adrenal Cortical Carcinoma Case Presented with Rapid Progression

Hızlı İlerleyen Dev Metastatik Adrenal Kortikal Karsinom Olgusu

Merve Durna[1], Atakan Topçu[2], İsmail Yurtsever[3], Melih Şimşek[2], Mehmet Aydın[4], Mesut Şeker[2]

[1]Department of Internal Medicine, Bezmialem Vakif University, Istanbul, Turkey
[2]Department of Medical Oncology, Bezmialem Vakif University, Istanbul, Turkey
[3]Department of Radiology, Bezmialem Vakif University, Istanbul, Turkey
[4]Department of Nuclear Medicine, Bezmialem Vakif University, Istanbul, Turkey

ABSTRACT

Adrenocortical carcinoma (ACC) is an uncommon and aggressive tumor. Despite the current treatment options commonly used in ACC, the prognosis is poor. No risk factors have been identified except for genetic predisposition. The most important factors affecting the prognosis are the stage at the time of diagnosis and the resectability of the primary tumor. Here, we present a metastatic ACC case of a 29-year-old woman presented with symptoms of swelling in her feet, abdominal striae, and mild abdominal pain for three months. The abdominal computed tomography scan revealed a 14 cm mass in the right adrenal gland, indistinguishable from the liver and right kidney. Clinicians should consider primary ACC, which has limited treatment options, in the differential diagnosis in the presence of findings such as edema, obesity, and striae.

Keywords: Adrenocortical carcinoma, case study, chemotherapy, metastatic, mitotane

ÖZET

Adrenokortikal karsinom (AKK) nadir görülen, agresif bir tümördür. AKK’de yaygın olarak kullanılan mevcut tedavi seçeneklerine rağmen prognoz kötüdür. Genetik yatkınlık dışında herhangi bir risk faktörü tanımlanmamıştır. Prognozu etkileyen en önemli faktörler, tanı anındaki evre ve primer tümörün rezektabilitesidir. Bu yazıda, üç aydır ayaklarda şişlik, karında çizgilenme ve hafif karın ağrısı şikayetleri ile başvuran 29 yaşındaki kadın hastada metastatik AKK olgusu sunulmaktadır. Bilgisayarlı tomografide sağ böbreküstü bezinde karaciğer ve sağ böbrekten ayırt edilemeyen 14 cm'lik kitle saptandı. Tedavi seçenekleri kısıtlı olan primer AKK; ödem, obezite, stria gibi bulguların varlığında ayırıcı tanıda düşünülmelidir.

Anahtar kelimeler: Adrenokortikal karsinom, olgu sunumu, kemoterapi, metastatik, mitotan

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Introduction

Adrenocortical carcinoma (ACC) is an uncommon and agressive tumor. The annual incidence is reported as 0.5-2 cases per million, and it is more common in women than men. A bimodal age distribution is seen, as under the age of five years and in the fifth decade[1]. Currently, except for genetic predisposition, no risk factors have been identified. While most of the patients present with symptoms related to excessive hormone production; the remaining cases are detected incidentally or as a result of complaints related to tumor size. In adrenocortical carcinomas, computed tomography (CT) and magnetic resonance imaging (MRI) are the preferred imaging modalities both for the localization of the tumor and detection of distant metastases. 25% of the cases has metastatic disease at the time of diagnosis, mostly to liver, lung, lymph nodes, and bone [2]. While 5-year survival rate is 60-80% in tumors confined to the adrenal gland, it is decreased to 0-28% in metastatic stage [3]. The most important factors affecting the prognosis are stage at the time of diagnosis and the resectability of primary tumor. In addition, advanced age, tumor size, presence of hormone-secreting tumor, high Ki-67 index (>10%) and mitotic activity, and tumor necrosis may be related to poor prognosis in ACC. Currently, the only curative approach is surgical resection. Palliative therapy is just limited to patients with unresectable or metastatic ACC [4]. Here, it was aimed to present a metastatic ACC case that passed away rapidly after the initiation of systemic treatment.

Case Report

A 29-year-old woman referred to our clinic with symptoms of swelling in her feet, abdominal striae, and mild abdominal pain that has begun three months ago. Medical history of the patient was remarkable for obesity (BMI: 43), type-2 diabetes mellitus, hypothyroidism, and thalassemia minor. The medications were levothyroxine sodium, metformin, and insulin aspart. Alopecia, acne, aphthous stomatitis, striae on the abdomen and feet, and bilateral pretibial edema were found in the physical examination at referral. Initial laboratory findings showed hyperglycemia, elevated liver function tests including total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, gamma glutamyl transferase, aspartate transaminase, alanine transaminase, and INR (international normalized ratio) levels. Ejection fraction was more than 60% without significant pathology in Echochardiography. No thrombus formation was detected with bilateral lower extremity doppler ultrasound screening. Further investigation was planned due to the Cushingoid appearance and abnormal laboratory results.

After consultation with department of endocrinology, hypercortisolemia (midnight level: 46,6 µg/dL), and low ACTH levels (5 pg/mL) were detected. 1 mg dexamethasone suppression test was compatible with hypercortisolemia. Aldosterone to renin ratio, cathecolamine and sex-hormone levels were in normal range. The Pituitary MRI showed no significant finding. Abdominal CT scan revealed a 14 cm mass in the right adrenal gland, indistinguishable from the liver and right kidney, and multiple parenchymal liver masses with the largest diamater 10 cm. (Figure 1, 2, 3). No pathological lesion was detected in thorax CT. The histopathological and immunohisto-chemical analysis of liver tru-cut biopsy was reported as the metastasis of primary adrenal cortex carcinoma. And, positive staining for synaptophysin, inhibin, melan A, vimentin and p53 was detected in the patohology specimen. A hypermetabolic mass with intense 18-FDG (18-fluorodeoxyglucose) uptake in the right surrenal region with tendency to coalesce in the liver was detected in 18-FDG positron emission tomography-computerized tomography (18-FDG PET-CT). A similarly heterogeneous

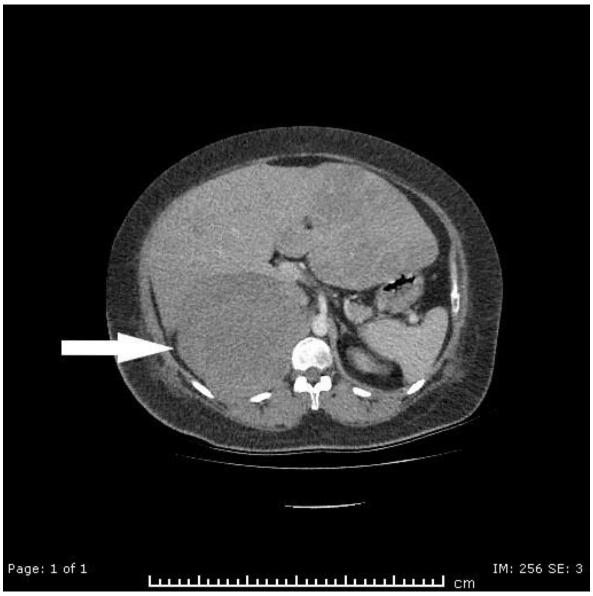

Figure 1. Contrast-enhanced CT image in the axial plane: Hypodense mass filling the right adrenal lodge and indenting the liver. Heterogeneously enhancing hypodense mass lesions in the liver parenchyma.

pattern of 18-FDG uptake was also demonstrated in the liver metastases. (Figure 4).

Surgery was not considered due to widespread liver metastasis, and systemic chemotherapy consisted of cisplatin and etoposide was immediately initiated with daily mitotane therapy. However, neutropenic sepsis occurred four days after the completion of first-cycle of chemotherapy, and no further chemotherapy could be given. The patient had hepatic failure and was in a state of visceral crisis at the time of admission and presented with serious signs and symptoms. In the follow-up, severe renal and liver impairment developed. Moreover, the mental status of the patient worsened progressively, and status epilepticus occurred. General condition of the patient deteriorated rapidly due to high disease burden, visceral crisis and sepsis. It was a chain of events that resulted in infectious manifestations and multiorgan failure on the basis of uncontrolled aggressive malignancy in the patient. The patient passed away on the 23rd day of the diagnosis. Hence, informed consent was obtained from the next kin of the patient for publication of this case report and related images.

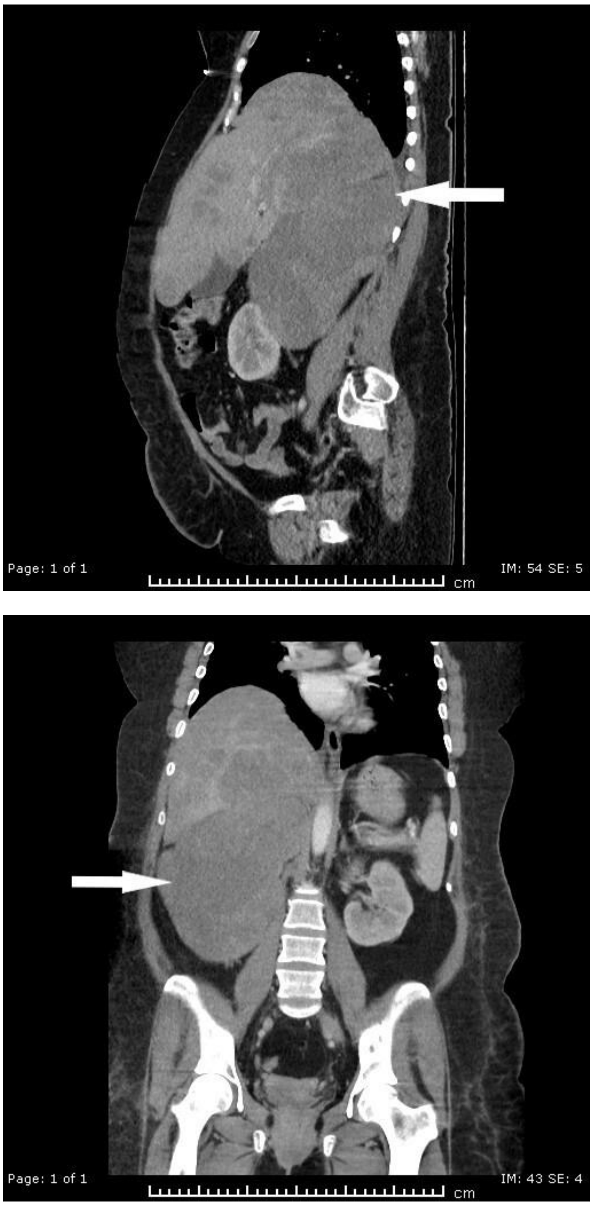

Figure 2 and 3. Contrast-enhanced CT image, coronal and sagittal section: A lobulated contoured hypodense mass filling the right adrenal lodge and extending inferior. The mass has a component on the superior part that erases the liver contours and invades the liver. It is seen that the mass depresses the right kidney downwards.

Discussion

ACC is an uncommon tumor with a five-year overall survival (OS) rate less than 50%. The well-established prognostic factors are age, disease stage, distant metastasis, Ki-67 index,

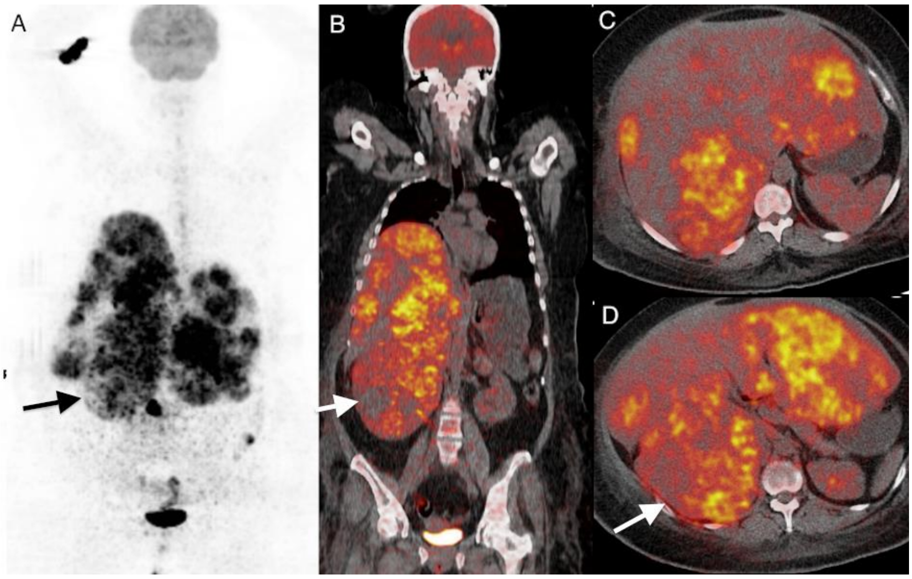

Figure 4. The primary mass was indicated with an arrow on maximum intensity projection (MIP) PET scan (figure A), coronal fusion image (figure B), axial fusion images (figure C and D).

hormone production status, and complete resection of the mass [5]. Surgery is the preferred treatment option and is recommended even in the presence of distant metastasis [6]. Despite resection, recurrence and metastasis rates are high for ACC. ACC can be functional or non-functional depending on hormone secretion. While functional carcinomas are usually detected early because of the symptoms related to excessive hormone production; nonfunctional carcinomas may not be diagnosed until the tumor has compression on adjacent tissue and organs or it may be detected incidentally in imaging [2].

For functional ACC; obesity, hypertension, Cushing's syndrome can be seen in cortisol-secreting masses; virilization in androgen-secreting masses; hypertension, muscle weakness, and hypokalemia due to aldosterone secreting tumors; gynecomastia in tumors that secrete estrogen [6]. In the present case, there were not any complaints due to the hormone excess despite hypercortisolism. Abdomen CT scan findings were consistent with typical characteristics of ACC. Furthermore, 18-FDG PET-CT showed high uptake in the right adrenal primary mass and in liver metastases.

Chemotherapy regimen consisting of cisplatin, doxorubicin, and etoposide in combination with mitotane therapy is usually given in the adjuvant, unresectable, and metastatic settings [7,8]. Moreover, radiotherapy can be applied for symptom palliation in patients with metastatic ACC [9].

Despite the current treatment options commonly used in ACC, the prognosis is poor. A rapid progression of the disease is also common in this patient group. Therefore, more effective and less toxic new treatment options such as immunotherapy and multi-kinase inhibitors are needed for advanced disease [10]. In our case, despite administration of one cycle of cisplatin and etoposide in combination with daily mitotane therapy, the disease progressed rapidly and the patient passed away in a few weeks.

Conclusion

In conclusion, we aimed to present a young patient with diagnosis of metastatic ACC with aggressive clinical course and mortal outcome. The presence of long-standing nonspecific symptoms precluded suspicion for clinical diagnosis, and the patient who lost the chance of early diagnosis was diagnosed in the metastatic stage. Rapidly initiated systemic treatments did not yield results and the patient passed away in a short time. Clinicians should consider primary ACC, which has limited treatment options, in the differential diagnosis in the presence of findings such as edema, obesity, and striae in the lower extremities.

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Corresponding author e-mail: mervedurna@hotmail.com

Orcid ID:
Merve Durna 0000-0002-3000-6708
Atakan Topçu 0000-0002-3634-4820
İsmail Yurtsever 0000-0001-7482-668X
Melih Şimşek 0000-0003-0633-8558
Mehmet Aydın 0000-0001-5349-8752
Mesut Şeker 0000-0002-3721-5406

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Original Article

Clinicopathological Features of Young Gastric Cancer and New Inflammatory Prognostic Markers

Genç Mide Kanserinin Klinikopatolojik Özellikleri ve Yeni İnflamatuar Prognostik Belirteçler

Ahmet Gülmez[1], Mustafa Dikilitaş[2]

[1]Adana City Education and Research Hospital, Department of Medical Oncology
[2]Inonu University Faculty of Medicine. Department of Medical Oncology. Malatya

ABSTRACT

Introduction: This study aimed to evaluate the clinicopathologic features of young gastric cancer (GC) patients and to investigate the factors affecting survival (OS).

Materials and methods: In this study, the data of 55 patients diagnosed under the age of 40 were obtained by retrospective evaluation of hospital records. Clinicopathological features and some laboratory parameters of this patient group and new inflammatory prognostic markers (IPM) obtained from these parameters were evaluated.

Results: The mean age of the patients in this study was 33 years. The majority of the patients were male. Patients were evaluated according to human C-erbB2 positivity too. The identified patients as positive were only 7% of all patients. Also, the patients were evaluated for platinum sensitivity too. It was found that 30% of the patients were sensitive to platinum treatments. Also, survival times of the patients were evaluated with IPM. Neutrophil-lymphocyte ratio (NLR), mean platelet volume/platelet count, C-reactive protein/albumin ratios were calculated separately. Survival results were analyzed based on the mean values of all 3 prognostic markers. Even though there was a significant numerical difference, no statistical significance was found.

Discussion: This study was conducted to examine the clinicopathological features and survival time of young GC patients. Low C-erbB2 positivity and high platinum resistance were found among this patient population. In addition, inflammatory prognostic markers, which were found to be associated with survival in most cancers, were found to cause significant numerical differences in terms of survival in our study.

Keywords: Young Gastric Cancer, Prognosis, Novel Prognostic Markers

ÖZET

Giriş: Bu çalışma genç mide kanseri (GC) hastalarının clinicopathologic özelliklerini değerlendirmek ve sağ kalıma (OS) etki eden faktörleri araştırmayı amaçladı.

Gereç ve yöntemler: Bu çalışmada, hastane kayıtlarının retrospektif olarak değerlendirilmesi ile 40 yaş altı tanı almış 55 hastanın verileri elde edilmiştir. Bu hasta grubunun klinikopatolojik özellikleri ve bazı laboratuvar parametreleri ile bu parametrelerden elde edilen yeni inflamatuar prognostik belirteçler (IPM) değerlendirildi.

Bulgular: Çalışmamızda hastaların ortalama yaşı 33'tü. Erkek hastaların sayısı çoğunluktaydı. Hastalar C-erbB2 pozitifliğine göre de değerlendirildi. Pozitif olarak saptanan hastalar, tüm hastaların sadece %7'siydi. Hastalar aynı zamanda platin duyarlılığı açısından da değerlendirildi. Hastaların %30'unun platin tedavilerine karşı duyarlı olarak saptandı. Hastaların SK süreleri inflamatuar prognostik belirteçler eşliğinde de değerlendirildi. Nötrofil-lenfosit oranı (NLR), ortalama platelet volümü/platelet sayısı (MPV/platelet sayısı), C-reaktif protein/albümin oranları (CAR) ayrı ayrı hesaplandı. Her 3 prognostik belirtecin de ortalama değerleri baz alınarak SK sonuçları incelendi. Bu değerler ve SK arasında rakamsal olarak belirgin farklılık olmasına rağmen istatistiksel bir anlamlılık saptanmadı.

Tartışma: Bu çalışma genç mide kanseri hastalarının klinikopatolojik özelliklerini ve SK sürelerini

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incelemek için yapılmıştır. Çalışmamız sonucunda bu hasta grubunda düşük C-erbB2 pozitiflik oranı ve yüksek platin direnci olduğu saptanmıştır. Ayrıca çoğu kanserde sağkalımla ilişkili olduğu saptanan inflamatuar prognostik belirteçlerin, çalışmamızda da SK açısından belirgin rakamsal farklılık oluşturduğu görülmüştür.

Anahtar kelimeler: Genç Mide Kanseri, Prognoz, Yeni Prognostik Belirteçler

Introduction

Gastric cancer (GC) is an important cancer worldwide. It is estimated that there will be more than 1,000,000 new cases and 783,000 deaths for GC in 2018. This makes GC the fifth most frequently diagnosed cancer worldwide and the third most common cause of cancer death [1]. Gastric cancer shows a marked variation for age at diagnosis. Gastric cancer is usually detected more frequently in older people in the United States, and the average age at diagnosis is 68. More than 95% of all newly diagnosed GC patients are over the age of 40 [2]. According to literature, patients under the age of 40 are referred to as young GC. Although few patients with young GC are seen in the literature, young GC patients have started to be seen more frequently in recent years. This situation can be caused by many different reasons. In addition to the development of cancer screenings and diagnostic procedures, the fact that people come into contact with carcinogens from an earlier age can be counted among the reasons for this situation.

Young adult patients with GC face unique challenges such as tumor biodiversity, differences in treatment efficacy, tolerance and compliance with treatment, fertility preservation, and psychosocial considerations associated with premature death [3-4]. There are some variation in the specific threshold used to define young adult GC patients. Large study groups, such as the National Cancer Institute [5], used age 39 as the upper limit to define young adult GC. Diffuse type GC is more common in this group of young adults. These patients are diagnosed later than elderly patients and have a more aggressive tumor biology [6].

In this study that we have completed, we evaluated the clinico-pathological features, treatments they received, and responses to these treatments in patients aged 40 years and younger. In addition, we aimed to evaluate some laboratory parameters, progression-free survival (PFS) and overall survival (OS) data of these patients.

Materials and Methods

In this study, we retrospectively evaluated GC patients who were diagnosed pathologically in our hospital between 2010 and 2020. When the hospital records were examined, it was seen that the number of young adult GC patients diagnosed between these years was 55. Gender, ECOG (Eastern Cooperative Oncology Group) performance status, predominant complaint at the time of diagnosis, diagnosis method, TNM stage at the time of diagnosis [7], surgical procedure and surgical technique, treatment modalities, hemoglobin (Hb), neutrophil (Neu) of the patients in our study, lymphocyte (Lym), platelet (Plt), albumin (Alb), total protein (Tp), C-reactive protein (CRP) results were obtained from hospital records. NLR was calculated as absolute neutrophil count / absolute lymphocyte count. MPR was calculated as mean platelet volume/absolute platelet count. CAR; It was calculated by taking the ratio of CRP to albumin. If patients receiving chemotherapy received platinum-based therapy, the platinum sensitivity of these patients was also evaluated. Treatment response assessment in metastatic patients was performed according to the Criteria for Evaluation of Response in Solid Tumors (RECIST) version 1.1 using magnetic resonance imaging (MRI), computed tomography (CT), or Positron Emission Tomography (PET/CT) at 6-8 week intervals. Patients who received adjuvant therapy were included in the follow-up after the end of the targeted treatment period. This study has ethics committee approval dated 29.09.2020 and numbered 2020-979. All procedures performed in studies involving human participants comply with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and later amendments or comparable ethical standards.

Statistical Analysis

Clinicopathological features were evaluated. Overall survival (OS) was calculated as the time from diagnosis to death from any cause. Overall survival was assessed using the Kaplan Meier method and compared using log-rank tests. Statistical analyzes were performed with IBM SPSS Statistics for Windows (version 22.0. Armonk, NY). A p value less than 0.05 was considered statistically significant. Patient survival was determined as mean ± standard deviation and was written in months.

Results

In this study, a total of 55 patients were evaluated in accordance with the inclusion and exclusion criteria. The patients were evaluated according to the complaint of predominance at the time of admission to the hospital. The predominant complaint was abdominal pain in 36 (65%) patients, and nausea and vomiting in 12 (27%) patients. Less common causes were weight loss in 5 (9%) patients and admission to the hospital with bleeding symptoms in two (4%) patients. When evaluated as a diagnosis method; 49 (89%) of the patients were diagnosed by endoscopy, while six (11%) patients were diagnosed by surgery. Patients were evaluated for differentiation from biopsy or postoperative pathology reports. Of the patients, five (9%) patients were diagnosed as well differentiated, seven (13%) patients moderately differentiated, 11 (20%) patients poorly differentiated, 18 (33%) patients with signet ring cell, and 14 (25%) patients with poorly cohesive carcinoma. The patients were also evaluated in terms of cerbB2 as a result of staining with immuno-histochemical evaluation. 37 (67%) of these patients were found to be cerbB2 negative. It was evaluated as +1 positive in 10 (19%) of the patients, +2 positive in four (7%) and +3 positive in four (7%) patients. The clinical and demographic data of these patients are shown in Table-1. The total number of patients who were considered locally advanced and operated for curative purposes was 35 (64%). On the other hand, the number of patients who were metastatic at the time of diagnosis was 20 (36%). When the patients were evaluated as surgical and non-surgical, it was seen that 40 (73%) patients were operated and 15 (27%) were not operated. While 35 of these operated patients were operated for curative purposes as previously stated, 5 patients were operated for palliative purposes. Subtotal gastrectomy was performed in 26 (65%) of 40 patients who underwent surgery, while total gastrectomy was performed in 14 (35%) patients. When the patients are classified according to the type of chemotherapy they receive; It was seen that five (9%) patients received neoadjuvant

Table 1. Demographic Data and Clinicopathological Characteristics of the Patients

	Number of Patients (n=55)	(%)
Age		
Median Age	33	
Range	(18-40)	
Gender		
Male	31	56
Female	24	44
ECOG		
0	15	27
1	21	38
2	19	35
Dominant Complaint		
Abdominal Pain	36	65
Nausea and Vomiting	12	22
Weight Loss	5	9
Bleeding	2	4
Diagnostic Method		
Endoscopy	49	89
Surgery	6	11
Subtype-Differential		
Well Differentiated	5	9
Poor Differentiated	7	13
Middle Differential	11	20
Ring Cell	18	33
Poorly Cohesive	14	25
CerbB2		
Negative	37	67
+1	10	19
+2	4	7
+3	4	7
Stage at Diagnosis		
Stage II	5	9
Stage III	30	55
Stage IV	20	36

Table 2. Surgical Characteristics and Treatments of the Patients

	Number of Patients (n 55)	(%)
Indication of Surgery		
Curative Approach	35	64
Palliative Approach	5	9
No Surgery	15	27
Type of Surgery		
Subtotal Gastrectomy	26	65
Total Gastrectomy	14	35
Lymph Node Dissection		
D1	4	10
D2	31	77
Unknown	5	13
Chemotherapy Reason		
Neoadjuvant	5	9
Adjuvant	27	49
Palliative	16	29
Could not get	5	9
No indication	2	4
Chemotherapy Type		
FUFA	11	23
FOLFOX	22	46
DCF	10	21
FLOT	3	6
EOX	2	4
Chemoradiotherapy	18	37,5
Completing Systemic Treatment	30	62,5
Platinum Sensitivity	11	30

FUFA: Fluorouracil/Folinic Acid, FOLFOX: Oxaliplatin Plus İnfusional 5-FU And Leucovorin, DCF: Docetaxel, Cisplatin and Fluorouracil, FLOT: Fluorouracil, Leucovorin, Oxaliplatin and Docetaxel, EOX: Epirubicin, Oxaliplatin, And Capecitabine

chemotherapy, 27 (49%) patients received adjuvant chemotherapy, and 16 (29%) patients received palliative chemotherapy. Although five (9%) patients had indication for treatment, they could not receive treatment due to poor performance status, and two (4%) patients had no indication for treatment. The patients were also evaluated according to the type of chemotherapy. 11 (23%) patients were treated with FUFA, 22 (46%) patients with FOLFOX, 10 (21%) patients with DCF, three (6%) patients with FLOT, and two (4%) patients with EOX. The patients were also evaluated according to the planned systemic treatment completion status. While 30 (62.5%) of 48 patients who started systemic treatment completed the planned treatment period, it was observed that the planned treatment period could not be reached in 18 (37.5) patients. The data from 37 patients treated with platinum agents were also re-evaluated for platinum sensitivity. The times determined for platinum sensitivity; at least 6 months after the end of treatment for metastatic disease, and 12 months after the end of treatment for patients who received adjuvant or neoadjuvant therapy. When evaluated with these criteria, a total of 11 (30%) patients were found to be platinum sensitive. The operation information of the patients and the systemic treatments of their received are shown in Table-2.

Some laboratory parameters of the patients were also evaluated. Patients were evaluated as neutrophil-lymphocyte ratio (NLR). The mean value was determined as 5.60 (0.99-21.20). The mean value for the evaluation of MPV/Platelet ratio, another inflammatory prognostic marker, was found to be 0.049 (0.011-0.450). Similarly, the mean ratio of CRP/Albumin, an inflammatory prognostic marker, was 1.38 (0.016-7.42). The relationship between inflammatory prognostic markers and OS is shown in Table 3.

Discussion

Gastric cancer patients are usually diagnosed over the age of 40. However, the frequency of GC patients under the age of 40 has been increasing in recent years, especially in western societies. And these patients are mostly diagnosed in the 30-39 age range [8]. In a previously published article, it was shown that young GC patients were diagnosed at a more advanced stage and their survival was worse [9]. The reasons for this poor prognosis are controversial. Some authors argue that GC diagnosed at an early age has genetic origins and therefore has a more aggressive course. According to another view, in many countries of the world, especially in countries where GC is endemic, young patients cannot be detected early due to inadequate screening programs and therefore the prognosis of these patients is worse. Possibly, both hypotheses may account for the poor course of these patients.

Table 3. Inflammatory Prognostic Markers and Survival Times

	Overall Survival-Month (OS)	Min	Max	p value
		%95 CI		
NLR				
<5,6 (n 18)	12,44±7,40	8,92	15,6	p>0,05
>5,6 (n 14)	7,08±4,72	5,11	9,27	
MPV/Platelet				
<0,049 (n=26)	9,73±7,20	7,02	12,78	p>0,05
>0,049 (n=6)	11,66±5,15	5,10	9,15	
CRP/albumin				
<1,38	11,18±4,93	8,95	13,38	p>0,05
>1,38	8,70±6,71	3,48	5,92	

NLR: Neutrophil-Lymphocyte Ratio, MPV: Mean Platelet Volume, CRP: C-Reactive Protein

Young GC has not been clearly defined yet. In previous studies, there are studies based on the age of 50, 40, and 34 years [10]. This definition of young GC varies due to the development level and life expectancy of the countries. In this study, we classified patients aged 40 years and younger as young GC. The mean age of the patients in this study was 33 years. More than half of the patients were male patients. In a previous study, the fact that GC seen at a young age was more common in women was attributed to hormonal changes. In addition, it has been stated that the reason for the excess of male cancer detected at advanced age is exposure to carcinogens more than women [10]. However, there is no clear cause and effect relationship related to this situation. Because the number of male patients was found to be higher in different series studies performed on young GC patients. In the same study, diffuse histology and poorly differentiated tumors were observed to be more common in younger patients. However, no difference was found regarding the diagnosis of younger patients at a later or more advanced stage. In addition, it has been observed that young GC patients have a shorter DFS period [10].

In another study, almost 5000 patients were evaluated and patients younger than 40 years of age were classified as young GC. There were 136 patients in this group. In this study, no difference in OS was found between younger patients and older patients. However, it has been reported that the performance status of young patients is better than that of elderly patients, and the complication rates after surgery are lower than those of the elderly. In addition to this situation, as in previous studies, pathologically worse differentiated tumors were found to be more common in younger patients. In addition, in this study, it was observed that the frequency of lymph node metastasis in young patients was higher than in patients over 40 years of age [11]. The reason why both OS and DFS durations were not different from patients aged >40 years in this study may be that the systemic treatments they received were more potent due to the better performance status of the younger patients. Another meta-analysis involving young GC patients was published in 2020. According to this study, the clinicopathologic features of GC patients diagnosed under the age of 40 were evaluated in 19 different studies between 2010 and 2019. In the light of these studies, the rate of female patients, the rate of diffuse type GC, the rate of poorly differentiated GC, and the rate of diagnosis at a more advanced stage were found to be higher in younger GC patients [12].

The standard treatment for Her-2 positive advanced GC is a combination of trastuzumab and platinum-based chemotherapy. The study that made this treatment standardized is the

ToGA study [13]. As mentioned in this study, Her-2 amplification or over-expression varies between 7-34%. However, Her-2 positivity rate was found to be only 7% in this study. This low Her-2 positivity rate also reduces the treatment options that can be used in young GC patients. Unfortunately, in this study that we have completed, the number of patients who can use the Her-2 targeted therapy option is extremely low.

Recently, treatment options without the use of conventional chemotherapy have been developed for some types of cancer. However, in treatment-naive and especially platinum-sensitive GC patients, a systemic treatment plan cannot be made without the use of platinum-based chemotherapy. However, platinum resistance in some patients renders these treatments ineffective. Many studies investigating which patients have resistance to these treatments have been reported in the literature [14,15]. In this study, approximately 70% of the patients had platinum resistance. Such a high level of platinum resistance in young GC patients may explain the poor prognosis of the patients. Investigation of the causes of platinum resistance in young GC patients; It should be the main subject of future studies both for genomic polymorphisms that can explain the pathogenesis of the disease and to aim to increase the extremely poor survival of the disease.

Due to both platinum resistance and low rate of Her-2 positivity, the treatment options available in young GC patients are decreasing. At this stage, immunotherapy treatments, which have gained importance in recent years, can be considered as an option. There is no clear biomarker for immunotherapy yet. Previous studies have shown that immunotherapies are beneficial in patients with high microsatellite instability (MSI-H), regardless of tumor type. With this demonstrated clinical benefit, pembrolizumab treatment has been approved by the American Food and Drug Administration (FDA) in patients with MSI-H [16]. However, according to a previous meta-analysis, there is a lower rate of MSI-H/dMMR in early young GC patients than in advanced age GC patients [17]. All these situations prove that young GC patients are more difficult patients and that more research is needed in this area.

Inflammatory prognostic markers are especially important in predicting the prognosis of the disease. Recently, it has been studied in almost all cancer types. As a result of studies supporting each other, they have become important parameters used in clinical practice. These parameters have also recently been studied in GC. It was evaluated in one study in patients with stage III GC, which included a total of 225 patients. C-reactive protein/albumin ratio (CAR) and platelet lymphocyte ratio (PLR) were found to be independent markers that affect overall survival [18].

There is also a meta-analysis result in patients with GC. The data from 41 studies published between 2007 and 2020 were analyzed [19]. According to this meta-analysis, which included a total of 18,348 patients, the increased NLR value was confirmed to be a negative prognostic marker for OS. Certain cut-off values were used for the inflammatory prognostic markers mentioned in these studies. These cut-off values were determined based on the average value of the patients in some studies, a target value was determined in some studies, and Roc Curve analysis was performed in some studies. However, the number of patients should be sufficient for Roc curve analysis. In this study, which we completed, the mean values of the patients were calculated due to the small number of patients and this mean value was taken as the cut-off value. A significant numerical difference was found in all three inflammatory prognostic markers in overall survival calculated with these values. However, this numerical difference was not statistically significant due to the insufficient number of patients.

The shortcomings of our study are the small number of patients, data from a single center, and being a retrospective study. The strengths of our study are that there are very few young

GC studies in the world. Another strength is that it is the first study to evaluate all three inflammatory prognostic markers in young GC patients. It is important to confirm with larger patient numbers. Considering all these data, early-stage GC is an important problem that should be emphasized. In this patient group, new treatment options are needed because of the poor biological behaviour of the disease and less use of targeted therapy agents.

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Corresponding author e-mail: doktor.ahmetgulmez@gmail.com

Orcid ID:
Ahmet Gülmez 0000-0002-3353-344X
Mustafa Dikilitaş 0000-0002-3763-7529

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Original Article

False-positive MRI Findings in Breast Cancer After Neoadjuvant Chemotherapy and Correlation Between Tumor Response Patterns and HER2 Status

Meme Kanserinde Neoadjuvan Kemoterapi Sonrası Yanlış-Pozitif MRG Bulguları ve Tümör Yanıt Paternleri ile HER2 Durumu Arasındaki Korelasyon

Aydan Avdan Aslan[1], Servet Erdemli[2], İbrahim Halil Erdoğdu[3], Serap Gültekin[1], Cihan Uras[4], Fatma Tokat[5], Ali Arıcan[6], Leyla Özer[6], Kemal Behzatoğlu[5], Nezih Meydan[7], Füsun Taşkın[2]

[1]Department of Radiology, Gazi University, Ankara, Turkey.
[2]Department of Radiology, Acıbadem M.A.A. University, İstanbul, Turkey.
[3]Department of Pathology, Adnan Menderes University School of Medicine, Aydın, Turkey
[4]Department of General Surgery, Acıbadem M.A.A. University, Istanbul, Turkey
[5]Department of Pathology, Acıbadem M.A.A. University, Istanbul, Turkey
[6]Department of Medical Oncology, Acıbadem M.A.A. University, Istanbul, Turkey
[7]Department of Medical Oncology, Adnan Menderes University, Aydın, Turkey

ABSTRACT

Objective: To demonstrate false-positive MRI findings after neoadjuvant chemotherapy (NAC) in patients with pathologic complete response (pCR) and investigate the correlation between post-NAC MRI findings and tumor response patterns based on human epidermal growth factor receptor 2 (HER2) status.

Methods: This retrospective multicenter study enrolled 118 patients with breast cancer who received NAC and achieved pCR. Tumors were evaluated with MRI pre- and post-NAC. MRI evaluation included lesion characteristics, kinetic curve analysis, background parenchymal enhancement (BPE), and post-NAC changes of MRI features. Tumor response patterns were also assessed and categorized based on MRI findings. Tumor response patterns and post-NAC MRI findings were correlated with HER2 status.

Results: The residual MRI findings following NAC differed significantly between HER2+ and HER2− groups ($p=0.02$). The most frequent false-positive MRI finding was focus and foci in HER2+ tumors, whereas non-mass enhancement (NME) in HER2− group. The presence of ductal carcinoma in situ (DCIS) and fibrosis in surgical pathology is significantly associated with NME on post-NAC MRI ($p<0.001$). Axillary pCR was achieved significantly higher in the HER2+ group ($p=0.04$).

Conclusion: Although MRI is considered the most reliable method for evaluating tumor response after NAC, over and underestimation is still possible. This study revealed that tumor response patterns and post-NAC MRI findings differ according to HER2 status. The diagnostic accuracy of post-NAC MRI is evolving by understanding the underlying mechanisms and tumor biology.

Keywords: neoadjuvant chemotherapy, magnetic resonance imaging, breast cancer, pathologic complete response

ÖZET

Amaç: Bu çalışmada patolojik tam yanıtlı (pTY) meme kanseri hastalarında neoadjuvan kemoterapi (NAK) sonrası yanlış-pozitif MRG bulgularını ortaya koymayı ve tümör yanıt paternleri ile insan epidermal büyüme faktörü reseptörü 2 (HER2) pozitifliği ile arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu retrospektif çok merkezli çalışmaya, Ocak 2016 ile Eylül 2020 tarihleri arasında NAK alan ve pTY elde eden meme kanseri tanılı118 hasta dahil edildi. Hastaların NAK öncesi ve sonrası MRG bulguları kayıt edildi. Tümör yanıt paternleri kategorilere ayrıldı. HER2 pozitifliği ile post-NAK MRG bulguları ve tümör yanıt paternleri arasındaki ilişki istatistiksel olarak analiz edildi.

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Bulgular: Post-NAK MRG bulguları HER2+ ve HER2− grupları arasında istatistiksel olarak anlamlı farklılık gösterdi (p=0.02). HER2+ tümörlerinde en sık yanlış-pozitif MRG bulgusu odak kontrast tutulumu iken, HER2− grubunda kitle dışı kontrastlanma (KDK) idi. Cerrahi patolojide duktal karsinoma in situ (DKİS) ve fibrozis varlığı ile post-NAK MRG'de KDK anlamlı olarak ilişkili bulundu (p<0,001). Aksiller pTY, HER2+ grubunda anlamlı derecede daha yüksek elde edildi (p=0.04).
Sonuç: MRG, NAK sonrası tümör yanıtını değerlendirmede en güvenilir yöntem olarak kabul edilse de, yanlış-pozitif ve yanlış-negatif sonuçlar elde edilebilmektedir. Bu çalışma, tümör yanıt paternlerinin HER2 durumuna göre farklılık gösterdiğini ortaya koymuştur. Bu alanda yapılacak yeni çalışmaların tümör biyolojisini anlamaya yardımcı olacağı ve NAK sonrası MRG'nin tanısal doğruluğunu arttırmaya yardımcı olacağı düşünülmektedir.

Anahtar Kelimeler: neoadjuvan kemoterapi, manyetik rezonans görüntüleme, meme kanseri, patolojik tam yanıt

Introduction

Neoadjuvant chemotherapy (NAC) has become the standard treatment in locally advanced breast cancer, and its use has been increasing recently [1]. NAC has also gained acceptance as an alternative therapeutic option in early-stage breast cancer, considering the studies reported no significant difference in survival rates and disease progression between patients who received neoadjuvant and adjuvant chemotherapy [2].

NAC enables breast-conserving surgery with a better surgical outcome in patients with large tumors by downstaging both primary tumor and axillary nodes. As pathologic complete response (pCR) is associated with better disease-free and overall survival, NAC provides valuable prognostic information in patients who achieved pCR [3, 4]. Other potential advantages of NAC over adjuvant chemotherapy include the ability to evaluate the efficacy of selected systematic therapy in vivo.

Accurate ascertainment after NAC is vital to evaluate tumor response and appropriate surgical planning. In the current medical practice, clinical examination and radiological modalities (mammography, ultrasound, and/or magnetic resonance imaging (MRI)) cannot exclude the presence of a residual tumor and surgical treatment must be applied even in the patients with clinical and radiological complete response [5]. As dynamic-contrast enhanced MRI provides information about morphology and function of the tumor, it has been shown that MRI is the most accurate imaging modality to assess tumor response to NAC [6].

Even though MRI is considered the most reliable method in evaluating tumor response following NAC, over and underestimating residual tumor is still possible. Several studies have shown that post-chemotherapy changes in the breast is the major cause of the discordance between pathology and MRI [7, 8]. Besides, tumor response patterns post-NAC are heterogenous and varies depending on subtype and Ki-67 index. Studies have shown that the diagnostic performance of MRI following NAC is better in human epidermal growth factor 2 (HER2) positive tumors with a high Ki-67 index [9-11]. Ballesio et al. evaluated the relation between molecular subtypes and tumor response patterns and demonstrated that concentric pattern is significantly correlated with HER2+ tumors [12]. To our knowledge, no study has investigated false-positive MRI findings following NAC.

Based upon the limited body of knowledge, we aimed to demonstrate false-positive MRI findings after NAC in patients with pCR and investigate the correlation between post-NAC MRI findings and tumor response patterns based on HER2 status.

Materials and Methods

Study population

From January 2016 to September 2020, a total of 292 consecutive women with breast cancer treated with NAC and achieved pCR were reviewed. Inclusion criteria were as follows:

(1), invasive breast cancer histologically proven with image-guided core needle biopsy before NAC; (2), underwent breast MRI pre- and post-NAC; (3), presence of residual contrast enhancement in tumor bed at MRI after NAC; (4), underwent surgery (breast-conserving or modified radical mastectomy) following NAC. According to these eligibility criteria, 118 patients were included in this study. This retrospective study involving three centers was approved by Local Ethics Committee and informed consent was waived (2021-01/07).

Treatment protocol

The NAC regimen included a combination of epirubicin/adriamycin and cyclophosphamide (4 cycles) and taxanes (4 to 12 cycles). Pertuzumab or Transtuzumab was also administered in HER2+ patients. Carboplatin was also applied in patients with BRCA mutation.

After completing NAC, surgery was performed for all patients.

MRI Acquisition and Evaluation

MRI scan was performed in three tertiary referral centers using 1.5T (Achieva, Philips Medical Systems, The Netherlands or Magnetom Aera, Siemens Healthinieers, Erlangen, Germany) or 3T (Skyra, Siemens Healthinieers, Erlangen, Germany) MRI systems with a dedicated 7- or 16-channel bilateral breast coil. Breast MRI protocol comprised high-resolution precontrast and dynamic contrast-enhanced imaging in axial plane including one pre-contrast and five or six post-contrast image sets after administration of gadolinium-based contrast agent. MRI scans were performed prior to NAC therapy and immediately before the surgery. MRI studies were evaluated using fifth edition of BI-RADS lexicon by four breast radiologists with 4 to 20 years of experience in breast imaging. For the patients with multifocal and multicentric disease largest tumor was accepted as index lesion. Largest diameter of tumor at peak enhancement was accepted as tumor size. Tumor response pattern following NAC was grouped according to the classification suggested by Kim et al [13].

Histopathological Evaluation

Before NAC, all patients underwent US-guided core needle biopsy procedure and invasive breast cancer diagnosis was confirmed histologically. Tumor histology and Ki-67 index were assessed using core biopsy samples. Ki-67 index was classified into three groups; ≤15%, 16-39% and ≥40% [14]. Estrogen receptor (ER) and progesterone receptor (PR) were assessed as negative if there was <10% nuclear staining. Human epidermal growth factor receptor 2 (HER2) was considered as positive if there was 3+ staining and negative if the staining score was 0 or 1+. In case of 2+ score, HER2 gene amplification testing was performed using fluorescent in situ hybridization. Patients were grouped into four categories according to hormone receptor (HR) and HER2 status: HR+/HER2−, HR+/HER2+, HR−/HER2+ and HR−/HER2−.

After NAC, surgery was performed for all patients and surgical specimen was evaluated for pCR. pCR was defined as absence of invasive cancer regardless of ductal carcinoma in situ or metastatic lymph node presence.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (version 22; IBM, USA). The categorical variables were expressed as counts and percentages, and the continous variables were expressed as means and ranges. Categorical variables were compared based on HER2+ status using Chi-square or Fisher's exact test. P values <0.05 were considered statistically significant.

Results

Study population and pre-NAC clinico-pathologic characteristics

This study included 118 breast cancer patients who received NAC consecutively. The median age was 47.0 (range: 27-85). The majority (66.7%) of the patients were premenopausal. Regarding molecular subtype, 43 (36.5%) tumors were HR+ HER2+, 34 tumors (28.8%) were HR− HER2+, 24 tumors (20.3%) were HR+ HER2−, and the remaining 17 (14.4%) were triple-negative. The mean tumor size by MRI before NAC was 30.4 mm (range:9-78 mm). Twelve patients (10.1%) had multifocal carcinoma, and one patient (0.8%) had bilateral invasive breast cancer. The histopathological analysis of surgical specimen revealed 103 (87.3%) invasive ductal carcinoma, seven (5.9%) invasive lobular carcinoma, three (2.5%) invasive ductal and lobular carcinoma, two (1.7%) invasive medullary carcinoma and one (0.8%) invasive mucinous. The majority of the patients (78.8%) were axillary node positive at presentation. The baseline clinico-pathological characteristics of patients were summarized in Table 1.

Table 1. Baseline clinicopathological characteristics of patients (n=118)

	All patients (n=118)
Median age, years (range)	47.0 (27-85)
Menopausal status	
Premenapausal	80(67.8)
Postmenapausal	38(32.2)
Basal MRI mean tumor size, mm (range)	30.4 (9-78)
Histologic type	
IDC	103(87.3)
ILC	7(5.9)
IDC+ILC	3(2.5)
Medullary carcinoma	2(1.7)
Mucinous carcinoma	1(0.8)
Other	2(1.6)
Molecular subtype	
HR+/HER2-	24(20.3)
HR+/HER2+	43(36.4)
HR-/HER2+	34(28.8)
HR-/HER2-	17(14.4)
Ki-67 index	
≤15%	5(4.2)
16-39%	57(48.3)
≥40%	56(47.5)
Node status at presentation	
Negative	25(21.2)
Positive	93(78.8)

Age presented as median (range) and tumor size presented as mean (range). All other variables are numbers of patients (percentages). MRI=Magnetic resonance imaging, IDC=Invasive ductal carcinoma, ILC=Invasive lobular carcinoma, HR=Hormone receptor, HER2=Human epidermal growth factor receptor 2

MRI findings of tumors before and after NAC

The mean tumor size by MRI after NAC was 9.9 mm (range:3-55 mm). The most frequent MRI findings at presentation were mass and non-mass enhancement (NME) in HER2+ and HER2− groups. The MRI findings following NAC differed significantly between HER2+ and HER2− groups (p=0.02). The most frequent false positive MRI finding was focus and foci in HER2+ tumors, whereas NME in HER2− group (Figure 1). In pre-NAC MRI peritumoral edema was significantly associated with HER2+ tumors (p=0.04). Pre- and post-NAC, the presence of the metastatic lymph nodes by MRI was similar in both groups (p>0.05). The most frequent enhancement curve pattern was type 3 at presentation, whereas the majority of tumors presented type 1 and type 2 enhancement curve pattern after NAC in both groups (p>0.05). Pre- and post-NAC MRI findings of tumors based on HER2 status were summarized in Table-2.

Changes of MRI features and pathologic findings after NAC

The majority of post-NAC tumor size by MRI was smaller than tumor size at presentation. Following NAC, three tumors (7.3%) in HER2− group and one tumor (1.3%) in HER2+ group showed increase in size. The post-NAC MRI finding was NME in all tumors that increased in size. Regarding the tumor size pre- and post-NAC, ≥50% reduction in size was significantly associated with HER2+ tumors (p<0.001). In pathologic evaluation, fibrosis in tumor bed was found more often in the HER2− group without significant difference (p=0.10). Presence of DCIS and fibrosis in surgical pathology was significantly associated with NME on post-NAC MRI (p<0.001). A high-risk lesion with atypia in the surgical specimen was found more likely in the HER2+ group, whereas failed to reach a significant difference (p=0.06). Axillary pCR was achieved significantly higher in the HER2+ group (p=0.04). There was no significant difference

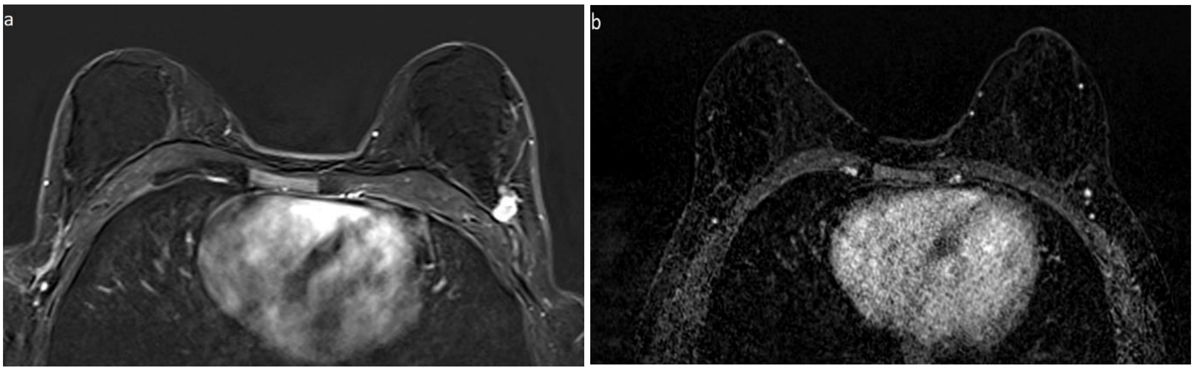

Figure 1. 36-year-old woman with invasive ductal carcinoma (hormone receptor-positive and HER2-positive)
(a) Axial substracted postcontrast T1-weighted image shows an irregular enhancing mass of left breast before chemotherapy.
(b) After completion of neoadjuvant chemotherapy, axial subtracted postcontrast T1-weighted image shows an enhancing focus at the original tumor site, which turned out to be a false-positive finding. No tumor or fibrosis was detected in the specimen after surgery.

Table 2. MRI findings based on HER2 status before and after NAC

	Before NAC			After NAC		
	HER2+(n=77) (65.2%)	HER2−(n=41) (34.7%)	p	HER2+(n=77) (65.2%)	HER2−(n=41) (34.7%)	p
BPE						
Minimal	21(27.3)	6(14.6)	0.36	39(50.6)	12(29.3)	0.04*
Mild	37(48.1)	20(48.8)		30(39.0)	20(48.8)	
Moderate	17(22.1)	13(31.7)		7(9.1)	9(22.0)	
Marked	2(2.6)	2(4.9)		1(1.3)	0(0)	
MRI finding						
Mass	41(53.2)	22(53.7)	1.0	11(14.3)	2(4.9)	0.02*
NME	1(1.3)	0(0)		32(41.6)	25(61.0)	
Mass+NME	35(45.5)	19(46.3)		1(1.3)	3(7.3)	
Focus	0(0)	0(0)		33(42.9)	11(26.8)	
Peritumoral edema						
Present	37(48.1)	12(29.3)	0.04*	4(5.2)	2(4.9)	1.0
Absent	40(51.9)	29(70.7)		73(94.8)	39(95.1)	
Axillary LAP						
Present	61(79.2)	32(78.0)	0.88	14(18.2)	9(22.0)	0.62
Absent	16(20.8)	9(22.0)		63(81.8)	32(78.0)	
Kinetic curve type						
1	1(1.3)	0(0)	1.0	47(61.0)	25(61.0)	1.0
2	20(26.0)	11(26.8)		29(37.7)	16(39.0)	
3	56(72.7)	30(73.2)		1(1.3)	0(0)	

Data are presented as n(%).
**p* values less than 0.05 regarded as statistically significant.
BPE=Background parenchymal enhancement, NAC=Neoadjuvant chemotheraphy, HER2=Human epidermal growth factor receptor 2, NME=Non-mass enhancement, LAP=Lymphadenopathy

Table 3. Changes of MRI features and pathologic findings based on HER2 status after NAC

	HER2+(n=77)	HER2−(n=41)	p
Tumor size difference in MRI			
≥50% reduction	68(88.3)	22(53.7)	<0.001*
<50% reduction	8(10.4)	16(39.0)	
Increase	1(1.3)	3(7.3)	
Tumor response pattern			
Concentric shrinkage	14(18.2)	4(9.8)	0.10
Crumble	6(7.8)	3(7.3)	
Focus or NME	48(62.3)	22(53.7)	
Diffuse enhancement	9(11.7)	12(29.3)	
BPE decrease (in categories)			
0	50(64.9)	28(68.3)	0.88
1	24(31.2)	11(26.8)	
2	3(3.9)	2(4.9)	
Tumor bed; fibrosis			
Present	28(36.4)	9(22.0)	0.10
Absent	49(63.6)	32(78.0)	
Tumor bed; DCIS			
Present	13(16.9)	10(24.4)	0.32
Absent	64(83.1)	31(75.6)	
Lesion with atypia in surgical specimen			
Present	21(27.3)	5(12.2)	0.06
Absent	56(72.7)	36(87.8)	
Axillary pathologic response			
Complete response	65(84.4)	28(68.3)	0.04*
Partial response	12(15.6)	13(31.7)	

Data are presented as n(%).
**p* values less than 0.05 regarded as statistically significant.
HER2=Human epidermal growth factor receptor 2, BPE=Background parenchymal enhancement, NME=Non-mass enhancement, DCIS=Ductal carcinoma in situ

regarding the frequency of residual in situ component in the surgical specimen and the degree of BPE reduction at MRI between groups. Changes in MRI features and pathologic findings following NAC were summarized in Table 3.

Discussion

In recent years, the use of NAC in breast cancer has become widespread. MRI is considered the most accurate method for evaluating tumor response after NAC; however, post-NAC MRI assessment may be challenging due to the heterogeneity of tumor response and the possibility of over and underestimation. To our knowledge, this study is the first study reporting false-positive MRI findings post-NAC and tumor response patterns based on molecular subtypes in breast cancer patients who achieved pCR. Our results revealed that residual MRI findings differ according to HER2 status. HER2+ tumors mostly present with focus or foci after NAC whereas non-mass enhancement more likely found in HER2− tumors.

The efficacy of NAC in breast cancer varies according to molecular subtypes. Studies have shown that HER2+ and triple-negative tumors are more responsive to chemotherapeutics due to their high cellular proliferation [15, 16]. Targetted agents used in the HER2+ group also increase this effectiveness. In agreement with the previous results, the majority of our study population (79.6%) consist of HER2+ and triple-negative breast cancer.

In a multicenter study, the overall accuracy of MRI after NAC was reported as 74% [17]. In a retrospective study with 98 patients, Choi et al. reported false positive rate of post-NAC MRI as 47% [18]. Confounding factors in radiology-pathology discordance should be taken into consideration to avoid inappropriate surgical planning. Post-chemotherapy changes including fibrosis, inflammation, and necrosis can mimic residual tumor and thereby may cause false-positive results on imaging. Molecular subtype, tumor size and chemotherapy regimen are also among the factors that influence the diagnostic performance of MRI. Studies have shown that the diagnostic accuracy of MRI was higher in HER2+ and triple negative tumors than hormone receptor-positive breast cancer. MRI-pathology discordance was also higher in tumors with >5 cm size and in tumors with low Ki-67 index [19]. Tumors presented with non-mass enhancement (NME) at pre-NAC MRI were also associated with lower diagnostic performance [20]. Furthermore, a decrease in contrast enhancement at post-NAC MRI resulting from the antiangiogenetic effect of taxanes may cause underestimation of residual tumor.

Another challenge in evaluating the post-NAC residual tumor is the heterogeneity of the tumor response patterns. Ballesio et al. evaluated MRI-based tumor shrinkage patterns (concentric, nodular and mixed pattern) and investigated its relationship between pCR rates and molecular subtypes. Results showed that concentric pattern is significantly associated with pCR and HER2+ subtype. However, mixed pattern is significantly associated with Luminal A tumors and non-pCR [12]. In our study, foci and NME was the most frequent response pattern post-NAC without significant difference according to HER2 status. This discrepancy may be attributable to the difference in the study populations and that only patients who achieved pCR were included in our study. Moreover, Lee et al. revealed that tumor response patterns differ histopathologically according to molecular subtypes [21]. According to this study, fibrosis within tumor bed was found more frequently in HR+ tumors which is in line with our results.

Imaging biomarkers based on MRI can be used in order to increase the diagnostic accuracy of post-NAC MRI. Studies have shown that decrease in background parenchymal enhancement (BPE) after NAC is correlated with pCR [22, 23]. Oh et al. also revealed that no significant correlation between post-NAC BPE decrease and molecular subtypes, which is consistent with our results [22]. In a retrospective study, Kim et al. used lesion-to-background parenchymal signal enhancement ratio (SER) on MRI in ≤ 5 mm lesions, and their results indicate that SER≤1.6 criterion significantly improves specificity to distinguish pCR from a residual tumor [24]. In regard to apparent diffusion coefficients (ADC), high ADC values post-NAC is associated with pCR. Santamaria et al. reported that pre- and post-NAC ADC ratio was >1.5 in 86% of patients who achieved pCR [25].

Our study has some limitations. First, this was a multi-center study thus MRI scans were performed with different MRI systems which could affect MRI assessment. Second, interobserver variability was not assessed even though MRI evaluation was made by two radiologists to reach consensus in ambiguous cases. At last, the definition of pCR may have an influence on MRI accuracy, and pCR was defined as the absence of invasive tumor regardless of DCIS presence in this study. However, Santamaria et al. revealed that pCR definition has no significant effect on the post-NAC MRI accuracy [26].

In conclusion, each breast tumor shows different response characteristics to NAC, and the diagnostic accuracy of MRI following NAC is evolving by understanding the underlying mechanisms and tumor biology. Our study revealed that tumor response patterns and post-NAC MRI findings differ according to HER2 status. It should be noted that focus and foci are the most frequent false-positive MRI finding in patients with pCR, particularly in HER2+ cases. With the help of further information in this field, avoidance of post-NAC surgery might be possible with an accurate prediction of pCR.

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Corresponding author e-mail: aydanavdanaslan@gmail.com

Orcid ID:
Aydan Avdan Aslan 0000-0002-7169-5933
Servet Erdemli 0000-0001-5545-768X
İbrahim Halil Erdoğdu 0000-0002-5445-2649
Serap Gültekin 0000-0001-6349-3998
Cihan Uras 0000-0002-6838-2311
Fatma Tokat 0000-0002-6976-1567
Ali Arıcan 0000-0002-6099-2000
Leyla Özer 0000-0001-8763-5268
Kemal Behzatoğlu 0000-0002-9843-9825
Nezih Meydan 0000-0003-4100-5804
Füsun Taşkın 0000-0001-7985-3660

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Original Article

How are the Results of Allogeneic Stem Cell Transplantation in Elderly Patients? A Single-Center Experience

Yaşlı Hastalarda Allojeneik Kök Hücre Nakli Sonuçları Nasıl? Tek Merkez Deneyimi

Ayse Uysal[1], Mehmet Ali Erkurt[2], İrfan Kuku[2], Emin Kaya[2], İlhami Berber[2], Ahmet Sarıcı[2], Soykan Biçim[2], Ahmet Kaya[2], Emine Hidayet[2]
[1]Fırat University School of Medicine, Hematology Department, Elazığ, Turkey
[2]İnönü University, Turgut Özal Medical Center, Adult Hematology Department, Malatya, Turkey

ABSTRACT

Aim: In this study, we aimed to present allogeneic hematopoietic stem cell transplantation (allo-HSCT) experience in elderly patients with hematological malignancy.

Materials and methods: Thirty-five patients aged 60 years and older who underwent allo-HSCT between 2017 and 2021 were retrospectively analyzed. Patient's demographic/clinical features, and the outcomes of transplantation were reviewed.

Results: The median age was 63 (range, 60-74) years and 25 (77,1%) were male. Twenty-seven (60%) were diagnosed with AML, followed by MDS (n:7, 20%). Twenty-three (65,8%) patients had intermediate, and 6 (17,1%) patients had a high hematopoietic cell transplantation-specific comorbidity index score. Karnofsky performance status of ≥ 90% was detected in 15 (42,9%) patients. Busulfan plus fludarabine plus anti-thymocyte globulin was used mainly as a reduced-intensity conditioning regimen, which was used in 18 (51,4%) patients. The median duration of neutrophil and platelet engraftments were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The median follow-up time was 4 months (range, 0-51), with the OS rate %14,2. The transplant-related mortality rate within the first 30 days after allo-HSCT was detected in 10 patients (28,6%) due to infection and/or GvHD. Response assessment could be performed in 25 (71,4%) patients after transplantation. The duration of PFS was 6 (range, 1-51) months in patients with response evaluation. The rate of PFS was 72% in 1 years and 5 (14,2%) patients were still alive with complete response at the last visit.

Conclusion: Reduced-intensity conditioning regimen has provided the advantage in allo-HSCT, for elderly patients with hematological malignancies such as AML and MDS.

Keywords: allogeneic hematopoietic stem cell transplantation, elderly patients, reduced-intensity conditioning regimen

ÖZET

Amaç: Biz bu çalışmada 60 yaş ve üzerindeki hematolojik malignitesi olan hastalarda allo-HSCT deneyimini ve sonuçlarını sunmayı amaçladık.

Gereç ve yöntemler: 2017-2021 yılları arasında allo-HSCT uygulanan 60 yaş ve üstü 35 hasta retrospektif olarak analiz edildi. Hastaların nakil anındaki demografik ve klinik özellikleri ile nakil sonuçları incelendi.

Bulgular: Ortanca yaş 63 (60-74) ve 25'i (%77,1) erkekti. Yirmi yedi (%60) hasta AML, 20 (%20) hasta MDS tanılıydı. Yirmi üç (%65,8) hastada orta, altı (%17,1)' sında yüksek hematopoietik hücre transplantasyonu spesifik komorbidite indeks skoru vardı. 15 (%42,9) hastada Karnofsky performans durumu ≥%90 olarak saptandı. Busulfan, fludarabin ve anti-timosit globulin kombinasyonu en sık kullanılan RIC rejimiydi ve 18 (%51,4) hastada kullanıldı. Ortanca nötrofil ve trombosit engraftman süresi sırasıyla 18 (11-27) ve 18 (11-33) gündü. Ortanca takip süresi 4 aydı (aralık, 0-51), toplam sağkalım oranı %14,2. Allo-HSCT' den sonraki ilk 30 gün içinde transplanta bağlı ölüm oranı enfeksiyon ve/veya GvHD nedeniyle 10 hastada (%28,6) tespit edildi. Nakil sonrası 25 (%71,4) hastada yanıt değerlendirmesi yapılabildi. Yanıt değerlendirmesi yapılan hastalarda PFS süresi 6 (dağılım, 1-51) aydı. PFS oranı 12 ayda %72 idi. Son kontrolde 5 (%14,2) hasta tam yanıtla halen yaşıyordu.

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Sonuç: Azaltılmış yoğunluklu şartlandırma rejimi, özellikle AML ve MDS gibi hematolojik maligniteleri olan yaşlı hastalarda allo-HSCT' de önemli bir avantaj sağlamıştır.

Anahtar Kelimeler: allojeneik hematopoietik kök hücre nakli, yaşlı hastalar, düşük yoğunluklu hazırlama rejimi

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the important treatment option for many hematological malignancies and benign hematological disorders [1]. However, complications such as post-transplant infection and graft versus host disease (GvHD) increase the rate of transplant-related mortality (TRM) and morbidity [2]. In the literature, high TRM (50%) rates have been reported [3]. Furthermore, many hematological malign diseases significantly affect the elderly. The median age at diagnosis is over 60 years in disease such as acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)in which allo-HSCT is very important [4-6]. Therefore, allo-HSCT as a salvage or consolidation treatment option could be used limitedly as a treatment option in elderly patients with multiple comorbidities [7].

The performance status and comorbidity are other factors determining the eligible transplant candidate and affecting the transplant outcome [8]. Hematopoietic cell transplantation-specific comorbidity index (HCT-CI) is used widely before the transplantation for transplant-risk assessment. Patients are stratified into 3 (score 0, 1–2, or ≥3) categories according to the HCT-CI. The TRM rate is found to be high in those with a score of 3 and above. [9]. Karnofsky performance score (KPS) is determined by evaluating functional abilities to perform routine daily activities. Generally, KPS below 60-70% is considered an exclusion factor for transplantation [8, 10].

Myeloablative conditioning regimen (MAC) could not be used in elderly and frail patients due to the significant risk of adverse effect. However, a reduced-intensity conditioning (RIC) regimen has shown significant benefits in TRM and morbidity [11-13]. In addition, TRM rates were reduced with the determination of the eligible transplant candidate, the development of GvHD prophylaxis, and the improvement in post-transplant supportive and infection therapy[4, 5, 14].

In this study, it was aimed to review allo-HSCT experience and outcomes in elderly patients who were 60 years old and older with hematological malignancy disorders.

Materials and Methods

We retrospectively analyzed 35 patients who were 60 years and older and underwent allo-HSCT between 2017 and 2021. The age, gender, performance score, comorbidity, disease status at the transplantation, number of treatment lines before the transplantation, donor type, the conditioning regimen, the quantity of CD34+ stem cells infused, the duration of neutrophil/platelet engraftment, the presence of febrile neutropenia/acute-chronic graft versus host disease, TRM, and duration of hospitalization, progression-free survival (PFS) and overall survival (OS) were examined. All data were collected from the hospitals' registries and patients' clinical notes.

Performance status was evaluated with KPS, and comorbidity status was evaluated with HCT-CI. The HCT-CI were each separated into 3 risk groups low (0), intermediate (1-2), and high (≥ 3) risk [9, 10].

Neutrophil engraftment duration was defined as the time from the first day of allo-HSCT to the first of three consecutive days with absolute neutrophil counts ≥0.5×10^9/L. Platelet engraftment duration was defined as the time from the first day of allo-HSCT to the first of three consecutive days with platelet counts of more than 20×10^9/L without transfusion. Febrile neutropenia was defined as the combination of granulocyte counts below 500 cells/µl and temperature over 38 oC. Acute GvHD was evaluated according to the revised Glucksberg scale. Chronic GvHD was diagnosed and staged according to the National Institutes of Health (NIH) Consensus Criteria[15, 16].

Transplant-related mortality was defined as death within the first 30 days after allo-HSCT without any evidence of disease relapse or progression. Progression-free survival was defined as the time from initiation of transplantation to the occurrence of disease relapse or death. Overall survival was defined from the first day of allo-HSCT to death from any cause.

This study was conducted with approval by the Ethics Committee of Inonu University with approval number 2021/2875 and was carried out by the principles of the Helsinki Declaration.

Statistical analysis

Numbers and percentages were used for categorical data in descriptive analyses. Continuous data were classified as parametric and non-parametric with skewness–kurtosis, Kolmogorov–Smirnov test, standard deviation/mean percentages, and histogram graphics with regular distribution lines. For parametric and non-parametric data, mean±standard deviation and median(min-max) values were used, respectively. For univariate analysis overall survival was calculated by Kaplan-Meier method and log-rank test was performed. Cox regression analysis was performed to determine significant predictors of age and the dose of CD34+ stem cells variables. Values of $p<0.05$ were accepted as statistically significant. All data analyzes were performed using Statistical Package for Social Sciences (SPSS) version 22.0 (Armonk, NY: IBM Corp.).

Results

Twenty-five (77,1%) of them were male. The median age at the time of transplantation was 63 (range, 60-74) years, and only two (5,7%) patients were older than 70 years old. Thirty-one (n:27, 60%) were diagnosed with AML, followed by MDS (n:7, 20%). Thirteen (48,1%) of 27 patients with AML had a complete response (CR) at the time of allo-HSCT. Twenty-three (65,8%) patients had intermediate, and six (17,1%) patients had a high hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score. The comorbidities were pulmonary dysfunction (17,1%), cardiac disease (14,2%), infection (14,2%), diabetes mellitus (11,4%), psychiatric disturbance (5,7%), arrhythmia (2,8%), cerebrovascular disease (2,8%), and rheumatologic disease (2,8%). Karnofsky performance status of ≥90% was detected in 15 (42,9%) patients. The demographic and clinical characteristics of the patients were presented in Table 1.

The median time from diagnosis to allo-HSCT was three (1-75) months. The HLA-matched sibling donor (MSD) was used most frequently as the donor type, which was used in 28 (80%) patients. A reduced conditioning regimen was used most frequently as the conditioning regimen, which was used in 31 (88,6%) patients. Busulfan plus fludarabine plus anti-thymocyte globulin (ATG) regimen was primarily used as a reduced-intensity regimen, which was used in 18 (51,4%) patients. Treosulfan plus fludarabine plus ATG therapy and fludarabine plus amsacrine plus cytarabine (FLAMSA) therapy were the other RIC regimens were used in nine (25,7%) and four (11,4%) patients, respectively. Busulfan plus cyclophosphamide was used as the MAC regimen, which was used in only

Table 1. The demographic and clinical characteristics of the patients at the time of transplantation

	N:35
Median age (range)	63 (60-74)
Gender, n (%)	
Male	27 (77,1)
Female	8 (22,9)
Disease type, n (%)	
AML	21 (60)
MDS	7 (20)
ALL	2 (5,7)
PMF	2 (5,7)
Others	3 (8,6)
Disease status, n (%)	
CR	18 (51,4)
PR	6 (17,1)
Refractory	11 (31,4)
The median time from diagnosis to transplant, (range), months	3 (1-75)
The median prior therapy line, (range)	1 (0-3)
Karnofsky performance score, n (%)	
≥90	15 (42,9)
<90	20 (57,1)
HCT-CI, n (%)	
Low	6 (17,1)
Intermedia	23 (65,8)
High	6 (17,1)
LDH, n (%)	
Normal	13 (37,1)
High	22 (62,9)
CRP, n (%)	
Normal	29 (82,9)
High	6 (19,1)
Cytomegalovirus serologic status, n (%)	
Positive	34 (97,1)
Negative	1 (2,9)

ASCT; autologous stem cell transplantation, AML; acute myeloid leukemia, ALL; acute lymphoblastic leukemia, CR; complete response CRP; C-reactive protein, HCT-CI; hematopoietic cell transplantation-specific comorbidity index, LDH; lactate dehydrogenase, MDS; myelodysplastic syndrome PMF; primary myelofibrosis, PR; partial response

Table 2. Peritransplantation features and outcome of transplantation

	N: 35
Donor type, n (%)	
Matched related	28 (80)
Matched unrelated	5 (14,3)
Haploidentical	2 (5,7)
Conditioning regimen n (%)	
Myeloablative	4 (11,4)
Reduced induced	31 (88,6)
The median count of infused CD34+stem cell $\times 10^6$/kg (range)	8,1 (5,1-19,4)
The median time to neutrophil engraftment (range), day	18 (11-27)
The median time to platelet engraftment (range), day	18 (11-33)
The rates of febrile neutrophile, n (%)	
Yes	25 (71,4)
No	10 (28,6)
The median duration of hospitalization (range), day	19 (1-50)
Transplant-related mortality, n (%)	
Yes	15 (42,8)
No	20 (57,2)
Disease status after transplantation	
CR	18 (51,4)
PR	2 (5,7)
Refractory/relaps	5 (14,3)
Not detectable	10 (28,6)
Acute GvHD status, n (%)	
Yes	10 (28,6)
Chronic GvHD status, n (%)	
Yes	3 (8,3)

CR; complete response, GvHD; graft versus host disease, PR; partial response

four (11,4%) patients. Cyclosporine A plus methotrexate combination was used in all patients due to GvHD prophylaxis.

The stem cell source was peripheral blood in all patients. The median counts of infused stem cells were 8,1x10^6/kg (range, 5,1-19,4x10^6/kg). The median duration of neutrophil engraftment and platelet engraftment were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The neutrophil and platelet engraftments did not occur in 11 (11,4%) and 11 (11,4%) patients, respectively. Febrile neutropenia was detected in 25 (71,4%) patients. The median time of hospitalization was 19 (range, 1-50) days. Transplantation characteristics and post-transplantation outcomes were shown in Table 2.

The median follow-up time was 4 months (range, 0-51), with the OS rate %14,2. The median OS was 4 months (95% CI: 2,1-5,8). The transplant-related mortality rate within the first 30 days after allo-HSCT was detected in 10 patients (28,6%) due to infection and/or GvHD. The age at the time of transplantation, gender, HCT-CI score, Karnofsky performance status, disease status at time of transplantation, the conditioning regimen, and

Table 3. The univariate analyses for overall survival

Variables	Median overall survival (months)	95% CI	p valuable
Gender			
Male	4,00	2,31-5,69	.889
Female	1,00	0-4,70	
Age*	0,969	0,842-1,115	.658
HCT-CI			
Score 0	4,00	0,60-7,40	
Score 1-2	4,00	2,45-5,55	.820
Score ≥3	1,00	0-3,40	
Karnofsky performance score			
<90%	4,00	0,21-7,79	.273
≥90%	2,00	0-6,38	
Disease status at the time of allo-HSCT			
Complete and partial response	4,00	0-8,78	.215
Refractory/progression	3,00	0-7,16	
The conditioning regimen			
Myeloablative	4,00	0-9,88	.424
Reduced induced	4,00	1,34-6,66	
The dose of CD 34 stem cell dose*	1,072	0,951-1,210	.254

HCT-CI; hematopoietic cell transplant comorbidity index, allo-HSCT; allogeneic hematopoietic stem cell transplantation
*Hazard ratio (95% confidence interval)

the dose of infused CD34+ stem cells were not statistically significantly associated with OS (Table 3).

Response assessment could be performed in 25 (71,4%) patients after transplantation. Ten (28,6%) patients died before a response assessment could be performed. The rate of PFS was 72% in 12 months. At the last follow-up, five (14,2%) patients were still alive with CR. Only three (10%) deaths were related to relapse/progressed disease.

Acute GvHD occurred in 10 (28,6%) patients as only gastrointestinal acute GvHD in four(11,4%) patients, only skin acute GvHD in five(14,2%) patients, and both gastrointestinal and liver acute GvHD in one (2,8%) patient. Grades III/IV acute GvHD occurred in six (17,1%) patients. Chronic GvHD occurred in three (8,3%) patients (one limited and two extended) surviving more than 100 days after allo-HSCT.

Discussion

Allo-HSCT can be used limitedly as a treatment option in elderly patients with comorbidities. However, in recent years, it has been more preferred in elderly patients due to the improvement of the conditioning regimens, the determination of prognostic factors before transplantation, and the improvement in post-transplant supportive treatments. In this retrospective study, 35 patients older than 60 years were evaluated who underwent allo-HSCT.

Comorbidity and performance status are the determining factors in selecting eligible patients in allo-HSCT. Sorror et al. presented the impact of HCT-CI and KPS on NMA allo-HCST outcomes and emphasized that both HCT-CI 3 and above scores and KPS percentages 80% or less were found to be important predictor of grade 3-4 toxicities and higher mortality (HCT-CI score: p=0.004, p=0.0002 and KPS: p=0.05, p=0.002, respectively). Furthermore, high HCT-CI scores were statistically significantly associated with increased NRM (p=0.0002) [17]. Other studies demonstrated that the HCT-CI score was a significant prognostic impact on OS (2-year OS, 58%, 53%, and 43% for scores 0, 1-2, and ≥3, respectively, p =0.004)[18]. In our study, 6 (17,1%) patients had low HCT-CI scores, 23 (65,8%) patients had intermediate HCT-CI scores, and six (17,1%) patients had high HCT-CI scores, whereas 20 (57,1%) patients had a KPS of

<90%. However, the comorbidity and KPS status in terms of overall survival could not be compared as they were small and heterogeneous groups.

Non-myeloablative (NMA) or RIC regimens are often preferred over myeloablative regimens to reduce toxicity for elderly patients in allo-HSCT. Wallen et al. presented the results of allo-HSCT with myeloablative regimens in adults 60 years of age and older. They evaluated 52 patients with a median age of 62.8 years who underwent allo-HSCT with MAC regimens. In their study, TRM rates at 100 days and 3 years are 27% and 43%, respectively. Grade ≥3 GVHD and extensive chronic GVHD occurred 20% and 53%, respectively [19]. However, the outcomes of allo-HSCT in elderly patients (median age, 69 years; range, 66-77) who underwent allo-HSCT using the RIC regimen were presented by Hsu et al. Most patients (85%) had received fludarabine/melphalan-based RIC regimen. The incidence of TRM mortality was 11,5% at 100 days. The grades II to IV GVHD at day 100 and 6 months was 29,5% and 34,5%, and chronic GVHD at 6, 12, and 24 months was 2.5%, 5.2%, and 6.3%, respectively[5]. In our study, the RIC regimen was used in 31 (88,6%) patients, and TRM was detected in 10 patients (28,6%) within the first 30 days after allo-HSCT. Acute GvHD occurred in 10 (28,6%) patients. Grades III/IV acute GvHD occurred in six (17,1%) patients. Chronic GvHD occurred in three (8,3%) patients. Although our TRM rates were higher than the literature, the outcome of both acute and chronic GVHD rates were similar with the literature. We attribute this to the frail of our cohort because most of them (57,1%) had KPS below 90% and majority of them (82,9%) had moderate and high HCT-CI score.

Although TRM is low with RIC regimens, the risk of relapse is more than with myeloablative therapies, as a disadvantage. Scott et al. presented the long-term follow-up of the study that MAC compared with RIC for AML and MDS. They reported that the risk of relapse was high in the RIC regimen compared to the received MAC (hazard ratio, 4.06; 95% CI, 2.59 to 6.35; p <0.001) [11]. Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation presented the comparative outcome of RIC and MAC regimen in HLA identical sibling allo-HSCT for patients older than 50 years with AML. They reported that the relapse rate was statistically significantly higher in the RIC group (RIC: 41% vs. MAC: 24%, p<0.0001) [20]. However, a phase 3 study compared the treosulfan-based conditioning regimen with the busulfan-based conditioning regimen in older patients with AML or MDS. The relapse or progression rates were detected at 20% and 21%, respectively. There was no significant difference between the two groups regarding recurrence or progression (p=0,50) [21]. In our study, the rate of PFS was 72%, and the progression rate was 14,3% in 12 months. Busulfan plus fludarabine or treosulfan plus fludarabine were used mainly as the conditioning regimen in our study, and our relapse rates were consistent with this phase 3 study.

In the RIC regimen, fludarabine is combined with an alkaline agent such as melphalan, busulfan, treosulfan, and thiotepa or with total body irradiation (TBI). The dose of alkylating agents or TBI is reduced in the RIC regimens, and thus the duration of cytopenia is shortened compared to MAC regimens[22, 23]. A study about the outcome of older patients who underwent allo-HSCT using RIC regimens reported the median time to neutrophil and platelet engraftment were 13 days (range, 8 to 37) and 17 days, respectively[5]. In a randomized and phase 3 trial, treosulfan plus fludarabine was compared with busulfan plus fludarabine for older patients with AML or MDS who underwent allo-HSCT. At day 28 after HSCT, neutrophil engraftment was achieved 96.8% in treosulfan-treated patients and 96.2% in busulfan-treated patients (p=0.34). Platelet engraftment was achieved in 97% and 98% of patients, respectively (p=0.077)[21]. In our study, busulfan and treosulfan-based conditioning regimens were mainly used (51,7%vs.25,7%, respectively). The median time of neutrophil engraftment and platelet engraftments were 18 (range, 11-27) and 18 (range, 11-33) days, respectively. The neutrophil and platelet engraftments did not occur in 11 (11,4%) and 11 (11,4%) patients, respectively. The duration of engraftment was consistent with the literature, but our engraftment rates were lower than the literature. This difference was thought to be due to infection-related deaths in the early transplant period (first 30 days after allo-HSCT).

The small and heterogeneous population was the most significant limitation of our study. Therefore, subgroup and comparison analyses were not performed. Another limitation was that it was a retrospective study.

In conclusion, RIC and NMA regimens provide a significant advantage for patients with advanced age with hematological malignancies such as AML and MDS, which have an essential role in the treatment of allogeneic transplantation. However, comorbidities and transplant-related mortality such as GVHD or infection still pose a significant transplant disadvantage for allo-HSCT in elderly and frail patients

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Corresponding author e-mail: erkurtali@hotmail.com

Orcid ID:
Ayse Uysal 0000-0002-5581-8104
Mehmet Ali Erkurt 0000-0002-3285-417X
İrfan Kuku 0000-0001-6126-0816
Emin Kaya 0000-0001-8605-8497
İlhami Berber 0000-0003-3312-8476
Ahmet Sarıcı 0000-0002-5916-0119
Soykan Biçim 0000-0001-7498-344X
Ahmet Kaya 0000-0002-0742-4629
Emine Hidayet 0000-0003-3121-7387

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Original Article

Risk Factors Associated with Progression of Myelodysplastic Syndrome: 13 Years of Experience from a Single Center

Miyelodisplastik Sendromun Progresyonu ile İlişkili Risk Faktörleri: Tek Merkezden 13 Yıllık Deneyim

Emine Gültürk
Department of Hematology, Bakırköy Dr Sadi Konuk Training and Research Hospital, Istanbul, Turkey

ABSTRACT

Aim: We aimed to assess the accuracy of the most widely-accepted prognostic classification systems in patients with myelodysplastic syndromes (MDS), and to investigate various parameters with respect to their association with MDS progression.

Material and Methods: Fifty-five patients diagnosed with MDS (January 1999 to December 2012) were reviewed retrospectively. Demographic characteristics, comorbidities, laboratory and pathological results, risk classifications (pathological and prognostic) at MDS diagnosis, treatment features, data regarding patient survival, and acute myeloid leukemia (AML) conversion were examined.

Results: Thirty-five male and 20 female patients (mean age: 70.95±9.80 years) were included. Twenty-four (43.46%) patients were defined to have had progression. Having an ECOG-PS score of ≥2 (OR: 6.939, 95%CI: 1.527-31.526; p=0.012) and being classified as 'high' or 'very high' risk according to the WPSS (OR: 10.115, 95%CI: 2.293-44.614; p=0.002) were found to be the only factors independently associated with MDS progression.

Conclusion: Although univariate differences were observed for various parameters, MDS progression was independently associated with ECOG-PS and WPSS class. It appears that singular classification systems are insufficient to predict MDS progression.

Keywords: Myelodysplastic syndrome, progression, prognostic factors, prognostic classification systems

ÖZET

Amaç: Miyelodisplastik sendrom (MDS) tanılı hastalarda en yaygın olarak kabul edilen prognostik sınıflandırma sistemlerinin doğruluğunu değerlendirmeyi ve MDS progresyonu ile ilişkisine göre çeşitli parametreleri araştırmayı amaçladık.

Gereç ve Yöntem: MDS tanısı konan 55 hasta (Ocak 1999-Aralık 2012) geriye dönük olarak incelendi. Demografik özellikler, komorbiditeler, laboratuvar ve patolojik sonuçlar, MDS tanısında risk sınıflamaları (patolojik ve prognostik), tedavi özellikleri, hasta sağkalımı ile ilgili veriler ve akut miyeloid lösemi (AML) dönüşümü incelendi.

Bulgular: Otuz beş erkek ve 20 kadın hasta (ortalama yaş: 70.95±9.80 yıl) dahil edildi. Yirmi dört (%43.4) hastada progresyon olduğu belirlendi. Sadece ECOG-PS skorunun ≥2 olması (OR: 6.939, %95 GA: 1.527-31.526; p=0.012) ve WPSS'ye göre 'yüksek' veya 'çok yüksek' riskli olarak sınıflandırmanın (OR: 10.115, %95) GA: 2.293-44.614; p=0.002), MDS progresyonu ile bağımsız olarak ilişkili faktörler olduğu belirlendi.

Sonuç: Çeşitli parametreler için tek değişkenli farklılıklar gözlemlenmesine rağmen, MDS progresyonu bağımsız olarak ECOG-PS ve WPSS sınıflandırması ile ilişkilendirilmiştir. Sınıflandırma sistemlerinin tek başına MDS progresyonunu tahmin etmede yetersiz olduğu görülmektedir.

Anahtar Kelimeler: Miyelodisplastik sendrom, progresyon, prognostik faktörler, prognostik sınıflandırma sistemleri

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Introduction

Hematopoietic cell transplantation is accepted Myelodysplastic syndrome (MDS) defines a group of diseases in which stem cell clonal disorders lead to bone marrow (BM) dysplasia and ineffective hematopoiesis. They have a high risk of progression to acute myeloid leukemia (AML) [1,2]. Annual MDS incidence is about three to four cases per 100,000 people, with a higher incidence in men and after the age of 80 years [3].

Since MDS demonstrates considerable clinical, pathological and cytogenetic heterogeneity, factors affecting survival and prognosis are highly variable [4]. Therefore, various classification systems have been developed, including pathological classification systems such as French-American-British co-operative group (FAB) and the World Health Organization (WHO) classifications. Also, various prognostic models have also been developed, such as the International Prognostic Scoring System (IPSS; and its revision, IPSS-R), the WHO classification-based Prognostic Scoring System (WPSS), and MD Anderson Cancer Center (MDACC) Risk Model [2,5-9]. Grading in these systems are made largely by considering chromosomal abnormalities, cytopenia, and BM blast percentages [10]. Patient comorbidities, physical performance status, various blood and BM parameters, treatment requirements at the time of diagnosis, and during the course of MDS are also likely to affect overall survival (OS) and progression [11-13]. The factors that determine the pathogenesis and progression of MDS have not been clarified [4] and considering that classification systems alone appear to be insufficient to predict the progression of this disease, it is evident that there is a need for further data to assess risk factors associated with progression in MDS [14].

In this study, we aimed to assess the accuracy of widely-accepted prognostic classification systems in MDS, and to investigate the roles of various parameters, many of which have not yet been included in these systems, in predicting MDS progression.

Methods

Study features and ethics

This retrospective study was conducted between January 1999 to December 2012 at the Department of Hematology, Faculty of Medicine, İstanbul University. The ethical approval of the study was obtained from the Clinical Research Ethics Committee of Istanbul University.

Participants

The files of 215 patients over the age of 18 who were diagnosed with MDS were reviewed retrospectively. Fifty-five patients whose files were sufficient for the study and who were followed up regularly in the outpatient clinic were included in the study. Patients with missing or inaccessible data were excluded.

Data collection instruments

Demographic characteristics of patients, comorbidity information, laboratory results, all histopathological information, and physical performance status were recorded. The results of classification systems listed below (at diagnosis of MDS), treatment, and follow-up data regarding survival and AML progression during disease course were obtained from hospital records.

MDS pathological classification

For MDS pathological grading, both the FAB classification [5,15] and the 2008 WHO classification [6] were used. There were 5 major groups according to the FAB classification system: Refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML) [5,15]. Using the 2008 WHO classification, MDS was grouped according to the findings of peripheral blood and BM as follows: Refractory cytopenia with unilineage dysplasia (RCUD), RARS, refractory cytopenia with multilineage dysplasia

(RCMD), RAEB-1, RAEB-2, MDS-unclassified (MDS-U), and isolated del(5q)-associated MDS [6].

MDS prognostic risk classification

Patients were classified in terms of prognostic risk using the IPSS, IPSS-R, WPSS, and MDACC models [7-9,16]. We used the 2011 revised version of the WPSS, that is, the original criterion of "transfusion requirement" was replaced by "severe anemia" (Hb<9g/dl in men, Hb<8g/dl in women) [9]. The patients were divided into 4 risk groups according to IPSS and MDACC (low, intermediate-1, intermediate-2, high), and 5 risk groups according to IPSS-R and WPSS (very low, low, intermediate, high, very high) [7-9,16].

Bone marrow assessment

Histopathological results of BM biopsy specimens were evaluated in terms of cellularity and dysplasia. Cellularity was categorized as “hypercellular, normocellular, hypocellular”; Dysplasia was categorized as “dysplasia in one, two or three cell line(s)” [17]. The European Myelofibrosis Network (EUMNET) scoring system was used to classify BM fibrosis which establishes 4 subgroups: MF-0, MF-1, MF-2, MF-3 [18].

Cytogenetic risk classification

Cytogenetic prognosis grouping was made according to the IPSS, and patients were divided into 3 risk groups as "good, moderate, poor" according to pre-specified chromosomal anomalies [1]. Patients with cytogenetically normal findings and those with del(5q), del(20q) or -Y were placed in the "good" subgroup, patients with complex (>2) abnormalities and chromosome 7 abnormalities were classified in the "poor" subgroup, and patients with other cytogenetic abnormalities were classified in the "moderate" subgroup.

Performance status assessment

The ECOG-PS was used to assess patients’ performance status at MDS diagnosis. In this scoring system, patients are classified according to their physical performance status in 6 degrees with the highest being 0 (fully active) and the lowest being 5 (dead) [19].

Progression criteria

Presence of at least one of the following 3 criteria was accepted to show MDS progression; (i) Conversion to AML, (ii) Death due to conversion to AML and/or BM failure, (iii) Later development of signs of BM failure that were not present at the beginning (i.e. Hb<9g/dl in men and <8g/dl in women, neutrophils count <0.8 x 10^9/L, platelet count <100 x 10^9/L). Progressive MDS cases were abbreviated as PG (presence of progression group), and non-progressive cases as non-PG (absence of progression group).

Statistical Analysis

All analyses were performed on SPSS version 25 (IBM, Armonk, NY, USA) with a significance threshold of <0.05 for p value. We employed the Shapiro-Wilk test to determine normality of distribution in numerical variables. Mean ± standard deviation or median (1st quartile-3rd quartile) summaries were used to describe numerical variables, in the presence and absence of normal distribution, respectively. Absolute and relative frequencies were reported for categorical variables. Numerical data were compared between groups by employing the independent samples t-test (normal distribution) or the Mann-Whitney U test (non-normal distribution). Chi-square tests were used to compare the distribution frequencies of categorical variables between groups, and the Fisher's exact test was utilized when assumptions for Pearson or continuity correction were not met. Variables’ prediction performance were assessed by using Receiver Operating Characteristic (ROC) curve analysis. Optimal cut-off points were determined by using Youden index. Multiple logistic regression analysis (forward conditional method) were performed to determine the best predictive factors associated with progression.

Results

Thirty-five male and 20 female patients were included in our study, and the mean age of the patients was 70.95 ± 9.80 (range 49-92) years. 31 (56.4%) of the patients were in the non-PG and 24 (43.6%) in the PG group. The PG and non-PG groups were similar in terms of age (p=0.8) and sex (p=1.000). The duration of follow-up in the PG group was significantly shorter (p=0.049).

According to the WHO classification, the non-PG group had a significantly higher percentage of patients with RCUD, while the PG group had a significantly higher percentage of patients with RAEB-2 (overall comparison, p=0.049). The FAB classification also showed significant difference between groups. The non-PG group had a higher proportion of RA patients, while the PG group had a higher proportion of RAEB patients (p=0.008). Mean hemoglobin level (p=0.004), monocyte count (p=0.017), and platelet count (p=0.011) were significantly lower in the PG group, while these patients had significantly higher mean ferritin levels (p<0.001). BM blast percentage was significantly higher among patients in the PG group (p=0.008). BM dysplasia in three cell lines was found to be significantly more common in the PG group (75.0%) compared to the non-PG group (45.2%) (p=0.043). The two groups were similar in terms of BM cellularity (p=0.26) and BM fibrosis grade (p=0.167). Patients in the PG group were found to have required significantly more transfusions (p<0.001). Median IPSS (p=0.004), IPSS-R (p=0.001), WPSS (p<0.001), MDACC (p=0.002) scores were found to be significantly higher in PG. The percentage of patients classified as having high (and very high) risks according to IPSS, IPSS-R, WPSS and MDACC scores was significantly higher in the PG group compared to the non-PG group; however, while comparisons for IPSS (p=0.027), IPSS-R (p=0.024) and WPSS (p=0.013) demonstrated significant difference between groups, the MDACC results were statistically similar (p=0.067) (Table 1).

Evaluation of various parameters with regard to their performance to predict progression (ROC analysis) yielded the following significant results: IPSS with ≥intermediate-2 cut-off (AUC: 0.728, 95%CI: 0.592-0.864; p=0.004), IPSS-R with ≥high cut-off (AUC: 0.748, 95%CI: 0.618-0.878; p=0.002), WPSS with ≥high cut-off (AUC: 0.761, 95%CI: 0.628-0.894; p=0.001), MDACC with ≥intermediate-2 cut-off (AUC: 0.702, 95%CI: 0.562-0.841; p=0.011). In particular, WPSS with ≥ high cut-off had 81.8% sensitivity and 83.3% negative predictive value (NPV) (Table 2, Figure 1).

Next, we performed multiple logistic regression analysis to determine the best predictive factors associated with progression. All parameters demonstrating significant difference in univariate analyses and previously suggested risk factors were included in the model. Patients with high ECOG-PS score (≥2) were found to have a 6.939-fold higher risk of progression than other patients (OR: 6.939, 95%CI: 1.527-31.526; p=0.012). Patients with high or very high WPSS were found to have a 10.115-fold higher risk of progression than other patients (OR: 10.115, 95%CI: 2.293-44.614; p=0.002) (Table 3, Figure 2, Figure 3). These results indicated that the ECOG-PS and WPSS combination was the best combination that could be used to predict progression. Other variables included in the model, age (p=0.733), sex (p=0.634), fibrosis grade (p=0.099), cytogenetics (p=0.484), dysplasia (p=0.513), IPSS (p=0.554), IPSS-R (p=0.354), and MDACC (p=0.974), were found to be non-significant.

Discussion

About two-thirds of patients with MDS die from bleeding, recurrent infections, and severe anemia due to progressive BM failure. Progression to AML is also associated with an extremely poor outcome and short survival [20]. Therefore, in our study, we identified BM failure and/or conversion to AML and/or death as the progression criteria of MD. We then aimed to identify various predictors that may be most associated with progression. We found that MDS progression could be associated with being classified as having RAEB-2 (WHO classification) and RAEB

Table 1. Summary of patient characteristics with regard to progression

		Progression		
	Total (n=55)	No (n=31)	Yes (n=24)	p
Age	70.95 ± 9.80	70.65 ± 9.06	71.33 ± 10.86	0.8
Sex				
Male	35 (63.6%)	20 (64.5%)	15 (62.5%)	1.000
Female	20 (36.4%)	11 (35.5%)	9 (37.5%)	
Comorbidity	31 (56.4%)	17 (54.8%)	14 (58.3%)	1.000
Diabetes mellitus	6 (10.9%)	5 (16.1%)	1 (4.2%)	0.216
Hypertension	10 (18.2%)	4 (12.9%)	6 (25.0%)	0.304
Ischemic heart disease	9 (16.4%)	4 (12.9%)	5 (20.8%)	0.48
COPD	4 (7.3%)	2 (6.5%)	2 (8.3%)	1.000
Other	7 (12.7%)	4 (12.9%)	3 (12.5%)	1.000
Malignancy	7 (12.7%)	3 (9.7%)	4 (16.7%)	0.69
Type of MDS, WHO				
RCUD	5 (9.1%)	5 (16.1%)	0 (0.0%)	0.049
RCMD	15 (27.3%)	11 (35.5%)	4 (16.7%)	
RARS	4 (7.3%)	3 (9.7%)	1 (4.2%)	
Isolated del(5q)	4 (7.3%)	3 (9.7%)	1 (4.2%)	
RAEB-1	7 (12.7%)	2 (6.5%)	5 (20.8%)	
RAEB-2	17 (30.9%)	6 (19.4%)	11 (45.8%)	
MDS/MPN	3 (5.5%)	1 (3.2%)	2 (8.3%)	
Type of MDS, FAB				
RA	22 (40.0%)	18 (58.1%)	4 (16.7%)	0.008
RARS	5 (9.1%)	4 (12.9%)	1 (4.2%)	
RAEB	23 (41.8%)	7 (22.6%)	16 (66.7%)	
RAEB-T	2 (3.6%)	1 (3.2%)	1 (4.2%)	
CMML	3 (5.5%)	1 (3.2%)	2 (8.3%)	
ECOG performance status				
0	15 (27.3%)	9 (29.0%)	6 (25.0%)	0.085
1	22 (40.0%)	16 (51.6%)	6 (25.0%)	
2	16 (29.1%)	5 (16.1%)	11 (45.8%)	
3	2 (3.6%)	1 (3.2%)	1 (4.2%)	
Hemoglobin (gr/dL)	9.17 ± 2.27	9.92 ± 1.94	8.20 ± 2.34	0.004
MCV (fL)	96.69 ± 13.71	95.17 ± 15.31	98.66 ± 11.32	0.354
WBC (/µl)	3300 (2360-5440)	3420 (2800-6060)	3125 (2075-5150)	0.175
Neutrophil (/µl)	1460 (900-2370)	1750 (1000-3000)	1295 (580-2030)	0.082
Lymphocyte (/µl)	1600 (1040-2340)	1400 (1090-2390)	1760 (1005-2260)	0.95
Monocyte (/µl)	330 (130-580)	380 (200-690)	185 (65-435)	0.017
Platelet (*10^3/µl)	107 (68-188)	141 (84-230)	87.5 (37-133)	0.011
LDH (IU/L)	233 (177-367)	228 (177-383)	234 (175.5-347)	0.96
Ferritin (ng/mL)	525 (143-1258)	160 (87-668)	1155 (412-1801)	<0.001
Bone marrow blast (%)	4 (2-12)	3 (2-7)	8 (3.5-14.5)	0.008
Bone marrow cellularity				
Hypercellular	46 (83.6%)	27 (87.1%)	19 (79.2%)	0.261
Normocellular	7 (12.7%)	4 (12.9%)	3 (12.5%)	
Hypocellular	2 (3.6%)	0 (0.0%)	2 (8.3%)	
Dysplasia (in … cell line(s))				
1	9 (16.4%)	8 (25.8%)	1 (4.2%)	0.043
2	14 (25.5%)	9 (29.0%)	5 (20.8%)	
3	32 (58.2%)	14 (45.2%)	18 (75.0%)	
Fibrosis grade				
MF-0	6 (10.9%)	4 (12.9%)	2 (8.3%)	0.167
MF-1	34 (61.8%)	22 (71.0%)	12 (50.0%)	
MF-2	11 (20.0%)	3 (9.7%)	8 (33.3%)	
MF-3	4 (7.3%)	2 (6.5%)	2 (8.3%)	

Cytogenetic				
Good	25 (45.5%)	17 (54.8%)	8 (33.3%)	0.262
Moderate	16 (29.1%)	8 (25.8%)	8 (33.3%)	
Poor	14 (25.5%)	6 (19.4%)	8 (33.3%)	
Transfusion need	30 (54.5%)	10 (32.3%)	20 (83.3%)	<0.001
Chelating agent use	4 (7.3%)	3 (9.7%)	1 (4.2%)	0.624
IPSS	1 (0-2)	0.5 (0-1.5)	1.5 (1-2.5)	0.004
Low	15 (27.3%)	12 (38.7%)	3 (12.5%)	0.027
Intermediate-1	17 (30.9%)	11 (35.5%)	6 (25.0%)	
Intermediate-2	11 (20.0%)	5 (16.1%)	6 (25.0%)	
High	12 (21.8%)	3 (9.7%)	9 (37.5%)	
IPSS-R	4 (2-6.5)	3 (2-5)	6 (3.75-7.25)	0.001
Very low	5 (9.1%)	5 (16.1%)	0 (0.0%)	0.024
Low	15 (27.3%)	11 (35.5%)	4 (16.7%)	
Intermediate	9 (16.4%)	6 (19.4%)	3 (12.5%)	
High	10 (18.2%)	4 (12.9%)	6 (25.0%)	
Very high	16 (29.1%)	5 (16.1%)	11 (45.8%)	
WPSS	3 (1-4)	1.5 (1-3)	4 (3-5)	<0.001
Very low	7 (13.5%)	6 (20.0%)	1 (4.5%)	0.013
Low	10 (19.2%)	9 (30.0%)	1 (4.5%)	
Intermediate	7 (13.5%)	5 (16.7%)	2 (9.1%)	
High	16 (30.8%)	6 (20.0%)	10 (45.5%)	
Very high	12 (23.1%)	4 (13.3%)	8 (36.4%)	
MDACC	6 (4-8)	5 (3-8)	8 (6-10)	0.002
Low	15 (27.3%)	12 (38.7%)	3 (12.5%)	0.067
Intermediate-1	15 (27.3%)	9 (29.0%)	6 (25.0%)	
Intermediate-2	12 (21.8%)	6 (19.4%)	6 (25.0%)	
High	13 (23.6%)	4 (12.9%)	9 (37.5%)	
Chemotherapy	3 (5.5%)	1 (3.2%)	2 (8.3%)	0.575
Follow-up time, month	22 (8-33)	26 (10-38)	12.5 (6.5-28)	0.049
AML transformation	12 (21.8%)	-	12 (50.0%)	-
Mortality	16 (29.1%)	-	16 (66.7%)	-

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

COPD: Chronic obstructive pulmonary disease, MDS: myelodysplastic syndromes, WHO: World Health Organization, RCUD: Refractory cytopenia with unilineage dysplasia, RCMD: Refractory cytopenia with multilineage dysplasia, RARS: Refractory anemia with ringed sideroblasts, RAEB: Refractory anemia with excess of blasts, MPN: Myeloproliferative neoplasms, FAB: French-American-British, RA: Refractory anemia, RARS: Refractory anemia with ringed sideroblasts, RAEB-T: Refractory anemia with excess of blasts in transformation, CMML: Chronic myelomonocytic leucaemia, ECOG: Eastern Cooperative Oncology Group, MCV: Mean corpuscular volume, WBC: White blood cell, LDH: Lactate dehydrogenase, MF: Myelofibrosis, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-revised, WPSS: WHO classification-based Prognostic Scoring System, MDACC: MD Anderson Cancer Center, AML: Acute myeloid leukemia

(FAB classification). In addition, we observed that the likelihood of progression appeared to increase in the presence of higher risk category in IPSS, IPSS-R, and WPSS. As a result of multiple logistic regression analysis, we found that having an ECOG-PS score of ≥2 and a WPSS classification of ≥high were the only factors independently associated with progression.

The prognosis of MDS patients, with respect to OS and risk of transformation to AML, is primarily defined by the IPSS and the IPSS-R scores [2,21]. IPSS-R has been shown to have improved accuracy over IPSS. In this study, IPSS(-R) scores were not found to be strongly associated with prognostic prediction, especially relative to ECOG-PS and WPSS. Median OS for high-risk MDS patients (IPSS: intermediate-2 and high-risk; IPSS-R: intermediate [with >3.5 points], high or very-high-risk score) ranges from a few months to 1.2 years [21]. The recent study by Papageorgiou et al. showed that IPSS or IPSS-R independently predicted shortened LFS and

Table 2. Performance of the variables to predict progression

	Cut-off	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC (95.0% CI)	p
ECOG-PS	≥ 2	50.0%	80.6%	67.3%	66.7%	67.6%	0.621 (0.466-0.776)	0.127
Fibrosis grade	≥ MF-2	41.7%	83.9%	65.5%	66.7%	65.0%	0.624 (0.472-0.776)	0.118
Cytogenetic	Moderate & Poor	66.7%	54.8%	60.0%	53.3%	68.0%	0.618 (0.468-0.769)	0.135
IPSS	≥ Intermediate-2	62.5%	74.2%	69.1%	65.2%	71.9%	0.728 (0.592-0.864)	0.004
IPSS-R	≥ High	70.8%	71.0%	70.9%	65.4%	75.9%	0.748 (0.618-0.878)	0.002
WPSS	≥ High	81.8%	66.7%	73.1%	64.3%	83.3%	0.761 (0.628-0.894)	0.001
MDACC	≥ Intermediate-2	62.5%	67.7%	65.5%	60.0%	70.0%	0.702 (0.562-0.841)	0.011

PPV: Positive predictive value, NPV: Negative predictive value, AUC: Area under ROC curve, CI: Confidence intervals, ECOG: Eastern Cooperative Oncology Group, IPSS: International Prognostic Scoring System, IPSS-R: International Prognostic Scoring System-revised, WPSS: WHO classification-based Prognostic Scoring System, MDACC: MD Anderson Cancer Center

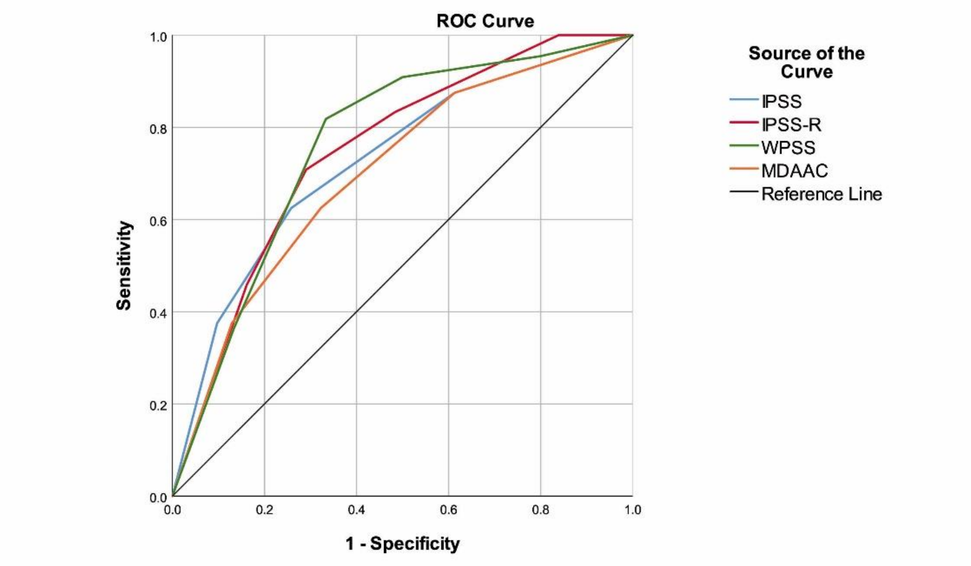

Figure 1. ROC curve of the risk scores to predict progression

Table 3. The best predictive factors of the progression, multiple logistic regression analysis

	β coefficient	Standard Error	p	Exp(β)	95% CI for Exp(β)	
ECOG-PS, ≥ 2	1.937	0.772	0.012	6.939	1.527	31.526
WPSS, ≥ High	2.314	0.757	0.002	10.115	2.293	44.614
Constant	-2.335	0.703	0.001	0.097		

Dependent variable: Progression; Nagelkerke R^2=0.430

CI: Confidence Interval, ECOG: Eastern Cooperative Oncology Group, WPSS: WHO classification-based Prognostic Scoring System

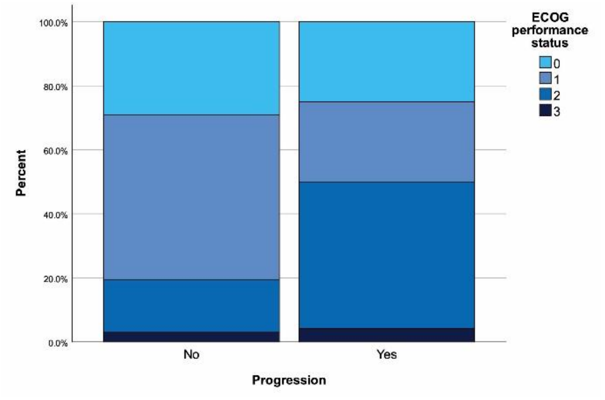

Figure 2. ECOG performance status score with regard to progression

OS [21]. Apart from these two, the other 2 classification systems developed and accepted as prognostic determinants are WPSS and MDACC models [16,22]. We believe the outcomes of our study may be associated with the fact that WPSS performs a dynamic risk assessment and has prognostic value not only at the time of diagnosis but also at other times [23]. Porta and colleagues studied OS and AML conversion time in 5326 MDS patients with respect to IPSS-R and WPSS classes. They found that according to, median OS was 121, 67, 35, 20, and 9 months in very low, low, intermediate, high and very high risk IPSS-R classes, respectively. Also, after excluding the “very low risk” group, median time for 25% of patients to develop AML was found to be 188, 34, 17 and 9 months, respectively. They also showed that according to WPSS classes median OS was 98, 76, 44, 21 and 9 months in very low, low, intermediate, high and very high risk, respectively, while median times for 25% of patients to develop AML (except very low) were 174, 72, 18 and 8 months, respectively.

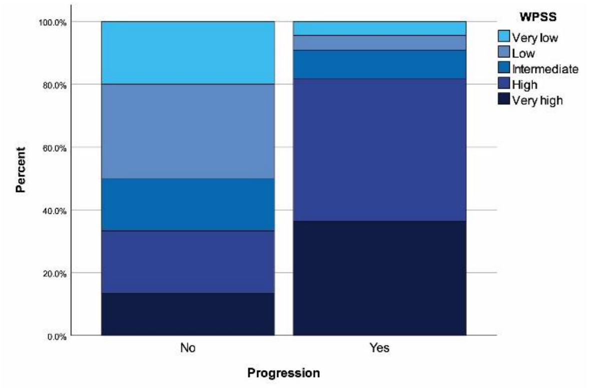

Figure 3. WPSS risk groups with regard to progression

They found the prognostic power of the WPSS was comparable to that of IPSS-R [22]. Comparing the IPSS and WPSS outcomes, it appears that the relatively steep decline regarding length of OS and time until AML conversion from the “intermediate” to the “high risk” groups of the WPSS may have had a role in establishment of statistical significance in the present study. The multivariable analysis results of our study support the relationship of the WPSS system with MDS progression. In our study, RAEB-2 was found to be significantly associated with progression and WHO-RAEB-2 significantly increased the WPSS score. Taken together, these provide support for the importance of blast percentage in determining prognosis, as this parameter is the primary parameter that distinguishes RAEB-2 from other WHO subclasses. However, before drawing direct conclusions regarding this matter, the non-homogeneous distribution of patient characteristics in MDS and the limited patient counts in several subgroups must be considered.

The MDACC is another prognostic system that assesses treated and untreated MDS patients, as well as patients with proliferative CMML and treatment-associated MDS [16,23]. Notwithstanding its reliable performance and wide inclusion criteria, the relative complexity of this model has limited its use in routine clinical practice [23]. The studies by Komrokji et al. and Nazha et al. also supported the prognostic value of MDACC in MDS [24,25]. Although we did not find an independent relationship between MDACC and MDS progression, ECOG-PS (which is included in the MDACC) was independently associated with MDS progression, further supporting the utility of MDACC in prognostic assessment while also showing the need for further data to improve patient risk stratification in MDS. When we evaluated ECOG-PS's prognostic value as a separate parameter, it was found that half of the patients with progression had an ECOG-PS score of 2 or higher. Perhaps more importantly, 80% of the non-PG group had an ECOG-PS score of <2. Similar to our study, the logistic regression analysis performed in one study showed that having a poor ECOG-PS (score ≥2) was an independent predictor of shortened LFS and OS, independent of IPSS-R risk class [21]. This relationships was also supported by another study in which an ECOG-PS score of 2 or higher was independently associated with shorter survival [26].

The FAB and WHO classifications are two widely accepted models in the pathological classification of MDS. The WHO classification was revised in 2016 [27,28], but since we used data obtained between 1999 and 2012 in our study, we classified patients according to the WHO 2008 classification. In a comprehensive study involving 5326 patients, OS for the types defined according to the WHO classification were as follows: median OS was 99 months for RCUD, RARS, and del5q (considered a single category), 66 months for RCMD, 28 months for RAEB-1, and 18 months for RAEB-2. The median time that surpassed until 25% of patients developed AML was 123 months for RCMD, 23 months for RAEB-1, and 9 months for RAEB-2 [22]. In the study by Ohyashiki et al., the conversion of RAEB-1 to AML was reported at a frequency of 37.5%, while the conversion rate of RAEB-2 to AML was 50% [29]. A recent study from Japan reported that MDS patients with high ferritin levels were significantly more likely to have RARS according to the FAB classification and were significantly less likely to have RA when compared to those with low ferritin levels [10]. Considering that high ferritin level is associated with worse survival in MDS, the ferritin elevation in these groups could be a factor contributing to survival [30]. We found that patients with RAEB-2 (WHO classification) and patients with RAEB (FAB classification) were significantly more likely to be in the PG group rather than the non-PG group. Furthermore, patients with RCUD (WHO classification) and patients with RA (FAB classification) were significantly more common in the PG group than in the non-PG group. We can say that these results are relatively consistent with the results of previous studies. Undoubtedly, the combination of the excess blast percentage with the presence of dysplasia in one or more cell lines has an important role in this relationship.

The limitations of our study can be listed as follows: the fact that it was a single-center study and the small number of participants limits the generalizability of the results. The retrospective analysis limited both the addition of new data and the use of the revised version of the WHO classification (2016) and comparison with other studies in this respect. In addition, since some patients had been diagnosed prior to access to advanced methods, we could not examine the effects of molecular genetics on the clinical course of MDS. The heterogeneity of the patient population is true for all studies evaluating patients with MDS, and therefore, is unavoidable; however, our data were further limited by the heterogeneous distribution of patients into prognostic subgroups. This may have influenced the statistical analyses.

Multivariable analysis showed that having an ECOG-PS score of ≥2 and being classified with ≥high risk according to the WPSS were independent predictors of MDS progression. Compared to the non-PG group, patients with progression had lower hemoglobin, monocyte, and platelet values, while BM blast percentage, transfusion need and ferritin levels were higher. In addition, the presence of dysplasia in more than one cell line was also found to be associated with progression. The development of different systems to predict the progression of MDS disorders, possibly with inclusion of genetic studies, will be beneficial to increase the accuracy of available classification systems, to determine the most appropriate and early treatment regimens, and ultimately, to improve survival.

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Corresponding author e-mail: gulturke@yahoo.com.tr

Orcid ID:
Emine Gültürk: 0000-0003-2836-6162

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Original Article

Opioid Administration for Mucositis-Related-Pain Using Patient Controlled Analgesia (PCA) Method is Associated with the Development of Early Posttransplant Complications

Mukozit İlişkili Ağrı için Hasta Kontrollü Analjezi Yöntemi Eşliğinde Uygulanan Opioid Tedavisinin Erken Dönem Nakil Komplikasyonları ile İlişkisi

Kübra Haşimoğlu Gürün[1], Zeynep Arzu Yeğin[2], Didem Akçalı[3], Zübeyde Nur Özkurt[2],
Oktay Tertemiz[3], Ferda Can[2], Asena Dikyar[2], Suzan Berkiten[2]

[1]Gazi University Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey
[2]Gazi University Faculty of Medicine, Department of Hematology, Ankara, Turkey
[3]Gazi University Faculty of Medicine, Department of Anesthesiology, Ankara, Turkey

ABSTRACT

Introduction: Mucositis is one of the major complications of allogeneic hematopoietic stem cell transplantation with myeloablative conditioning. Several measures have been developed to improve pain palliation and quality of life in transplant recipients. This study was performed to evaluate the association of opioid administration using patient controlled analgesia (PCA) method with early posttranplant complications.

Materials and Methods: Medical records of 452 patients [median age: 35(15-67) years, male/female: 285/167] were retrospectively reviewed.

Results: PCA was used in 157 patients (34.7%) for median 9(1-24) days. The proportion of patients who received myeloablative conditioning regimen was significantly higher in PCA+ group ($p<0.001$). Severe mucositis was more common in patients who required PCA administration ($p<0.001$). Total body irradiation ($p<0.001$) and methotreaxate prophylaxis ($p<0.001$) were more frequently used in PCA+ patients. Hypoxia, bleeding, sinusoidal obstruction syndrome, invasive fungal infections, neurotoxicity, hepatotoxicity and nephrotoxicity were significantly more common in PCA+ patients. Duration of hospitalization was significantly longer in PCA+ group ($p<0.001$).

Discussion: Opioid administration with PCA, which was more frequently used in patients who had myeloablative conditioning and mucositis, was found to be associated with the development of early posttransplant complications.

Keywords: Patient Controlled Analgesia; Myeloablative Conditioning; Mucositis; Allogeneic Hematopoietic Stem Cell Transplantation; Pain Palliation

ÖZET

Giriş: Mukozit, myeloablatif hazırlama rejimiyle allojeneik kök hücre nakli yapılan hastalarda gelişebilen önemli komplikasyonlardan biridir. Kök hücre nakil alıcılarında ağrı palyasyonu sağlamak ve yaşam kalitesini artırmak için farklı yöntemler geliştirilmiştir. Bu çalışmanın amacı, hasta kontrollü analjezi (HKA) yöntemi eşliğinde uygulanan opioid tedavisinin erken dönem nakil komplikasyonlarıyla ilişkisini araştırmaktır.

Gereç ve yöntemler: Toplam 452 hastanın [ortanca yaş: 35(15-67) yıl, erkek/kadın: 285/167] verileri geriye dönük olarak incelendi.

Bulgular: Hasta kontrollü analjezi 157 hastada (%34.7) ortanca 9(1-24) gün süreyle uygulandı. HKA+ grupta myeloablatif rejim uygulanan hasta sayısı anlamlı yüksekti ($p<0.001$). HKA gereksinimi olan hastalarda ağır mukozit gelişiminin daha sık olduğu gözlendi ($p<0.001$). Tüm beden ışınlaması ($p<0.001$) ve metotreksat kullanımı ($p<0.001$) HKA+ grupta daha sıktı. Hipoksi, kanama, sinuzoidal obstrüksiyon sendromu, invaziv fungal enfeksiyonlar, nörotoksisite, hepatotoksisite ve nefrotoksisite

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HKA+ grupta daha sık görüldü. Hastanede kalış süresi HKA+ grupta anlamlı uzun saptandı (p<0.001). **Tartışma:** Bu çalışmada, myeloablatif hazırlama rejimi uygulanan ve ağır mukozit gelişen hastalarda daha sık kullanılan HKA eşliğinde opioid uygulamasının erken dönem nakil komplikasyonlarıyla ilişkili olduğu gösterildi.

Anahtar kelimeler: Hasta Kontrollü Analjezi; Myeloablatif Hazırlama Rejimi; Mukozit; Allojeneik Kök Hücre Nakli; Ağrı Palyasyonu

Introduction

Allogeneic hematopoietic stem cell transplantation (alloHCT) is considered as a curative modality in the treatment of various hematological disorders. Despite favorable improvement in patient care and supportive measures, unacceptable morbidity and mortality rates remain a major problem in high risk patients. Although chronic graft versus host disease (GvHD) and relapse seem to be responsible for the long-term adverse outcomes, early posttransplant complications including mucositis, infection, acute GvHD and sinusoidal obstruction syndrome (SOS) may cause significant toxicity which may result in prolonged hospitalization and impaired quality of life [1-3].

Among a variety of transplant related factors which may increase the risk of periengraftment complications, the prominent role of conditioning regimen intensity should be pronounced in the development of severe mucositis and other complications due to endothelial dysfunction. Myeloablative conditioning (MAC) which contains high dose chemotherapy and/or radiotherapy has an adverse impact on rapidly dividing cells and may cause severe mucositis in the early posttransplant course. Approximately 75% of alloHCT recipients develop oral mucositis in the preengraftment phase of transplantation. The severity of mucositis is associated with the intensity of conditioning regimen as well as immunosuppressive medications which are used for GvHD prophylaxis such as methotrexate [4-7]. Oral nutrition may be impaired in these patients as a result of mucositis associated pain. Bacterial translocation and catheter related infections may develop in patients who require parenteral support because of oral nutrition impairment. Therefore, pain palliation including topical local anesthetics and systemic opioid analgesics is indispensable to maintain normal gastrointestinal function in order to accelerate the healing process of mucosal barriers and improve quality of life [7-9].

Patient controlled analgesia (PCA) is a pain relief method which enables self administration of the analgesic substance via intravenous bolus and/or infusion using a specific pump which is programmed by an expert, preferably by an anesthesiologist. Maximum drug dose, dose ranges and infusion rates can be individualized by this procedure. The total amount of opioid substance was shown to be significantly reduced in patients who receive PCA [8,10].

To our knowledge, the role of opioid administration via PCA method in the development of transplant complications has not been previously studied. Therefore, this retrospective study is performed to evaluate the effect of opioid use with PCA in the early posttransplant course and to clarify its possible association with transplant related complications and hospital stay.

Materials and Methods

Patients

A total of 452 patients [median age: 35(15-67) years, male/female:285/167] who underwent alloHCT between 2003 and 2018 were included in this study. Medical records of the patients were analyzed retrospectively. Demographic and clinical characteristics of the patients were recorded. Transplant risk assessments including European Society for Blood and Marrow Transplantation (EBMT) score and Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) were evaluated [11,12]. National Cancer Institute Common Toxicity Criteria (version 4) was used for toxicity assessments. Patient and transplant characteristics are represented in Table 1.

Pain Management and PCA Schedule

Pain scores of the transplant recipients, which range from 0 to 10 points (pts), were determined by numeric rating scale (NRS) [9,13]. Daily pain status of all patients was questioned and recorded by transplant nurses. Tramadol infusion with PCA was started when the pain score was greater than 3 pts. Tramadol was mixed with normal saline at a concentration of 5 mg/mL. Lockout time was identified as 30 minutes while 4-hour infusion limit was indicated to be 200 mL. Initial dose arrangements were 20 mg and 5 mg/mL for bolus and infusion rates, respectively. All steps of the setting, including basal and subsequent modifications, were adjusted by an anesthesiologist. In patients with a permanent pain score greater than 5 pts, which was considered as refractory to appropriate dose increments, intravenous morphine and/or transdermal fentanyl patch were used to support PCA infusion. Antiemetic drugs such as serotonin 5-HT3 antagonists or metoclopramide were used for PCA induced nausea and vomiting. PCA infusion was stopped in case of severe side effects including dizziness, confusion and hypoxemia.

Transplant Protocols

The criteria of the Centre for International Blood and Marrow Transplant Research (CIBMTR) was used for the classification of conditioning intensity [14]. Myeloablative conditioning regimens consisted total body irradiation (TBI) (1200 cGy)/ cyclophosphamide (120 mg/kg) or busulfex (12.8 mg/kg)/cyclophosphamide (120 mg/kg), whereas fludarabine (150 mg/m^2)/melphalan (140 mg/m^2) and TBI (400 cGy)/fludarabine (150 mg/m^2) were designated as reduced intensity conditioning (RIC) regimens. Cyclosporine A / methotrexate and cyclosporine A / mycofenolate mofetil combinations were used for GvHD prophylaxis in MAC and RIC transplants respectively.

Supportive Care

Standards for antibacterial and antifungal prophylaxis, febrile neutropenia, invasive fungal infections (IFI) and cytomegalovirus reactivation were assessed based on the European Conference on Infections in Leukemia (ECIL) and Infectious Diseases Society of America (IDSA) guidelines [15-17]. The diagnosis and grading of SOS was identified according to the EBMT guidelines [18].

Statistical Analysis

Categorical and continuous variables were represented as frequency (percentage) and median (range) respectively. Kolmogorov-Smirnov and Shapiro Wilk tests were performed for normality analysis with $p>0.05$ taken as evidence of normality. Parametric and non-parametric tests were used in case of normal and abnormal distributions. Continuous variables were compared using Student T-test, Mann Whitney U and Kruskal Wallis tests. Chi-square test was used for the comparison of categorical variables. Correlation analysis was performed using Pearson and Spearman tests. Kaplan-Meier method was used for survival analysis and log rank test for the comparisons of Kaplan-Meier curves. Cox proportional hazards regression model with the calculation of HRs and 95% confidence intervals (CI) was used for univariate and multivariate analysis in order to determine statistically significant prognostic factors. IBM SPSS Statistics Version 22.0 (IBM Corp, Armonk, NY, USA) programme was used for statistical analysis. All P values were two-sided and $P<0.05$ was considered as statistically significant.

Ethical Standards

The study was approved by the institutional review board of Gazi University Faculty of Medicine (Date: 11.06.2018; Number: 449) All procedures in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Table 1. Patient and Transplant Characteristics

Age (years) [median (range)]	35 (15-67)
Gender (male/female) [n(%)]	285 (63.1) / 167 (36.9)
Diagnosis [n(%)]	
Acute myeloid leukemia	169 (37.4)
Acute lymphoblastic leukemia	109 (24.1)
Myelodysplastic syndrome	29 (6.4)
Non Hodgkin lymphoma	32 (7.1)
Hodgkin lymphoma	19 (4.2)
Multiple myeloma	25 (5.6)
Chronic lymphocytic leukemia	2 (0.4)
Chronic myeloid leukemia	14 (3.1)
Primary myelofibrosis	10 (2.2)
Aplastic anemia	34 (7.5)
Paroxysmal nocturnal hemoglobinuria	5 (1.1)
Thalassemia major	4 (0.9)
Pretransplant Disease Status (n=378) [n(%)]	
Complete remission	262 (69.3)
Partial remission	33 (8.7)
Progressive disease / Relapse	66 (17.5)
Primary refractory	15 (4)
Stable disease	2 (0.5)
ECOG Performance Status [median (range)]	1 (0-4)
HCT-CI [median (range)]	1 (0-6)
EBMT Score [median (range)]	3 (0-7)
HLA Compatibility [n(%)]	
Matched sibling	365 (80.8)
Mismatched related	14 (3.1)
Unrelated	71 (15.7)
Haploidentical	2 (0.4)
Graft Source [n(%)]	
Peripheral blood	429 (94.9)
Bone marrow	23 (5.1)
Conditioning Regimen [n(%)]	
Myeloablative	276 (61.1)
Reduced intensity	176 (38.9)
Total Body Irradiation [n(%)]	109 (24.1)
GvHD Prophylaxis [n(%)]	
Cyclosporine A–methotreaxate	379 (83.8)
Cyclosporine A–mycophenolate mofetil	73 (16.2)
Infused $CD34^+$ Cell Count ($x10^6$/kg) [median (range)]	4.2 (0.3-9.5)
Neutrophil Engrafment (days) [median (range)]	17 (7-43)
Platelet Engraftment (days) [median (range)]	15 (0-89)
Total Parenteral Nutrition [n(%)]	194 (42.9)
Duration of parenteral nutrition (days) [median (range)]	10 (2-46)
Sinusoidal Obstruction Syndrome [n(%)]	97 (21.5)
Grade [median (range)]	2 (1-3)
Thrombotic Microangiopathy [n(%)]	4 (0.9)
Duration of Febrile Neutropenia (days) [median (range)]	3 (0-52)
Septic Shock [n(%)]	35 (7.7)
Invasive Fungal Infection [n(%)]	116 (25.7)
Mechanical Ventilation [n(%)]	52 (11.5)
Pain Score [median (range)]	6 (0-10)
PCA Administration [n(%)]	157 (34.7)
Duration of PCA (days) [median (range)]	9 (1-24)
Duration of Hospitalization (days) [median (range)]	31 (9-130)

EBMT European Society for Blood and Marrow Transplantation; ECOG Eastern Cooperative Oncology Group; GvHD Graft versus Host Disease; HCT-CI Hematopoietic Cell Transplantation Comorbidity Index; PCA Patient Controlled Analgesia

Results

Median pain score was indicated to be 6(0-10) pts in the whole study population. Patient controlled analgesia was used in 157 patients (34.7%) for median 9(1-24) days. A total of 118 patients (75.2%) were diagnosed as acute leukemia in PCA+ group.

Patient controlled analgesia requirement was observed to be significantly predominant in acute leukemia patients (P<0.001). Furthermore, PCA was more commonly used in patients who received TBI (P<0.001) and cyclosporine A-methotrexate as GvHD prophylaxis (P<0.001). Patients who developed SOS (P<0.001), febrile neutropenia (P<0.001) and IFIs (P<0.001) required significantly more PCA support.

Comparison of PCA+ and PCA- Groups

Based on PCA administration, the study population was seperated into two subgroups, each of which implicates PCA+ (n=157, 34.7%) and PCA- (n=295, 65.3%) patients. Median pain score was significantly higher in PCA+ group compared to PCA- group [8(0-10) vs 4(0-10) pts; P<0.001)]. Patients in PCA+ group were found to be younger than PCA- patients [29(16-65) vs 38(15-67) years; P<0.001] which may be associated with the predominance of acute leukemia patients in PCA+ group who were frequently exposed to MAC regimens. Thus, the proportion of patients receiving MAC in PCA+ group was found to be significantly higher compared to PCA- group (79% vs 51.5%, P<0.001). Patient controlled analgesia was administered in 44.9% of the patients who received MAC regimen and 18.9% of the patients who had RIC (P<0.001). Total body irradiation (42.7% vs 14.2%; P<0.001) and methotreaxate prophylaxis (97.5% vs 76.6%; P<0.001) were observed to be more frequently used in PCA+ patients. Neutrophil [17(10-43) vs 16(7-29) days; P<0.001] and platelet engraftments [16.5(0-89) vs 14(0-64) days; P<0.001] occured later in PCA+ group compared to PCA- group. Total parenteral nutrition (TPN) was extensively used in PCA+ patients (76.4% vs 24.8%; P<0.001). Duration of febrile neutropenia was significantly longer [(5(0-52) vs 3(0-28) days; P<0.001] and IFIs were found to be more frequent in PCA+ group [38.2% vs 20%; P<0.001)]. Similarly, incidence of SOS was indicated to be higher in patients who received PCA [36.3% vs 13.6%; P<0.001]. Duration of hospitalization was recorded to be significantly longer in PCA+ patients [32(16-130) vs 29(9-94) days, P<0.001) (Table 2).

Conditioning regimen and transplant related toxicities including hypoxia (p=0.032), bleeding (P<0.001), neurotoxicity (P=0.003), hepatotoxicity (P=0.001) and nephrotoxicity (P=0.033) were observed to be more common in PCA+ patients. Table 3 represents the comparison of toxicity profiles between two groups.

Subgroup Analysis Based on Pain Status

The study cohort was further divided into two distinct subgroups based on the severity of pain, such as “mild-to-moderate” and “severe”. Maximum pain score ≥7 pts was classified as “severe” pain, whereas pain score <7 pts was referred to “mild-to-moderate” pain. Acute leukemia diagnosis (P<0.001), MAC (P=0.005) and TBI administration (P<0.001) were more frequently observed in the severe-pain group.

Survival Analysis and Prognostic Factors

Probability of overall survival (OS) was estimated to be 35.5% in the whole population at the end of 539(1-5435) days of follow-up. Probability of OS was not different between PCA+ and PCA- groups (33.2% vs 37.7%) (P>0.05) (Figure 1).

Factors which had a significant impact on OS in univariate analysis are represented in Table 4. Eastern Cooperative Oncology Group (ECOG) performance status [P<0.001; HR: 3.869 (95% CI: 1.849-8.098)], EBMT risk score [P=0.022; HR: 1.222 (95% CI: 1.029-1.451)], duration of febrile neutropenia [P=0.005; HR: 1.110 (95% CI: 1.032-1.193)], hypoxia [P=0.031; HR: 1.372 (95% CI: 1.029-1.830)] and nephrotoxicity [P<0.001; HR: 2.494 (95% CI: 1.566-3.972)] were indicated to be significant prognostic factors in multivariate analysis.

Table 2. Distribution of Comparative Variables among PCA$^+$ and PCA$^-$ Groups

	PCA$^+$ Group n=157	PCA$^-$ Group n=295	*P* Value
Age (years) [median (range)]	29 (16-65)	38 (15-67)	<0.001
Neutrophil Engraftment (days) [median (range)]	17(10-43)	16 (7-29)	<0.001
Platelet Engraftment (days) [median (range)]	16.5 (0-89)	14 (0-64)	<0.001
Red Blood Cell Transfusion (units) [median (range)]	4 (0-50)	3 (0-33)	0.005
Platelet Transfusion (units) [median (range)]	6 (0-75)	4 (0-63)	<0.001
Duration of Febrile Neutropenia (days) [median (range)]	5(0-52)	3(0-28)	<0.001
Duration of Hospitalization (days) [median (range)]	32 (16-130)	29 (9-94)	<0.001
Maximum Pain Score (points) [median (range)]	8 (0-10)	4 (0-10)	<0.001
Myeloablative Conditioning Regimen [n(%)]	124 (79)	152 (51.5)	<0.001
Total Body Irradiation [n(%)]	67 (42.7)	42 (14.2)	<0.001
Methotrexate Administration [n(%)]	153 (97.5)	226 (76.6)	<0.001
Sinusoidal Obstruction Syndrome [n(%)]	57 (36.3)	40 (13.6)	<0.001
Total Parenteral Nutrition [n(%)] Duration of parenteral nutrition (days) [median (range)]	120 (76.4) 11 (2-46)	73 (24.8) 8 (2-32)	<0.001 0.031
Invasive Fungal Infection [n(%)]	60 (38.2)	59 (20)	<0.001

Table 3: Comparison of Toxicity Profiles between PCA$^+$ and PCA$^-$ Groups Based on NCI Common Toxicity Criteria

	PCA$^+$ Group (n=157)	PCA$^-$ Group (n=295)	*P* Value
Mucositis [median (range)]	4 (0-4)	1 (0-4)	<0.001
Febrile Neutropenia [median (range)]	2 (0-4)	2 (0-4)	<0.001
Infection [median (range)]	3 (0-4)	3 (0-4)	<0.001
Nausea [median (range)]	1 (0-3)	0 (0-3)	0.01
Vomiting [median (range)]	2 (0-4)	1 (0-4)	0.01
Diarrhea [median (range)]	1 (0-4)	0 (0-4)	<0.001
Constipation [median (range)]	0 (0-4)	0 (0-3)	0.001
Hypoxia [median (range)]	0 (0-4)	0 (0-4)	0.03
Bleeding [median (range)]	0 (0-4)	0 (0-2)	<0.001
Neurotoxicity [median (range)]	0 (0-3)	0 (0-3)	0.003
Hepatotoxicity [median (range)]	1 (0-4)	0 (0-3)	0.001
Nephrotoxicity [median (range)]	0 (0-4)	0 (0-4)	0.03

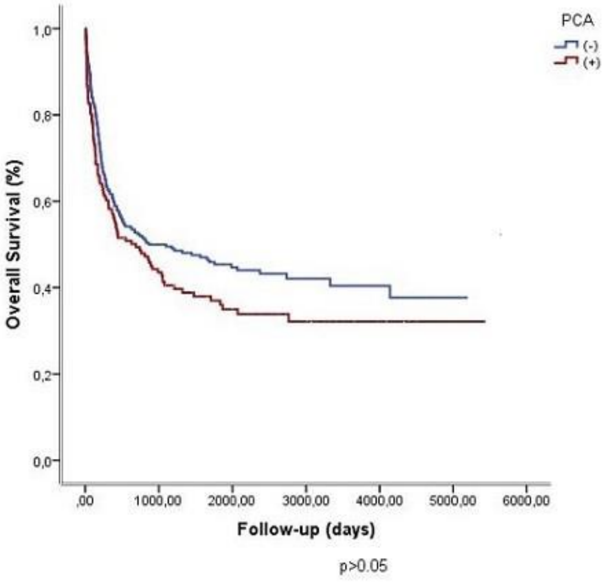

Figure 1. Probability of Overall Survival in PCA$^+$ and PCA$^-$ Groups (33.2% vs 37.7%) (p>0.05)

Table 4. Prognostic Risk Factors for Survival in Univariate Analysis

Risk Factors	*P* Value	Hazard Ratio	95% Confidence Interval
Pretransplant disease status	<0.001	1.44	1.28-1.62
ECOG performance status	<0.001	2.57	2.01-3.3
EBMT score	<0.001	1.26	1.12-1.43
Mismatched donor	0.02	1.46	1.05-2.02
Pretransplant CRP	<0.001	1.00	1.00-1.01
Pretransplant ferritin	<0.001	1.00	1.00-1.00
ATG for GvHD prophylaxis	0.03	0.6	0.39-0.94
Sinusoidal obstruction syndrome	<0.001	2.15	1.64-2.83
Defibrotide treatment for SOS	<0.001	1.46	1.27-1.69
Thrombotic microangiopathy	0.04	2.78	1.03-7.49
Infused CD34$^+$ cell count	0.04	0.89	0.81-0.99
Red blood cell transfusion	<0.001	1.04	1.02-1.05
Platelet transfusion	<0.001	1.02	1.01-1.03
Total parenteral nutrition	<0.001	1.82	1.43-2.33
Mucositis	<0.001	1.16	1.07-1.27
Febrile neutropenia	0.002	1.29	1.10-1.51
Duration of Febrile Neutropenia	<0.001	1.04	1.02-1.05
Infection	<0.001	1.26	1.12-1.43
Invasive fungal infection	<0.001	1.52	1.27-1.82
Diarrhea	0.02	1.13	1.02-1.26
Hypoxia	<0.001	1.57	1.45-1.71
Bleeding	0.002	1.38	1.12-1.70
Pscycological toxicity	<0.001	1.42	1.18-1.71
Neurotoxicity	0.02	1.46	1.06-2.02
Hepatotoxicity	<0.001	1.4	1.24-1.59
Nephrotoxicity	<0.001	1.72	1.55-1.92

ATG Anti-thymocyte Globulin; CRP C Reactive Protein; ECOG Eastern Cooperative Oncology Group; EBMT European Society for Blood and Marrow Transplantation; GvHD Graft versus Host Disease; SOS Sinusoidal Obstruction Syndrome

Discussion

In this study, the potential role and tolerability of opioid administration for mucositis-related-pain were investigated in a retrospective cohort of alloHCT recipients. Intensive conditioning, TBI administration and methotrexate use were shown to potentiate opioid requirement. Febrile neutropenia, IFIs and SOS were found to be more common in patients who received opioids with PCA. Discharge from hospital was delayed in the same group of patients. Early complications including hypoxemia, neurotoxicity, hepatotoxicity and nephrotoxicity were more frequently observed in PCA+ patients. Opioid administration with PCA did not represent a significant impact on OS.

Conditioning regimen is one of the most important factors for the development of mucositis in the early course of alloHCT. The intensity of the preparative regimen has a direct impact on epithelial cell damage [5-7]. Eduardo et al showed that myeloablative doses of busulfan may result in more frequent and long lasting mucositis [19]. Current study confirms and underlines the association of the conditioning regimen with the severity of mucositis and mucositis associated pain. As mucositis was more severe in patients who received MAC regimen, opioid and TPN requirement were more frequent in the same group of patients as expected. The frequency and grade of mucositis were found to be higher in patients who received methotrexate for GvHD prophylaxis. Leucovorine, which was not routinely used in our patients, was shown to shorten the duration of mucositis, neutrophil engraftment and hospital stay in previous reports [4,20]. Methotrexate may also prolong the healing process of mucositis in these patients [4,6,7,21]. In our study, patients who received methotrexate represented an increased requirement for opioid support which was potentially attributed to severe mucositis. Therefore, less toxic regimens for conditioning and GvHD prophylaxis may help to reduce the frequency and severity of mucositis, as well as opioid requirement.

Total body irradiation has a significant role in early transplant related complications including mucositis [6,21-23]. In a study by Anand et al, the incidence and severity of mucositis were reduced in patients who received low dose TBI. In addition, TPN and opioid analgesics were more frequently used in patients with severe mucositis. Duration of hospitalization was significantly longer in the same group of patients [21]. In our study, opioid administration was more common in patients who were treated with TBI, independent from the dosing schedule. Similarly, the duration of TPN was significantly longer in PCA+ group. As maintenance of enteral nutrition is essential for the prevention of TPN related complications, appropriate and effective pain palliation can be lifesaving in these circumstances [4,7,21,23].

The association of age and mucositis was pronounced in several studies indicating that mucositis may be more severe and prolonged in younger patients which is also confirmed in the present study [1,24]. Nevertheless, this association was mainly attributed to the predominant use of MAC regimens in young and fit patients. On the contrary, as RIC regimens are generally preferred in relatively fragile elderly population with comorbidities, early transplant complications due to conditioning toxicity are expected to be lower in this group of patients.

Infections are important causes of non relapse mortality in the early posttransplant course. Delayed engraftment, which was also found to be associated with severe mucositis in the present study, may have a major role in the development of severe infections. Studies have shown that infectious morbidity was higher in patients with severe mucositis in concordance with our results which underline the potential intercourse between neutrophil engraftment and recovery of mucositis. In the present study, SOS was also found to be more frequent in patients who received opioids with PCA. Intensive conditioning regimens may cause a significant tendency for the development of preengraftment complications including mucositis and SOS, since they share a similar etiopathology mainly based on endothelial cell damage [2,3,25,26].

On the other hand, the association of opioid administration and early transplant toxicities including hypoxia, bleeding, neurological, hepatic and renal complications, may be attributed to the underlying conditions and comorbidities which may generate an additional risk for the development of severe toxicities. Nevertheless, transplant physicians should be aware of the potential drug side effects and/or interactions although average opioid dose is considered to be relatively lower and tolerable with PCA than standard methods [2,7,27].

Several studies have shown that hospitalization may be prolonged in patients with severe mucositis [10,25,28]. In a study by McCann et al, the length of hospital stay was found to be associated with a variety of factors including age, poor performance status, severe mucositis and delayed neutrophil engraftment [25]. Vera-Llonch et al demonstrated a significant relationship between the severity of mucositis and the length of hospital stay [28]. In concordance with these previous reports, duration of hospitalization was also found to be significantly longer in PCA+ group in the present study, which may be associated with the higher frequency of transplant related complications in this group, such as prolonged mucositis.

Although there are several reports which represented the prognostic impact of mucositis in transplant candidates, any significant association of mucositis with OS was not shown in the present study [5,29]. Mucositis was indicated to be a significant prognostic factor in univariate analysis, however the significance was not confirmed in multivariate analysis. Despite relatively large cohort of patients included, heterogeneity of the study population may be a potential explanation for the lack of survival effect.

Despite the association of opioid administration with serious posttransplant complications, any significant impact of opioid use on OS was not demonstrated. This fact may draw attention to a potential additive role of opioid administration on transplant complications rather than being the primary underlying cause. Nevertheless, multifactorial nature of the milieu, as well as complex microenvironmental background, should also be taken into account in order to generate a more global and accurate vision for the development of posttransplant toxicities.

Based on the presented results, early and prompt treatment of mucositis and optimal supportive care including maintenance of oral hygiene, local and systemic measures for pain palliation, may prevent consecutive associated complications and improve quality of life in the early posttransplant setting. Reduced intensity conditioning, fractionated and low dose TBI, less toxic regimens for GvHD prophylaxis and integration of new therapeutic approaches which may overcome or compensate drug side effects may not only prevent mucositis and related complications, but also reduce the necessity for further recovery attempts.

In conclusion, opioid administration with PCA may be considered as an easy, safe and humanistic procedure with a tolerable side effect profile compared to its alternatives, particularly in patients who are exposed to intensive regimens and predicted to have a tendency for severe transplant related complications. The intensity of the conditioning should be determined based on a highly selected list of contributing factors including patient, disease and transplant characteristics. In consideration with its potential toxicity profile, pain palliation with PCA remains to be a privileged attempt to improve patient's quality of life in the early posttransplant course.

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Corresponding author e-mail: zeyneparzuyegin@gmail.com

Orcid ID:
Kübra Haşimoğlu Gürün 0000-0002-0110-4325
Zeynep Arzu Yeğin 0000-0002-0212-9663
Didem Akçalı 0000-0003-3590-5531
Zübeyde Nur Özkurt 0000-0001-9834-6058
Oktay Tertemiz 0000-0002-6131-1756
Ferda Can 0000-0002-9899-1441
Asena Dikyar 0000-0002-9108-876X
Suzan Berkiten 0000-0001-7226-4636

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Original Article

Relationship Between Staging FDG PET/CT Findings and Distribution of Metastatic Sites in Metastatic Breast Cancer

Metastatik Meme Kanserinde Evreleme FDG PET/BT Bulgularının Metastatik Bölge Dağılımı ile İlişkisi

Bedriye Büşra Demirel, Seda Gülbahar Ateş, Hüseyin Emre Tosun, Süleyman Aksu, Gülin Uçmak

Ankara Oncology Research and Training Hospital, Department of Nuclear Medicine, Ankara, Turkey

ABSTRACT

Introduction: We aimed to investigate the relationship between staging FGD PET/CT findings and metastasis distribution and histopathological features of primary tumor in patients with metastatic breast cancer at diagnosis time.

Materials and Methods: Eighty patients with breast cancer who underwent F-18 FDG PET/CT for staging were included. The patients with newly diagnosed metastatic disease were included. Age and histopathological features of the primary tumor were recorded. The distant metastases sites, the numbers of metastasis and metastatic axillary/non-axillary lymph nodes were reviewed from PET/CT. The maximum standardized uptake(SUVmax) values were measured.

Results: All patients(n:80,mean age 58.0±14.4) had invasive breast carcinoma. Age was significantly related to the presence of lung metastases(p=0.006, mean ages 54y vs 64y).Only liver metastasis had a significant relationship with primary tumor SUVmax values and tumor molecular profile. The patients with HR+/HER2- (7/60 patients, 11.7%) had relatively less liver metastasis than with the other subtypes (9/20patients, 45%). There were significant associations between SUVmax of axillary lymph node(p=0.02), primary tumor(p=0.001), liver metastasis(p=0.02) and tumor subtypes. The numbers of distant metastasis were related with the numbers of axillary lymph node metastasis(p=0.02) and the highest SUVmax of distant metastasis(p=0.001).

Discussion: Accurate detection of distant metastases in breast cancer at the time of diagnosis is of great importance in terms of treatment planning and prognosis of the disease. FDG PET/CT is a very reliable modality in determining distant metastasis and their distribution, and as a result of our study, we suggest that PET/CT findings can predict factors with prognostic importance.

Keywords: breast cancer, metastasis, 18f fluorodeoxyglucose positron-emission tomography, cancer staging

ÖZET

Giriş: Tanı anında metastatik meme kanserinde evreleme FDG PET/BT bulgularının metastaz dağılımları ve tümör histopatolojik özellikleri ile ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Meme kanseri tanısıyla bölümümüzde evreleme FDG PET/BT görüntülemesi yapılan 80 hasta çalışmaya dahil edildi. Daha önce tedavi almamış hastalar çalışmaya alındı. Yaş, primer tümörün histopatolojik özellikleri geriye dönük olarak kaydedildi. Uzak metastaz alanları, metastaz odak sayıları, aksilla-aksilla dışı metastatik lenf nodlarıi PET/BT görüntülerinden tarandı. Standart maksimum tutulum (SUVmaks) değerleri hesaplandı.

Bulgular: Tüm hastalar (n:80, ort. Yaş 58.0±14.4) invaziv meme kanseri tanılı idi. Hasta yaşı akciğer metastazı ile ilişkiliydi (p=0.006, ort yaşlar 54, 64). Uzak metastaz alanlarından sadece karaciğer metastazının primer tümör SUVmaks değeri ve tümör moleküler profili ile ilişkisi olduğu gösterildi. Karaciğer metastaz sıklığı HR+/HER2- olan hastalarda (7/60, %11.7) diğer tümör subtipleri (9/20, %45) olanlara göre daha düşüktü. Primer tümör (p=0.001), aksilla lenf nodu(p=0.02) ve karaciğer metastaz(p=0.02) SUVmaks değerleri ile tümör subtipleri arasında anlamlı ilişki gözlendi. Uzak

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metastaz alan sayısı ile metastatik aksiller lenf nodu sayısı (p=0.02) ve en yüksek uzak metastaz SUVmaks değeri (p=0.001) arasında anlamlı ilişki gözlendi.
Tartışma: Meme kanserinde tanı anında metastaz varlığının doğru olarak saptanmasının tedavi planı ve hastalığın seyri açısından önemi büyüktür. FDG PET/BT uzak metastazı ve hatta dağılımını belirlemede oldukça güvenilir bir modalite olup, çalışamamız sonunda FDG PET/BT bulgularının prognostik öneme sahip faktörleri öngörebileceğini düşünmekteyiz.

Anahtar kelimeler: meme kanseri, metastaz, f18 florodeoksiglukoz positron-emisyon tomografi, kanser evreleme

Introduction

Breast cancer is the most commonly diagnosed cancer accounting for 29% of all newly diagnosed cancers and the major cause for the death of women worldwide [1,2]. About 6% of breast cancer patients have metastatic disease at presentation [3]. The five-year relative survival rate of patients diagnosed with distant metastasis is significantly less than that of patients with early-stage disease at the time of diagnosis [4].The median five-year survival of metastatic breast cancer patients is only 33.8% [5].Despite advances in the current treatments for metastatic breast cancer that based on a strategy of systemic chemotherapy, endocrine or HER2-targeted therapy (depending on estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor type-2 [HER2]status), and palliative therapies, there are no specific standard-of-care therapeutic strategies indicated for patients with organ-specific metastases [6,7].

Precise evaluation of disease extent is quite essential for metastatic breast cancer patients before determining treatment strategy.18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography(PET/CT) has been widely used in various malignant diseases for initial stage, disease extent assessment, therapy response assessment, metastasis detection and prognosis prediction[8].FDG-PET/CT has shown high accuracy in detecting distant metastases and also, it allows on a single “whole-body” examination to assess for locoregional as well as distant metastases with a high positive predictive value [9,10].The maximum standardized uptake (SUVmax) value of 18F-FDG is useful for diagnosing high-grade malignancy and predicting the prognosis in breast cancer patients. It was reported that SUVmax and the HR status were useful for predicting malignancy grades and prognosis of patients with breast cancer [11].

We aimed to investigate whether pretreatment FDG PET/CT findings are related to metastatic sites distribution and histopathological features of the primary tumor, and whether SUVmax values may be associated with primary tumor molecular profile for breast cancer patients with metastatic disease at presentation.

Material and Methods

Eighty patients with breast cancer who underwent F-18 FDG PET/CT for staging in our department were included in the retrospective study. The inclusion criteria were newly diagnosed metastatic breast cancer that are not previously treated for metastatic disease and at least one visible lesion as metastatic with positive FDG uptake. Patients with prior excisional biopsy of breast, patients without distant metastasis and patients with second primary malign disease were excluded from the study.

This study adheres to the ethical principles of the Declaration of Helsinki and was approved by the ethics committee of our institution (2022-09/168).

Age and histopathological features of the primary tumor such as grade, hormone receptor (HR), human epidermal growth factor receptor type-2 (HER2) status and Ki-67 index were recorded from the institution patient information system, retrospectively.

PET/CT Acquisition and Imaging Analysis

Patients were imaged on an integrated PET/CT scanner (Siemens Biograph 6-True Point PET/CT systems). Patients were fasted for at least 6 hours prior to injection of 90µCi/kg 18F-FDG by using automatic infusion system (Intego PET Infusion System). The blood glucose levels were less than 150 mg/dl in all patients at the time of the FDG injection. Unenhanced CT images were acquired for attenuation correction from the vertex of the skull to distal thigh using 3 mm slice thickness and calculated effective mAs due to patient weight. The PET and CT images were reviewed on a workstation (Syngovia, Siemens Medical Solutions) in all standard planes along with maximum-intensity-projection images and were visually and quantitatively by two specialists experienced in interpreting PET/CT scans.

According to PET/CT findings; The sites of distant metastasis, the numbers of metastatic site, the numbers of metastatic axillary lymph node, the presence of retropectoral, internal mammarian and supraclavicular lymph nodes, T and N stages were recorded. The size of primary tumor and the size of enlarged axillary lymph node were measured. The maximum standardized uptake (SUVmax) values of primary tumor, axillary and non-axillary lymph nodes, each site of distant metastasis were measured by drawing of region of interest (ROI). To provide the most accurate measurement of SUV, voxels were created large enough to maintain tumor inside the boundaries.

Statistical Analysis

The statistical analysis was performed using commercial software (SPSS 21.0, IBM SPSS Statistics for Windows, Version 21.0. Armonk NY: IBM Corp.). The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Descriptive analyses were presented using frequencies for the ordinal/nominal variables and medians, minimum, and maximum values for the non-normally distributed variables. Kruskal-Wallis tests were conducted to compare the parameters and tumor molecular profiles, and metastatic sites distribution. The Mann-Whitney U test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. The Chi-square test or exact method, where appropriate, was used to compare the proportions in different groups. An overall 5% type-1 error level was used to infer statistical significance.

Results

Patient characteristics are listed in Table 1.

The mean age of patients was 58.0±14.4 with a range of 23-90 years. All patients had invasive carcinoma.

Axillary lymph node metastasis was observed in 75 (93.8%) patients, followed by retro-pectoral lymph node metastasis in 58 (72.5%) patients.

Bone metastasis was seen as the most common distant metastasis site with a rate of 83.8% (n:67), followed by mediastinal lymph node (43.8%), lung (33.8%), and liver metastasis (20.0%), respectively.

The numbers of distant metastasis were>10 in 45 (56.2%) patients, and 5-10 in 15 (18.8%) patients and <5 in 20 (25%) patients.

We did not observe significant difference between the presence of bone metastasis and primary tumor SUVmax (p=0.55) and axillary lymph node SUVmax (p=0.75), the number of metastatic axillary lymph node (p=0.1). There was significant association between bone metastasis and the presence of retropectoral lymph node metastasis (p=0.03).Fifty-two (89.7%) of 58 patients with retropectoral lymph node metastasis had bone metastases.

We found that the patients with liver metastasis had a higher primary tumor size (median 33.0 mm vs 52.5 mm p=0.04), primary tumor SUVmax (median 10.1 vs 15.8 p=0.012), and Ki-67 index (median 30% vs 40% p=0.004) (Table 2). There was statistically significant difference between the presence of liver metastasis and the status of PR (p<0.001), ER (p=0.003), and HER2

Table 1. Patient Characteristics

Characteristics			
Age, years (mean)			58.0±1.6
Primary tumor size (mm) (median)			34 (9-134)
Primary tumor	Grade (N, %)	1	4 (5.2%)
		2	42 (54.5%)
		3	31 (40.3%)
	ER (N, %)	Positive	70 (87.5%)
		Negative	10 (12.5%)
	PR (N, %)	Positive	64 (80%)
		Negative	16 (20%)
	HER2 (N, %)	Positive	15 (18.8%)
		Negative	65 (81.3%)
	HR+/HER2- (N, %)		60 (75%)
	HR+/HER2+ (N, %)		10 (12.5%)
	HR-/HER2+ (N, %)		5 (6.3%)
	HR-/HER2- (N, %)		5 (6.3%)
	Ki-67 (%) (median)		30 (5-90)
Number of axillary metastatic lymph nodes (median)			6 (1-20)
Size of axillary metastatic lymph nodes (mm) (median)			13 (2-45)
Number of local metastatic lymph nodes (N, %)	Axillar lymph node		75 (93.8%)
	Inter-pectoral lymph node		27 (33.8%)
	Retro-pectoral lymph node		58 (72.5%)
	Internal mammarian lymph node		14 (17.5%)
	Infra-clavicular lymph node		14 (17.5%)
	Supra-clavicular lymph node		19 (23.8%)
T Stage (N, %)	T1		6 (7.5%)
	T2		27 (33.8%)
	T3		4 (5%)
	T4		43 (53.8%)
N Stage (N, %)	N0		5 (6.3%)
	N1		40 (50%)
	N2		6 (7.5%)
	N3		29 (36.3%)
Number of distant metastases (N, %)	<5		20 (25%)
	5-10		15 (18.8%)
	>10		45 (56.2%)
Sites of distant metastases (N, %)	Contralateral axillar and/cervical lymph node node		20 (25%)
	Mediastinal lymph node		35 (43.8%)
	Abdominal lymph node		10 (12.5%)
	Lung		27 (33.8%)
	Liver		16 (20%)
	Bone		67 (83.8%)
	Others (soft tissue, adrenal, pleura)		6 (7.5%)

ER, estrogene receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor type-2.

Table 2. Association between primary tumor SUVmax, histopathological features of primary tumor and the presence of liver metastasis

	Liver metastasis		P value
	Negative	Positive	
Primary tumor size (mm)	39.7±21.7 33.0 (9.0-98.0)	57.2±33.1 52.5 (21.0-134.0)	p=0.04*
Primary tumor SUVmax	10.8±5.4 10.1 (1.09-33.3)	15.6±6.9 15.8 (5.6-27.2)	p=0.01*
Ki-67 index (%)	33.1±19.0 30.0 (5.0-90.0)	48.1±19.0 40.0 (25.0-80.0)	p=0.004*

*p value <0.05 was regarded as significant

(p=0.04) receptors and the presence of abdominal lymph node metastasis (p=0.003). The patients with HR+/HER2- (7 of 60 patients, 11.7%) had relatively less liver metastasis than with the other molecular profiles (9 of 20 patients, 45%). Also, it was demonstrated that there were significant associations between axillary lymph node SUVmax (p=0.02), primary tumor SUVmax (p=0.001), liver metastasis SUVmax (p=0.02) and tumor molecular profiles (Table 3). In the statistical sub-analysis, the primary tumor SUVmax of the patients with HR+/HER2- were significantly lower than patients with HR+/HER2+ (p=0.007), and patients with HR-/HER2+ or triple negative (p=0.006). Moreover, liver metastasis SUVmax values of patients with HR-/HER2+ or triple negative were higher than patients with HR+/HER2- (p=0.008).

As a result of the study, it was shown that the presence of lung metastases was significantly related to the patient age (p=0.006, mean ages 54.5 y vs 64.5 y). Moreover, there was a significant association between lung metastasis and mediastinal lymph node metastasis (p=0.02).

We observed that the numbers of distant metastasis related with the numbers of axillary lymph node metastasis (p=0.02) and the highest SUVmax of distant metastasis (p=0.001). In the statistical sub-analysis, in the patients with <5 distant metastases the highest SUVmax of distant metastasis was significantly lower than in the patients with >10 distant metastases (p<0.001, median 8.9 vs 13.9).

Discussion

FDGPET/CT has proven to be an effective imaging modality for detecting distant metastases in the initial staging of breast cancer [10,12]. In our study, we investigated the association of initial staging PET/CT findings and tumor histopathological features with metastatic sites distributions in newly diagnosed breast cancer patients with distant metastasis.

As stated in previous studies, PET/CT is more sensitive and more specific than conventional imaging modalities such as contrast-enhancement CT or bone scan to detect lytic or mixed bone metastases, or bone marrow involvement [13,14]; and by careful reading of the CT-scan data PET/CT can help to detect osteoblastic metastases because of variable FDG uptake [15]. Most recently, a National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database analysis indicated that specifically, the incidence of bone metastasis is highest inluminal subtypes. Furthermore, the study

Table 3. Association between tumor molecular subtypes and SUVmax

		SUVmax	
Primary tumor	HR+/HER2-	(10.5±5.8) 9.6 (1.1-33.3)	p=0.001*
	HR+/HER2+	(14.5±3.4) 15.5 (10.0-20.2)	
	HER2+ or triple negative	16.6±6.5 15.8 (7.6-27.2)	
Axillary lymph node metastasis	HR+/HER2-	8.5±5.6 7.2 (1.3-29.0)	p=0.02*
	HR+/HER2+	13.0±5.2 12.7 (6.3-21.0)	
	HER2+ or triple negative	12.0±5.9 13.2 (4.5-22.1)	
Liver metastasis	HR+/HER2-	8.0±2.4 8.0 (4.4-12.3)	p=0.02*
	HR+/HER2+	11.3±1.1 11.9 (10.1-12.0)	
	HER2+ or triple negative	13.7±4.5 12.3 (9.5-21.0)	

HR, Hormone receptor; HER2, human epidermal growth factor receptor type-2
*p<0.05 was regarded as significant

revealed that all breast cancers regardless of subtype, were prone to metastasize to bone over other locations [16]. A recent study which examined HER2+ patient data deposited within the SEER database, uncovered that breast cancers which are HR+/HER2+ are significantly more likely to metastasize to the bone when compared to HR−/HER2+ disease, and that patients with HR−/HER2+ disease have a worse overall prognosis than those with HR+, HER2+ malignancy [16]. At the current study, bone metastasis was the most common distant metastasis detected by PET/CT. We did not find association with bone metastasis and findings derived from PET/CT and tumor histopathological features. We observed that bone metastasis is more common in those with only the presence of retropectoral lymph node metastasis.

We defined that lung metastasis as the third most common distant metastasis site is associated with the presence of second most common site mediastinal lymph node metastasis and advanced age. The mean age of patients without lung metastases was 54 years, while the mean age of patients with lung metastases was 64 years. To the results of studies, triple-negative and basal-like disease is more likely than other types of breast cancer to metastasize to the lungs [18], and patients with triple negative, especially basal-like type, primarily presented with lung metastasis. However, there was no difference in the total probability of lung metastasis across all subtypes [16]. We also did not find any relationship between lung metastasis and primary tumor histopathological features and PET/CT findings (such as primary tumor SUVmax, axillary lymph node SUVmax) in our study. The reason for this result may be due to the fact that the number of triple negative patients is less than the patients with HR+/HER2-.

Prognosis is poor in breast cancer with liver metastasis, with median survival time being 2 to 3 years [19]. In the analysis based on SEER database, it was reported that 1.4% of breast cancer patients assessed harbored liver metastasis at the time of diagnosis, and that the presence of liver metastasis significantly reduced patient overall survival compared to patients without liver metastasis (HR 1.94 [1.86, 2.02]) [20]. In the present study, liver metastasis was the fourth most common distant metastasis site and it is the only distant metastasis site found to be associated with PET/CT findings and tumor molecular profile. Liver metastasis was associated with hormone [progesterone (PR) and estrogen (ER)] status and HER2. Patients with HR+/HER2- had less liver metastasis than HR+/HER2+, HR-/HER2+ and triple negative subtypes. Patients with liver metastasis had higher primary tumor size, higher primary tumor SUVmax and higher Ki-67 index.

In a prospective study which was performed with luminal type breast cancer patients with newly diagnosed metastases, baseline (maximum one of SUVmax of metastatic lesions) SUVmax was found significantly related to the number of metastatic sites and presence of visceral metastasis but could not effectively differentiate patients with luminal A from luminal B subtype. Baseline SUVmax as determined on PET//CT was predictive of both progression-free survival and overall survival. In multivariate analysis, the baseline SUVmax, relapse-free interval, and number of metastatic sites were independent prognostic factors for progression-free survival. For overall survival, the significant predictors were only baseline SUVmax and relapse-free interval [21].

In a recent study, the authors suggested that SUVmax of metastatic site would be useful biomarker of molecular subtypes in patients with metastatic breast cancer while yet with unknown HR and HER2 status and SUVmax also an independent prognostic factor on overall survival [22]. In our study, we demonstrated the association with the presence of synchronal liver metastasis and high SUVmax of primary tumor, and also the relation with primary tumor subtypes and primary tumor SUVmax, axillary lymph node SUVmax, liver metastasis SUVmax values. It was observed that SUVmax values of primary tumor, axillary lymph node and also liver metastasis were significantly lower in HR+/HER2- subtype compared to other subtypes. Although there is no survival data in our study as a limitation, we think that defining on staging PET/CT that liver metastasis is more common in patients with high primary tumor SUVmax, regardless of tumor subtypes, may be an important prognostic indicator and may predict the tumor subtype in patients whose tumor histopathological characteristics are not clearly known.

It is known that high SUVmax values are an indicator of tumor aggressiveness in many malignancies including breast cancer and the number of metastatic axillary lymph nodes is predicting poor prognosis in breast cancer [11,23,24]. In compatibility with this knowledge, in this study, we defined that the numbers of distant metastasis is related with the number of metastatic axillary lymph nodes and the highest SUVmax of distant metastasis. The highest SUVmax of distant metastasis was significantly elevated in the patients with >10 distant metastasis sites than in patient with <5 distant metastasis sites. To our results, we predict that further prospective studies can support the thesis that higher distant metastasis SUVmax value may be a worse prognostic indicator.

Primary tumors of breast cancer have high structural and molecular heterogeneity and may present with minor components of differing tumor cell types, in example, cells with differing molecular profiles [25]. To the authors, when a cancer spreads to other tissues, the metastases can be of a different type to the primary cancer, and sometimes the metastases are even different to each other [26,27]. This may be due to heterogeneity in the primary tumor that comprises more than one cell clone [26]. This heterogeneity of metastatic breast cancer has stimulated the development of new treatment approaches such as estrogen- and HER2-receptor targeting therapies. Survival with metastatic breast cancer is improving along with the rapid development of new treatments [28]. In clinical practice, treatment planning of metastatic breast cancer is based on the histopathological molecular profile of the disease dominant cell type [29]. Despite all these treatment improvements, insufficient therapy response in some patients is maybe due to the cellular differences between primary tumor and metastases. Although treatment is based on primary tumor histopathological features, due to heterogeneity of tumor and also metastasis we believe that a more aggressive treatment approach can be initiated in patients with high SUVmax of distant metastasis especially with high SUVmax of liver metastasis in order to increase the treatment response. The limitation of our study is that it is a retrospective study without patient follow-up information. More prospective studies with larger series and with follow-up data may be required to support our suggestions.

In conclusion, accurate detection of distant metastases in breast cancer at the time of diagnosis is of great importance in terms of treatment planning and prognosis of the disease. FDG PET/CT is a very reliable modality due to superiority in determining distant metastasis and their distribution, and it can lead to alter treatment approach in newly diagnosed metastatic breast cancer patients. As a result of our study, we suggest that PET/CT findings can predict factors with prognostic importance in breast cancer patients with metastasis at time of diagnosis.

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Corresponding author e-mail: demirelbbusra@hotmail.com

Orcid ID:
Bedriye Büşra Demirel 0000-0002-6494-062X
Seda Gülbahar Ateş 0000-0003-0422-0863
Hüseyin Emre Tosun 0000-0002-0169-6316
Süleyman Aksu 0000-0002-7146-393X
Gülin Uçmak 0000-0002-0268-4747

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Original Article

Investigation of BRCA2 Gene K3326X Variant in Patients with Breast and Ovarian Cancer by Next-Generation Sequencing Technique

Yeni Nesil Dizileme Tekniği ile BRCA2 Geninde K3326X Varyantı Tespit Edilen Meme ve Over Kanseri Hastalarının İncelenmesi

Neslihan Düzkale[1], Cengiz Karaçin[2], Serap Yörübulut[3], Haktan Bağış Erdem[4],
Özlem Öz[5], Mustafa Altınbaş[6]

[1]Dışkapı Yıldırım Beyazit Training and Research Hospital, Department of Medical Genetics, Ankara, Türkiye
[2]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Oncology, Ankara, Türkiye
[3]Kırıkkale University Faculty of Science and Letters, Department of Statistics, Kirikkale, Türkiye
[4]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Genetics, Ankara, Türkiye
[5]Harran University Faculty of Medicine, Department of Medical Genetics, Sanliurfa, Türkiye
[6]Dışkapı Yıldırım Beyazit Training and Research Hospital, Department of Medical Oncology, Ankara, Türkiye

ABSTRACT

Introduction: The BRCA2 gene is a tumor suppressor gene involved in the repair of double-stranded DNA damage by homologous recombination. Until now, many cancer-related variants of the BRCA2 gene have been reported. There are conflicting publications in studies of the possible effect of the K3326X variant of this gene in cancer. This study investigates the K3326X BRCA2 gene variant and its role in the cancer pathogenesis of Turkish patients diagnosed with breast and ovarian cancer.

Materials and methods: In the study, 1957 patients with cancer diagnosis for BRCA1 and BRCA2 genetic analysis and 432 healthy individuals without a history of cancer were included. The K3326X variant was investigated using the next-generation sequencing method from the genomic DNA sample obtained from the individuals.

Results: K3326X variant was detected in 54 of 1957 (2.75%) cancer patients. For the non-cancerous group, 11 of 432 (2.5%) patients were carrying the K3326X variant. When both groups were compared in terms of K3326X variant carriage, a statistically significant result could not be obtained for the individuals (p=0.934).

Discussion: BRCA2 K3326X variant did not have a significant role in cancer etiopathogenesis. As a result, the variant whose clinical significance is not still been fully understood, was investigated for the first time for Turkish population. Our results suggest that the variant could be a benign variant.

Keywords: BRCA2, Breast cancer, Ovarian cancer, K3326X

ÖZET

Giriş: BRCA2 geni, homolog rekombinasyon ile çift sarmallı DNA hasarının onarımında yer alan bir tümör baskılayıcı gendir. Şimdiye kadar, BRCA2 geninin kanserle ilgili birçok varyantı rapor edilmiştir. Bu genin K3326X varyantının kanserdeki olası etkisine ilişkin çalışmalarda çelişkili yayınlar bulunmaktadır. Bu çalışmada meme ve yumurtalık kanseri tanısı almış Türk hastaların K3326X BRCA2 gen varyantı ve kanser patogenezindeki rolü araştırılmıştır.

Gereç ve yöntemler: Çalışmaya BRCA1 ve BRCA2 genetik analizi için kanser tanısı konan 1957 hasta ve kanser öyküsü olmayan 432 sağlıklı birey dahil edildi. Bireylerden elde edilen genomik DNA örneğinden yeni nesil dizileme yöntemi kullanılarak K3326X varyantı araştırıldı.

Bulgular: 1957 kanser hastasının 54'ünde (%2.75) K3326X varyantı tespit edildi. Kanserli olmayan grup için 432 hastanın 11'i (%2,5) K3326X varyantını taşıyordu. Her iki grup K3326X varyant

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taşıyıcılığı açısından karşılaştırıldığında, bireyler için istatistiksel olarak anlamlı bir sonuç elde edilemedi (p=0,934).

Tartışma: Çalışmamızda BRCA2 K3326X varyantının kanser etyopatogenezine anlamlı etkisi tespit edilememiştir. Sonuç olarak, klinik önemi henüz tam olarak anlaşılamayan bu varyant, ilk kez Türk popülasyonu için araştırılmıştır. Sonuçlarımız, varyantın benign bir varyant olabileceğini düşündürmektedir.

Anahtar kelimeler: BRCA2, Meme kanseri, Over kanseri, K3326X

Introduction

BRCA2 gene is one of the important tumor suppressor genes that play a role in maintaining genomic stability in breast cancer. This gene was determined as Fanconi anemia (FA), complementation group D1 (FANCD1), which helps to repair DNA double-strand breaks by its homologous recombination mechanism. This powerful tumor suppressor gene is responsible for the formation of the BRCA2 protein, which is actively involved with some other proteins in many processes such as cell cycle and DNA replication control, telomere hemostasis, and maintenance of genomic integrity [1]. BRCA2 is one of the genes responsible for hereditary breast and ovarian cancer syndrome (HBOC), and its germline disease-related variants cause susceptibility to certain types of cancer such as; breast, ovarian, and prostate in the individual, and show intermediate penetrance (20–50%) in terms of cancer [2]. Meta-analysis results have shown that in carriers of pathogenic variants of the BRCA2 gene, the mean cumulative risk increase in female sex up to age 70 is 38-84% for breast cancer and 16.5 -27% for ovarian cancer. Male BRCA2 pathogenic variant carriers were estimated to have breast cancer risk by 6.8%, and lifetime risk of prostate cancer is 20% up to the age of 70 [3].

In many studies in the literature, it has been reported that disease-related variant carriers of BRCA2 in both sexes also increase the risk of some other types of cancer such as pancreatic cancer, gastric cancer, and malignant melanoma [4]. According to the universal mutation database (UMD), 3454 different variants of the BRCA2 gene have been reported until today, the clinical significance of the majority of them is still unknown [5]. One of these variants, BRCA2 c.9976A>T (K3326X), results in a termination codon at the penultimate exon, predicted to cause a truncation of the last 91 amino acids. There are conflicting publications in the literature regarding the possible effect of this variant on cancer. In this study, the importance of BRCA2 K3326X variant, detected in patients diagnosed with Turkish breast and ovarian cancer, in the etiopathogenesis of the disease, was investigated.

Method

In this retrospective study between January 2018 and January 2020, the K3326X variant was investigated in patients with breast/ovarian cancer whose genetic analysis to detect a genomic change associated with hereditary cancer was performed in Diskapi Yildirim Beyazit Training and Research Hospital Department of Medical Genetics. All of 1957 patients included in the study were older than 18 years of age and were suspected of having BRCA1/2 genes in the etiopathogenesis of their existing cancers. General demographic and clinicopathological characteristics and gene analyses results of the patients were obtained retrospectively from the patient files.

This study was conducted by considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. A written informed consent was obtained from all participants prior to the study and this descriptive case series study was approved by the Harran University Local Ethics Committee (Approval number: HRU/21.08.14).

Peripheral blood samples were obtained from patients and Genomic DNA investigated by the next-generation sequencing method. Analysis of the BRCA1/2 genes was performed on the Illumina MiSeq system (Illumina Inc., San Diego, CA, USA) with the GeneRead QIAact BRCA Advanced DNA UMI Panel (Qiagen, Hilden, Germany). This panel provides 100% coverage for all exons and exon/intron junctions (up to 25 base pairs) of the BRCA1/2 genes. In addition, this panel made possible the analysis of SNVs and Indels. QIAGEN Clinical Insight (QCI™) software was used for the analysis of the data obtained. NM_007294.3 for the BRCA1 gene and NM_000059.3 for the BRCA2 gene, set as reference transcripts. In the study, the detected gene variants were classified based on the criteria in the American College of Medical Genetics and Genomics guideline.[6] In order to investigate the possible effect of the K3326X variant detected in patients with cancer on the etiopathogenesis of cancer, a control group of 432 people without cancer diagnosis were included. The control group consisted of patients with neurological, metabolic, cardiological, nephrological, ophthalmological and musculoskeletal disorders.

Sequence analysis of DNA sample obtained from the peripheral blood of these control group patients was performed using the Next Generation Sequencing (NGS) method using the Hereditary Disease Solution by Sophia Genetics (HDS_v3) on Nextseq Platform (Illumina, USA). HDS_v3 panel contained 569 genes. The raw data of the patients obtained by NGS were analyzed in a web-based bioinformatics program (https://www.sophiagenetics.com/home.html) and according to the reference genome (GRCh37 (h19)). In this group, 11 individuals were found with the K3326X variant in a heterozygous state. This group and the group with cancer patients were compared statistically in terms of the rate of having the K3326X variant.

The software "SPSS for Windows v23.0 (SPSS Inc., Chicago, IL, USA)" was used in the statistical evaluation of all results obtained. "Mean values (±) and standard deviation (SD), ±SD" were presented for scale data and percentage (%) for nominal variables Pearson chi square test. " were used in the study of the relations of the two qualitative variables. When the p-value used for the level of statistical significance was "0.05 or less", which was accepted as a meaningful result.

Results

In this study, K3326X variant was detected in 54 (2.75%) of 1957 cancer patients. Among 54 cancer patients, 52 (96.3%) carried this variant as heterozygous, two of them homozygous (3.7%). Of these 54 cancer cases, two (3.7%) were being followed up with a diagnosis of ovarian cancer and 52 (96.3%) with a diagnosis of breast cancer. The ages of diagnosis of two patients with ovarian cancer were 48 and 56, respectively, and the histopathological subtype of cancer in both patients was detected as serous adeno-carcinoma. The mean age at diagnosis of patients with breast cancer was 46.26 ± 9.32 years. Histopathological subtypes of cancer of these patients were mostly determined as invasive ductal carcinoma (IDC) (78.8%) and invasive lobular carcinoma (ILC) (11.5%). Breast cancer subtypes of the other five patients were medullary (1.9%), mucinous (IMC) (1.9%), IDC/ILC (1.9%), IDC/ILC / IMC (1.9%), IDC/IMC (1.9%). It was determined that 77.1% of the tumors of breast cancer patients were estrogen receptor (ER) positive, 73.5% progesterone receptor (PR) positive, and 61.4% had c-erbB-2 (HER2/neu) amplification. 11.1% of these patients were triple negative (TNBC). The mean age at diagnosis of TNBC patients was 48.33 ± 7.11 and the mean age at diagnosis of non-TNBC patients was 46.00 ± 9.59, and no statistically significant difference was found in the mean age at diagnosis of both groups ($p = 0.568$). Genomic changes of NM_007294.3 (BRCA1): c.5035delC(p.Asn 1678_ Leu1679 insTer) and NM_000059. 3(BRCA2): c.5969delA(p.Asp1990Valfs) were detected in two of the carriers heterozygously. Two patients were diagnosed with HBOC. In the other 52 patients with the K3326X variant, a

Table 1. Relationship between K3326X carrier status and cancer

K3326X	The group of patients with cancer (n=1957) n	%	The group of patients without cancer (n=432) n	%	Statistical analysis* Probability
Carrier	54	2,8	11	2,5	p=0,934
Non-carrier	1903	97,2	421	97,5	

* Chi-Square Test: Analysis of Contingency Tables

causal variant was not found in BRCA1 and BRCA2 genes. There were 432 patients in the non-cancerous group, of which 11 carried the K3326X variant. The group which included cancer patients, and other group were compared in terms of the frequency of K3326X variant carriage, and no statistically significant difference was found between the groups (p = 0.934) (Table I).

Discussion

Amino acids subjected to truncation caused by the K3326X variant in the BRCA2 gene have functional importance due to the C-terminus region where they are located. In deletions of this region, it has been observed that BRCA2 colocalization does not occur with FANCD2 protein that plays a role in the repair of DNA damage, and regulation of the checkpoint of the cycle after injury [7, 8]. Various studies investigating the cellular and biochemical effects of this variant on cancer cell lines have been reported in the literature. As a result of some studies, it has been shown that the K3326X variant has no effect on BRCA2 function, while some studies have yielded opposite results [9-11]. In the study of, Morimatsu et al; the importance of this region in mouse cells with deletion of the region containing the last 188 amino acids at the COOH terminal of the BRCA2 gene was investigated. It has been observed that the cell cycle progression rate of these cells and wild type cells are similar. However, it has been observed that cells with deletion age faster than wild ones and are more radiosensitive. As a result, it has been shown that BRCA2 deletion can accelerate cell proliferation and induce cancer through defective DNA repair.[11] These studies on BRCA2 K3326X variant have conflicting results. Sergey et al., designed an assay using mouse embryonic stem cells and bacterial artificial chromosomes to investigate the functional significance of mutations in BRCA2. In their study, they showed that the K3326X genomic modification had no effect on BRCA2 gene functions and that it was a neutral variant [9]. In another study, Wu et 190 al. investigated the functional importance and cancer relationship of various VUSs in the BRCA2 gene, and found that the K3326X variant did not cause a change in BRCA2 function at a level that would cause cancer susceptibility. In their study using three independent assays evaluating homologous recombination, cell survival, and centrosome regulation, they showed that this variant did not affect the function of the BRCA2 gene in any of the assays [10].

Various researchers have investigated the importance of this variant in cancer susceptibility in many malignancies, especially breast and ovarian cancer, and different results have been obtained. The K3326X variant, which was first described by Mazoyer in the literature, was detected at approximately 1% in both the 462 control and 513 breast cancer patients has suggested to be a polymorphic variant [12]. While the same variant was detected in the control population by Wagner et al [13], it was found by Bergthorsson et al in a patient with breast cancer and was evaluated as a polymorphism [14]. As a result of a study conducted by Offit et al. with patients followed up for Fanconi Anemia (FA), they concluded that the BRCA2 K3326X allele could not be evaluated pathogenic [15]. Reid et al; claimed that this variant was not pathogenic, as it did not show segregation with the disease in some cancer families and its incidence in the population was the same as that of breast cancer patients [16].

In some studies, researchers claimed that the K3326X variant, considered a polymorphism, may be a risk factor. Martin et al found this variant at a higher prevalence in patients with familial pancreatic cancer than in healthy controls. The researchers have claimed that this variant has a detrimental effect and leads to an increased risk of pancreatic cancer [17]. Michailidou et al., in a meta-analysis based on GWAS (genome-wide association studies) they performed in 2013, suggested that this variant may cause a small increase in the risk of breast cancer in the individual [18]. In another GWAS conducted by the same researcher in 2015, breast cancer-related common variants located in 79 different loci were investigated and it was found that the K3326X variant could increase the risk of breast cancer by 1.26-fold [19]. In addition to these studies, we have suggested that this variant may cause an increase in the risk of some cancer types other than breast and ovarian cancer.

Howlett et al have argued that if the BRCA2 K3326X variant is compound heterozygous, it may cause FA [20]. Wang et al suggested that the BRCA2 K3326X sequence variant may have a direct effect on lung cancer development [21]. Akbari et al. detected the K3326X variant at a higher rate in 220 patients diagnosed with esophageal squamous cell carcinoma compared to healthy controls, and suggested that this variant may be a risk factor for the disease [22]. In a case diagnosed with bilateral breast cancer and melanoma, variants Q563X in the BRCA1 gene and K3326X in the BRCA2 gene were defined as double heterozygous by Palmirotta et al. It has been emphasized that the presence of a second variant with K3326X induces to have an earlier onset of the neoplasia to develop, and this variant has a strong penetrance modifier role [23]. One of the most comprehensive studies on this variant is the study by Meeks et al in 2016 involving approximately 77000 patients and 84000 controls diagnosed with breast, ovarian and prostate cancer. The researchers found a statistically significant relationship between the K3326X variant and all invasive breast cancer cases in this study, especially cases with triple-negative breast cancer and estrogen receptor negative breast cancer. In patients with lobular breast cancer, there was no significant relationship between this variant and the disease. In the same study, a strong association was observed between this variant and the disease in cases with serous ovarian cancer, but not in non-serous ovarian cancer patients. In addition, no significant association was reported between prostate cancer and K3326X. The results of this large study have suggested that the BRCA2 K3326X variant may play a role in the etiopathogenesis of breast and ovarian cancer [24,25]. In another study in the literature, the mean age at diagnosis of breast/ovarian cancer patients carrying the K3326X variant was reported as 43.2 ± 9.6 (range 28-67), and no significant difference was found in mean age at diagnosis with non-carrier patients (45.5 ± 10.6). In the same study, the researchers claimed that this variant has a different clinical significance from the BRCA2 truncating mutations located at the other 5'end, and its effect on breast and/or ovarian cancer development cannot be ignored. Therefore, they were suggested that the K3326X variant should be included in panels of all low penetration susceptibility SNPs [26].

In our study, the mean age at diagnosis of breast cancer patients was found to be 46.26 ± 9.32, similar to the literature. Although breast cancer is frequently diagnosed between the ages of 55-64 in developed countries, it has been reported that the breast cancer patient population in Turkey is between the ages of 45-49 mostly [27].

Breast cancer is a disease that can occur with the effect of many environmental, individual and genetic risk factors, and the age of onset may vary geographically and ethnically. The age at onset of breast cancer is significantly younger in patients with BRCA1/2 pathogenic variants compared to 250 patients without BRCA1/2 [28]. For this reason, National Comprehensive Cancer Network (NCCN) guidelines include the age factor, in the testing criteria for hereditary breast and ovarian cancer [29].

Up to 70% of breast cancers are hormone-dependent, and they are usually ER-positive. TNBC is detected only in 10-20% of invasive breast cancers [30]. In some studies, it has been shown that BRCA1-associated tumors, usually TNBC and BRCA2 mutation carriers, tend to develop mostly ER-positive breast cancer. In addition, in some publications, it was reported that patients with the same causal variant of BRCA1 were diagnosed with breast cancer at a younger age compared to others [31]. In our study, no significant difference was observed between the ages of cancer diagnosis between patients with variant carriers, those with TNBC, and non-TNBCs ($p = 0.568$).

In the Genome Aggregation Database (GnomAD), it is stated that the frequency of this variant allele is approximately 1 in 151. The allelic frequency of BRCA2 K3326X variant has been reported as 1 in 845 in the African population, 1 in 251 in Ashkenazi Jewish, 1 in 379 in Latinos, 1 in 100 in Europeans, and 1 in 144 in South Asian population [32]. In this study, we investigated the frequency of BRCA2 K3326X variant carriage in cancer and non-cancerous patients who were genetically analyzed in our own laboratory, and we have found that this variant does not play an important role in the etiopathogenesis of breast/ovarian cancer.

Conclusion

We have examined the role of the K3326X variant, which has been investigated many times in the literature and whose clinical significance is not fully understood in the etiopathogenesis of the breast and ovaries in the Turkish population. Our results have provided evidence in favor that BRCA2 K3326X variant may be a benign variant. In order to determine the possible mechanism of action of this variant in cancer, comprehensive studies are needed in different populations.

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Corresponding author e-mail: neslihanduzkale@gmail.com

Orcid ID:
Neslihan Düzkale 0000-0001-6122-5316
Cengiz Karaçin 0000-0002-7310-9328
Serap Yörübulut 0000-0003-0781-4405
Haktan Bağış Erdem 0000-0002-4391-1387
Özlem Öz 0000-0002-5533-6025
Mustafa Altınbaş 0000-0002-8024-2362

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Original Article

The Efficacy and Safety of CDK 4/6 Inhibitors Plus Endocrine Therapy with Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2-Negative Metastatic Breast Cancer Patients

Hormon Reseptörü-Pozitif, İnsan Epidermal Büyüme Faktörü Reseptörü-2-Negatif Metastatik Meme Kanseri Hastalarında CDK 4/6 İnhibitörleri ile Endokrin Tedavisinin Etkinliği ve Güvenliği

Özgür Açıkgöz, Sabin Göktaş Aydın, Ahmet Bilici, Yasin Kutlu, Harun Muğlu, Ebru Karcı,
Jamshid Hamdard, Elkhan Mammadov, Ömer Fatih Ölmez, Özcan Yıldız

Department of Medical Oncology, Istanbul Medipol University Hospital, Istanbul, Turkey

ABSTRACT

Introduction: Combining cyclin-dependent kinases 4/6 inhibitors with endocrine therapy are indicated as first or second-line treatment for hormone receptor-positive, HER2-negative advanced or metastatic breast cancer.We aimed to investigate the efficacy and safety of adding CDKIs to endocrine therapy in patients whose tumors might have differing degrees of endocrine sensitivity.

Materials and methods: Totally, 99 patients with HR+, HER2-, ABC who received CDK4/6 inhibitor and hormonotherapy were included.Clinicopathological features of patients and progression-free survival (PFS) and overall survival (OS) outcomes were analyzed.The toxicity, combine drugs and the factors that may predict survival were also evaluated.

Results: This study with a median age of 51 years (range;31-80).The molecular subtypes of the patients were as follows; 51 patients (51.5%) were in the luminal A group, and 48 patients (48.5%) were in the luminal B HER2- group. Before CDK 4/6 inhibitor therapy, visceral and non-visceral metastasis were seen in 48 and 46 patients, respectively.At the median follow-up time of 13.7 months (range:3-48 months), the median OS was 38.5 months, the median PFS was 5.2 months. Univariate analysis demonstrated that the choice of CDK 4/6 agent was significantly associated with PFS. 6-months PFS rate with ribociclib was 42.3%, in palbociclib, it was 63.6%, in abemaciclib it was NA (not aplicable) (p=0.01).Univariate analysis revealed that the luminal type of tumor (p=0.002), advanced stage disease at the initial diagnosis (p<0.001), and presence of visceral metastasis (p=0.006) were significant factors for OS.

Discussion: In this study we demonstrated that there is a survival benefit for all three agents and there is a significant difference especially between first and second-line usage.

Keywords: breast neoplasm, cyclin-dependent kinases, survival, safety

ÖZET

Giriş: Sikline bağımlı kinaz 4/6 inhibitörlerinin endokrin terapi ile birleştirilmesi, hormon reseptörü pozitif, HER2 negatif ilerlemiş veya metastatik meme kanseri için birinci veya ikinci basamak tedavi olarak endikedir. Tümörleri farklı derecelerde endokrin duyarlılığa sahip olabilecek hastalarda endokrin tedaviye CDKI'lerin eklenmesinin etkinliğini ve güvenliğini araştırmayı amaçladık.

Gereç ve yöntemler: CDK4/6 inhibitörü ve hormon tedavisi alan HR+, HER2-, ABC'li toplam 99 hasta dahil edildi. Hastaların klinikopatolojik özellikleri ve progresyonsuz (PFS) ve genel sağkalım (OS) sonuçları analiz edildi. Toksisite, kombine ilaçlar ve sağkalımı öngörebilecek faktörler de değerlendirildi.

Bulgular: Ortanca yaşı 51 (31-80) olan bu çalışmada hastaların moleküler alt tipleri şöyleydi; 51 hasta (%51,5) lümen A grubunda, 48 hasta (%48,5) lüminal B HER2-grubunda.CDK 4/6 inhibitör tedavisi

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öncesi sırasıyla 48 ve 46 hastada visseral ve visseral olmayan metastaz görüldü. Medyan 13,7 aylık takip süresinde (dağılım:3-48 ay) , medyan OS 38,5 aydı, medyan PFS 5.2 aydı. Tek değişkenli analiz, CDK 4/6 ajanı seçiminin PFS ile önemli ölçüde ilişkili olduğunu gösterdi. Ribosiklib ile 6 aylık PFS oranı %42,3, palbosiklib ile %63,6, abemaciclib ile NA idi (p=0,01). Tek değişkenli analiz tümörün lüminal tipi (p=0,002), ilk tanı anındaki ileri evre hastalık (p<0,001) ve visseral metastaz varlığının (p=0,006) OS için anlamlı faktörler olduğunu ortaya koydu.

Tartışma: Bu çalışmada, her üç ajan için de sağkalım yararı olduğunu ve özellikle birinci ve ikinci basamak kullanım arasında anlamlı bir fark olduğunu gösterdik.

Anahtar kelimeler: meme kanseri, siklin bağımlı kinazlar, sağkalım, güvenlik

Introduction

Hormone receptor (HR) positive, human epidermal growth factor receptor-2 (HER2)-negative advanced breast cancer (ABC) constitutes approximately 70% of all metastatic breast cancer (MBC) [1,2]. Although effective results are obtained with various endocrine treatment options, resistance to treatment develops after a certain period of time and disease progression is observed. Many molecular resistance mechanisms have been defined, and in recent years, the effectiveness of various treatment combinations in overcoming resistance through these mechanisms has been proven and it has been demonstrated that they show significant survival advantages [1,2]. For this purpose, agents such as aromatase inhibitors (AI), gonadotropin-releasing hormone analogues and cyclin-dependent kinase (CDK) 4/6 inhibitors, the efficacy of which has been proven by recent studies, in patients with HR+, HER2-, ABC, according to menopausal status. It is used alone or in combination as the main components of treatment [1,3-6].

CDK4/6 inhibitors are rapidly transforming this treatment landscape for these patients. There are currently three CDK4/6 inhibitors that have been approved by the US Food and Drug Administration (FDA): palbociclib, ribociclib, and abemaciclib. All three CDK 4/6 inhibitors have been studied in combination with a non-steroidal aromatase inhibitor in the first-line setting. They have shown similar progression-free survival (PFS) contribution, but only ribociclib and abemaciclib provided overall survival (OS) benefit [4-6]. Moreover, they have also been studied in combination with the selective estrogen-receptor degrader fulvestrant in the first and second-line setting (7-9). PALOMA-3 with palbociclib, MONELESSA-3 with ribociclib, and MONARCH-2 with abemaciclib are all three conducted phase III studies. although there are some key study population differences between the phase III trials, these combination studies demonstrated significant improvement in PFS which is primary end point of them [7-9].

The aim of our study was to provide a real-life analysis of the efficacy and safety of CDK 4/6 inhibitors and combination patterns reported in HR+, HER2- for patients with ABC in the first and second-line setting.

Patients and Methods

In this study, a total of 99 patients with HR+, HER2-, ABC who were treated between 2018 and 2022 were retrospectively analyzed. Our study was conducted in accordance with the Declaration of Helsinki. The Local Ethics Committee of Istanbul Medipol University approved the study on January 2023 with E-10840098-772.02-269 decision number.

The data include demographic characteristics of patients, menopausal status, histo-pathology, stage of diagnosis, visceral metastasis, molecular characteristics of breast cancer, as well as adjuvant chemotherapy or endocrine therapy for operated patients. The CDK4/6 inhibitor used as treatment, combined drugs, side effects and toxicity secondary to treatment, objective response rate (ORR), OS and PFS were evaluated and recorded. Eastern Cooperative Oncology Group (ECOG) performance score (PS) was used for the detection of performance status [10].

The response to treatment of all three CDK4-6 was assessed by thorax CT scan and abdomino-pelvic CT scan. It was evaluated with the Response Evaluation Criteria in Tumors (RECIST) version 1.1. A complete response (CR) was defined as the disappearance of all measurable disease, a partial response (PR) represented a decrease of at least 30% of the tumor volume and stable disease (SD) defined small changes that do not meet above criteria without actual progression of disease. Progressive disease (PD) was defined as more than 20% increase in tumor volume or any new sites of disease.

Statistical analysis

IBM SPSS Statistics for Windows (Version 20.0. Armonk, NY: IBM Corp IBM Corp. Released 2011) was used for statistical analysis. Parameters were described with their median values. Response rates and toxicity profiles according to CDK 4-6 inhibitor treatment choice were compared using the chi-squared test and Fisher's exact test. OS was defined as the time from diagnosis to the date of the patient's death. PFS was defined as the time from the diagnosis of advanced-stage disease to progression. Survival analysis and curves were established using the Kaplan-Meier method and compared with the long-rank test. Univariate analyses were carried out to assess the significant prognostic factors on survival. These significant prognostic factors were further analyzed by multivariate Cox regression in order to determine independent prognostic factors on survival. The 95% confidence interval [CI] was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests, and p values less than or equal to 0.05 were accepted to be statistically significant.

Results

Fifty-three of the patients were premenopausal, and 46 were postmenopausal with a median age of 51 years (range; 31-80). Disease recurrence <12 months after adjuvant treatment occurred in 25 patients. Before CDK 4/6 inhibitor therapy, visceral and non-visceral metastasis were seen in 48 and 46 patients, respectively. 47.5% of patients were treated with CDK 4/6 inhibitor in the first-line setting, 49.5% were in the second-line, and 3% were in the later-line setting. The rate of treatment-related toxicity was 64.7%, and grade 3 or higher toxicity was 26.3%. The CDK 4/6 agent dose was adjusted in 33 patients concerning toxicity. No treatment-related death or discontinuation to CDK 4/6 inhibitor agent was observed. (Table 1)

CR was observed in 22 (34.9%) patients with ribociclib, 7 (23.3%) with palbociclib, and 1 (20%) with abemaciclib. ORR in ribociclib, palbociclib and abemaciclib groups were 66.7%, 63.3%, 100% respectively. The best response did not significantly differ between CDK 4/6 inhibitor agents. Any grade of toxicity and grade 3 or higher toxicity were detected in 47 (74.6%), 22 (73.3%), 5 (100%) and 20(31.7%), 15 (50.0%), 1(20%) in groups, respectively. There was no significant difference between toxicity rates. However, hematological toxicity rates were significantly higher in patients treated with palbociclib and ribociclib compared with abemaciclib (89.8% and 81.0% vs 20%) (p<0.001). The diarrhea rates were significantly higher in patients treated with abemaciclib (p<0.001). (Table 2)

At the median follow-up time of 13.7 months (range: 3-48 months), the median OS was 38.5 months and the median PFS was 5.2 months. Univariate analysis demonstrated that the choice of CDK 4/6 agent was significantly associated with PFS. 6-months PFS rate with ribociclib was 42.3%, in palbociclib, it was 63.6%, in abemaciclib, it was NA (p=0.01). (Figure 1) Age, disease recurrence <12 months after adjuvant therapy, menopausal status, ECOG PS, history of curative surgery, the treatment line of CDK 4/6 inhibitor therapy and luminal type of disease had no significant impact on PFS. In patients with non-visceral metastasis, the median PFS was 5.2 months with ribociclib; 12.2 months with palbociclib; not reached in abemaciclib (p=0.06). In patients with visceral metastasis,

Table 1. Patient and tumor characteristics

Characteristics	N=99	%
Age	median 51(range 31-80)	
Menopausal status		
Premenopausal	53	53.5
Postmenopausal	46	46.5
Advance Stage Disease at initial diagnosis	55	56.1
History of		
Curative surgery	54	54.5
Adjuvant endocrine treatment	52	52.5
Luminal A disease	51	51.5
Luminal B disease	48	48.5
Disease recurrence < 12 months after adjuvant treatment	25	25.3
Metastatic site		
Non-visceral metastasis	46	46.5
Visceral metastasis	48	48.5
CDK 4-6 inhibitor		
1^{st} line	47	47.5
2^{nd} line	49	49.5
≥ 3^{rd} line	3	3
Choice of CDK 4-6 inhibitor		
Ribociclib	63	63.6
Palbociclib	30	30.3
Abemaciclib	6	6.1
Choice of antiestrogen treatment		
Letrozole	54	54.5
Fulvestrant	45	45.5
Any Grade of toxicity with CDK 4-6 inh.	64	64.7
Grade 3 or higher toxicity	26	26.3
Dose adjustment due to toxicity	33	(33.3)

*CDK: cyclin-dependent kinases

Table 2: Response rates and toxicity profile according to the choice of CDK 4-6 inhibitor treatment

Characteristics	Ribociclib N (%)	Palbociclib N(%)	Abemaciclib N(%)	P
RECIST 1.1				
Complete response	22 (34.9)	7 (23.3)	1 (20.0)	0.4
Partially response	20 (31.7)	12 (40.0)	4 (80.0)	
Stable Disease	3 (4.8)	3 (10.0)	0	
Progressive Disease	18 (28.6)	8 (26.7)	0	
ORR	42 (66.7)	19 (63.3)	5 (100)	0.2
Any grade of toxicity	47 (74.6)	22 (73.3)	5 (100)	0.4
Grade ≥3 toxicity	20 (31.7)	15 (50.0)	1 (20.0)	0.1
Toxicity				
Hematological toxicity	35 (89.8)	17 (81.0)	1 (20.0)	<0.001*
Liver toxicity	2 (5.1)	1 (4.8)	0	
Cardiac toxicity	1 (2.6)	0	1 (20.0)	
Diarrhea	0	1 (4.8)	3 (60.0)	
Other	1 (2.6)	2 (9.5)	0	
Toxicity-related dose adjustment	22 (50.0)	12 (57.1)	1 (20.0)	0.24

ORR: Objective response rate
* p values <0.05 was regarded statistically significant.”

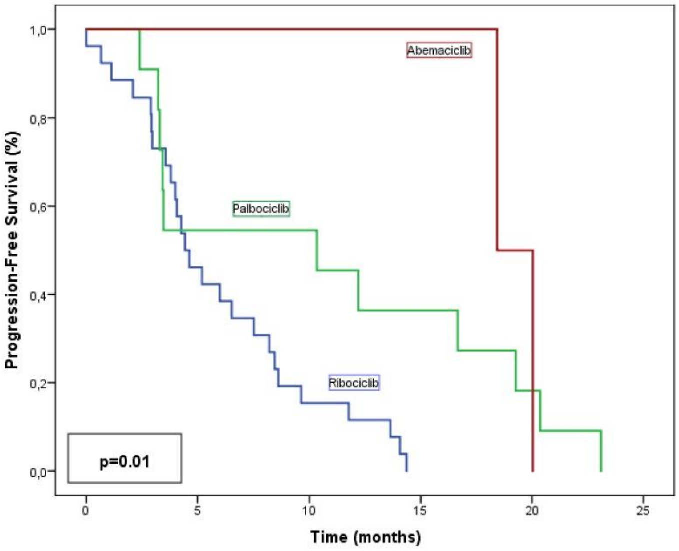

Figure 1. PFS according to CDK

Table 3. Prognostic factors for overall and progression-free survival

	PFS		OS	
Factor	Univariate analysis (p)	Multivariate analysis p (HR 95%CI)	Univariate analysis (p)	Multivariate analysis p (HR 95%CI)
Age (median 51 years)	0.9		0.8	
Performance status 0/1 vs. 2	0.2		0.3	
Menopausal status Premenopausal vs postmenopausal	0.2	0.7	0.1	
Advanced stage at initial diagnosis Yes vs. no	<0.001	0.9	0.5	0.7
Metastatic site (visceral vs. non-visceral)	0.006	0.03 (14.2; 1.25-16.6)	0.7	0.5
History of curative surgery Present vs. absent	0.9		0.7	0.5
Luminal A vs Luminal B	0.002	0.09	0.5	0.4
CDK 4-6 inhibitor in 1st line vs. later lines	0.002	0.05 (13,5; 1.02-17.7)	0.1	0.3
Choice of CDK 4-6 inhibitor agent	0.3	0.1	0.01	0.02 (0.2; 0.06-0.80)
Disease recurrence < 12 months after adjuvant treatment Yes vs. no	0.6	0.2	0.4	0.6

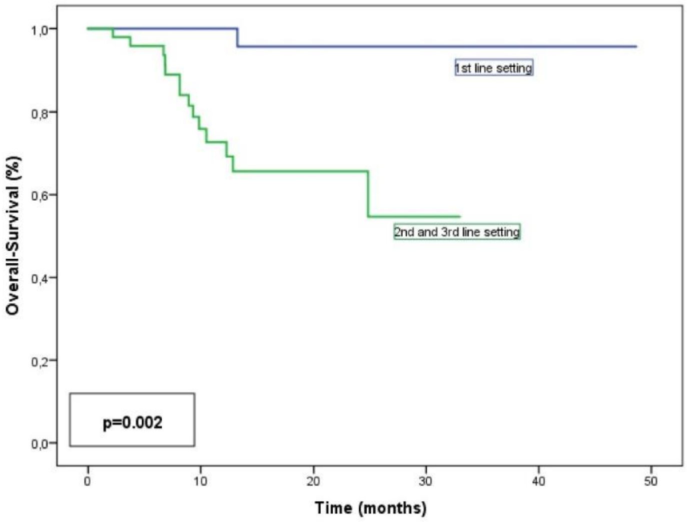

Figure 2. OS acording to CDK line

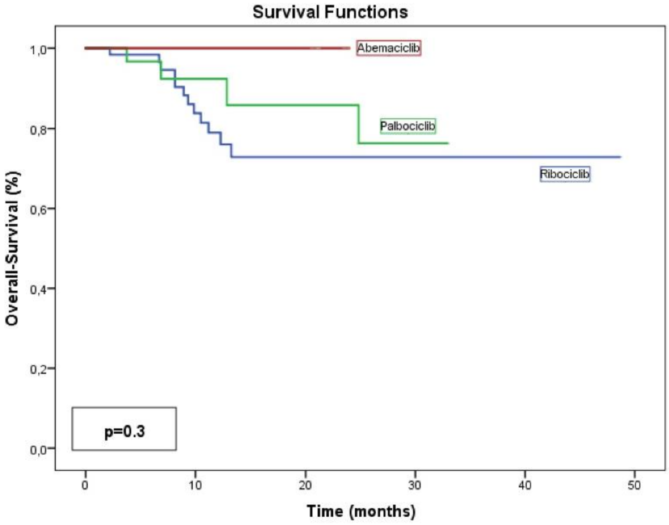

Figure 3. OS according to CDK

median PFS was 4.2 months with ribociclib, 3.3 months with palbociclib, and 18.4 months with abemaciclib (p=0.1). (Table 3)

The choice of CDK 4/6 inhibitor in first-line and later-line setting had a significant impact on PFS (p=0.002). 24-months OS rates were 95.7% vs 64.5%, respectively. (Figure 2)

Univariate analysis revealed that the luminal type of tumor (p=0.002), advanced stage disease at the initial diagnosis (p<0.001), and the presence of visceral metastasis (p=0.006) were significant factors for OS. There was no significant correlation between OS and CDK 4/6 inhibitor agent, disease recurrence <12 months after adjuvant therapy, menopausal status, EGOG PS and history of curative surgery. 24-months OS rate with ribociclib was 72.9%, in palbociclib it was 85.9%, in abemaciclib it was NR. (Figure 3)

Multivariate analysis was performed to identify independent prognostic factors for survival. It demonstrated that the choice of CDK 4/6 inhibitor agent was a significant independent prognostic factor for PFS (p=0.02, HR:0.2 95% CI 0.06-0.80). On the other hand, metastatic site of disease (visceral vs non-visceral) and the line of CDK 4/6 inhibitor therapy (first-line vs later-lines) were independent prognostic factors for OS (p=0.03, HR:14.295% CI; 1.25-16.6; p=0.05, HR:13.5 95% CI 1.02-17.7, respectively).

Discussion

The development of CDK 4/6 inhibitors such as abemaciclib, palbociclib and ribociclib has changed the therapeutic approach in patients with HR+, HER2- MBC. The combination of these drugs with aromatase inhibitor and fulvestrant has been approved by all health authorities. Although there is no clinical study comparing all three agents, there are meta-analyzes in the literature where they are indirectly compared [11]. In this study, we evaluated the efficacy differences between the addition of each of the three CDK 4/6 inhibitors to the endocrine treatment according to PFS, OS, toxicity, and visceral involvement in patients with HR+, HER2-, ABC, treated and followed-up in our center. CDK 4/6 inhibitors were used in combination with NSAI (anastrozole/letrozole) in the first-line and received FDA approval. Phase III studies were conducted for PALOMA-2 for palbociclib, MONELESSA-2 for ribociclib, and MONARCH-3 for abemaciclib, all showing PFS contribution [4-6]. In conclusion, the choice of CDK 4/6 inhibitor agents in HR+, HER2-, ABC depends on several factors such as patient preference, comorbidities and disease burden. Although there is a difference in survivals between agents, it is not sufficient to influence our choice of treatment. Despite our limitations, in this study we demonstrated that there is a survival benefit for all three agents and there is a significant difference especially between first and second-line usage. In the future, studies including real-life analysis are needed in which all three CDK 4/6 inhibitors with more patients are compared in both first- and second-line setting.

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Corresponding author e-mail: ozgur_acikgoz@yahoo.com

Orcid ID:
Özgür Açıkgöz 0000-0003-2715-4002
Sabin Göktaş Aydın 0000-0002-0077-6971
Ahmet Bilici 0000-0002-0443-6966
Yasin Kutlu 0000-0003-2184-634X
Harun Muglu 0000-0001-9584-0827
Ebru Karcı 0000-0001-8802-6376
Jamshid Hamdard 0000-0002-5823-1704
Elkhan Mammadov 0000-0002-3386-1427
Ömer Fatih Ölmez 0000-0001-7934-7039
Özcan Yıldız 0000-0003-2342-073X

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Original Article

Investigation of Clinical and Histopathological Features in Invasive Lobular Breast Cancers

Memede Lobüler Kanserlerin Klinik ve Histopatolojik Özelliklerinin İncelenmesi

Giray Gökhan Akgül[1], Ebru Esen[1], Müjdat Turan[2], Şevket Barış Morkavuk[1], Simay Akyüz[2],
Yasin Gülap[2], Pelin Seçken[3], Mehmet Ali Gülçelik[1]

[1]University of Health Sciences, Gülhane Research and Training Hospital,
Department of Surgical Oncology, Ankara
[2]University of Health Sciences, Gülhane Research and Training Hospital,
Department of General Surgery, Ankara
[3]University of Health Sciences, Gülhane Research and Training Hospital,
Department of Pathology, Ankara

ABSTRACT

Introduction: Analyze the clinical and immunohistopathological characteristics of lobular breast cancers, which are one of the more common subtypes of breast cancer among a wide range, which are important in terms of diagnosis, treatment, and monitoring.

Methods: Our study was conducted retrospectively. Patients diagnosed with and treated for breast cancer between January 2019 and August 2022 were included in the study after obtaining the necessary ethics committee permissions.

Results: Patients included in the study were between 28 and 81 years of age, and the median age was 53.04. While 26 (35.6%) of the patients were premenopausal, 47 (64.4%) were postmenopausal. The number of patients with unilateral characteristics was 71 (97.3%). The number of patients with bilateral ILC was 2 (2.7%). There were 38 patients with tumors (44.3%) in the upper outer quadrant (UOQ). Patients with tumors in the UOQ were followed by 11 patients with tumors in the lower outer quadrant (LOQ) and 8 patients in the central location (15.1% and 11%). Among the patients, 42 (57.5%) had undergone breast-conserving surgery and 31 (42%) had undergone mastectomy. Sentinel lymph node biopsy (SLNB) was performed in 51 (69.9%) of the patients.

Discussion and Conclusion: Although invasive lobular carcinoma has histopathologically bilateral and multicentric features, it is a disease that can be treated surgically not only with mastectomy but also with breast-conserving surgery, similar to invasive lobular carcinomas.

Keywords: Lobular carcinoma, immunohistopathological feature, mastectomy, breast conserving surgery

ÖZET

Giriş ve Amaç: Meme kanserinin en sık görülen alt tiplerinden biri olan lobüler meme kanserlerinin; tanı, tedavi ve takip açısından önem taşıyacak, klinik ve immünohistopatolojik özelliklerini analiz etmektir.

Yöntem ve Gereçler: Araştırma retrospektif olarak yapılmıştır. Ocak 2019 – Ağustos 2022 tarihleri arasında meme kanseri tanısı alan ve tedavisi yapılan hastalar çalışmaya dahil edilmiştir.

Bulgular: Çalışmaya dahil edilen hastaların yaşları 28-81 (yıl) aralığında olup medyan yaş 53,04'tü. Hastaların 26'sı (%35,6) premenapozal iken 47'si (%64,4) postmenapozaldır. Unilateral özellikteki hasta sayısı 71'dir (%97.3). Bilateral invaziv lobüler karsinomlu hasta sayısı 2'dir (%2,7). 38 hasta ile en sık üst dış kadran lokalizasyonunda tümörlü hasta bulunmaktadır (%44,3). Üst dış kadranı sırası 11 hasta alt dış kadran ve 8 hasta ile santral lokalizyon da tümörlü hastalar takip etmektedir (%15,1 ve %11). Hastaların 42'sine (%57,5) meme koruyucu cerrahi, 31'ine (%42)mastektomi uygulandı.

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Hastaların 51'ine (%69,9) sentinal lenf nodu biyopsisi uygulandı. Aksiller diseksiyon uygulanan hasta sayısı 22'dir (%30,1).
Tartışma ve Sonuç: İnvaziv lobüler karsinom histopatolojik olarak bilateral ve multisentrik özelliklere sahip olsa da cerrahi olarak invaziv lobüler karsinomlar ile benzer şekilde sadece mastektomi değil meme koruyucu cerrahiyle de tedavi edilebilen bir hastalıktır

Anahtar Kelimeler: Lobüler karsinom, immünohistopatolojik özellik, mastektomi, meme koruyucu cerrahi

Introduction

Breast cancer is the most common cancer among women. It is the second most important cause of death due to cancer in women after lung cancer [1]. The incidence of breast cancer has increased in recent decades, especially in the younger age group. Despite the increase in the incidence and improvements in the treatment modalities of breast cancer, which is diagnosed early due to the developments in all screening and imaging methods, the mortality rate of the disease continues to be important and frightening. Conventional treatment methods for breast cancer include surgery, chemotherapy, radiotherapy and hormone therapy. Despite the developments in all treatment methods, especially chemotherapy, the need for new treatment modalities has increased due to the inability to achieve the expected survival rates in some subgroups. Patients with breast cancer have different prognoses after diagnosis, and there are differences in the disease biology in terms of progression and metastasis pathways; therefore, breast cancer has been classified, and different morphological variants have been defined. The final tumor classification of the WHO published in 2019 includes many variants of breast cancer, including a total of 44 major types and minor subtypes [2]. Nevertheless, some concerns have been raised about the biological significance of the identified variants. Despite the fact that many variants have been defined, they have not yet led to any changes in the clinical diagnosis, treatment, or follow-up practices of the disease.

Breast cancer is a heterogeneous disease. Invasive breast cancers are currently classified as the no special type of ductal carcinoma and special subtypes. Breast cancers of special subtypes have specific definitions, while the no special type is a general definition that includes carcinomas other than special subtypes. Non-specific type invasive ductal carcinomas (IDC) constitute approximately 60-75% of all breast cancers. Special subtypes account for 20-25% of all tumors and metaplastic, lobular, tubular, papillary, and mucinous tumors represent the most common types within this group [3, 4]. The histopathological features should be revealed effectively and in detail, and pathologic indicators concerning good and bad prognoses should be reviewed to treat patients with breast cancer under optimal conditions [5, 6].

Invasive lobular carcinomas (ILC) account for 15% of all breast cancers in women [7]. It is the most common group among special subtypes and has clinical and histo-pathological differences in terms of disease biology, with varied treatment and surgical options for the disease [8, 9]. The IDC usually emerges as a separate, palpable mass. In contrast, ILC is not well palpable and is often diagnosed late with multifocal, multicentric, or contralateral involvement [10]. Therefore, ILC develops differently, requiring different treatment modalities and prognoses [11].

In this study, we aimed to analyze the clinical and immunohistopathological characteristics of lobular breast cancers, which are one of the more common subtypes of breast cancer among a wide range, which are important in terms of diagnosis, treatment, and monitoring.

Materials and Methods

Our study was conducted retrospectively in the General Surgery-Surgical Oncology Clinic of the Gulhane Training and Research

Hospital of the University of Health Sciences. Patients diagnosed with and treated for breast cancer between January 2019 and August 2022 were included in the study after obtaining the necessary ethics committee permissions (Approval number E-50687469-199-210072112, Date 24.02.2023).

The demographic characteristics of patients with invasive lobular carcinoma were primarily recorded as age and menopausal status. The size and location of the disease at the time of diagnosis, its laterality, and the quadrants where the tumor was located were evaluated. The stage of cancer was determined by combining the type of surgery performed on the patients, the number of patients who had undergone sentinel lymph node biopsy and axillary dissection, the total number of lymph nodes removed in sentinel lymph node biopsy and axillary dissection, T(tumor size), N (metastatic lymph node count), and M (distant metastasis) results.

Tumor grades, immunohistochemical distribution of hormone profiles, estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptors (HER2), and Ki67 proliferation index values of the patients were recorded. The status of surgical margins after surgery was examined. All data were recorded and analyzed using the SPSS 25.0 statistical software. Descriptive statistics were performed.

Results

Among the 728 patients diagnosed and treated in our clinic during the period specified, 73 had been diagnosed with ILC. Demographic, clinical, and pathological characteristics of patients with ILC were summarized in Table-1.

Patients included in the study were between 28 and 81 years of age, and the median age was 53.04. While 26 (35.6%) of the patients were premenopausal, 47 (64.4%) were postmenopausal. The number of patients with unilateral characteristics was 71 (97.3%). The number of patients with bilateral ILC was 2 (2.7%). There were 38 patients with tumors (44.3%) in the upper outer quadrant (UOQ). Patients with tumors in the UOQ were followed by 11 patients with tumors in the lower outer quadrant (LOQ) and 8 patients in the central location (15.1% and 11%). Among the patients, 42 (57.5%) had undergone breast-conserving surgery and 31 (42%) had undergone mastectomy. Sentinel lymph node biopsy (SLNB) was performed in 51 (69.9%) of the patients. The number of lymph nodes removed in a sentinel lymph node biopsy was in the range of two and 12. The mean number of lymph nodes excised was 3.82 ± 1.42. The number of patients who had undergone axillary dissection was 22 (30.1%). The number of lymph nodes removed in axillary dissection was between eight and 25. The mean number of lymph nodes dissected was 14.82 ± 4.79. The distribution range for the number of metastatic lymph nodes was 1-5. The mean number was 2.86 ± 1.39.

Histologically, 62 (84.9%) of the patients with ILC had isolated lobular carcinoma, while 11 (15.1%) had mixed lobular carcinoma. Among the patients, 73 (100%) had ER, 67 (91.8%) had positive PR, and all had negative HER2. Ki-67 was evaluated in 67 of the patients. The distribution range for Ki-67 was 1.0-80.0 and the median Ki-67 proliferation index value was 20%. The tumor sizes were observed below 2 cm (T1) in 47.9%, between 2 and 5cm (T2) in 42.5%, and above 5 cm (T3) in 9.6% of the patients. In pathological staging, the number of patients without lymph node metastasis (N0) was 46 (63%), the number of patients with lymph node metastasis between 1 and 3 (N1) was 17 (23.3%), and the number of patients with lymph node metastasis between 4 and 9 (N2) was 10 (13.7%). There were 3 patients with histological grade 1 (4.1%), 65 patients with histological grade 2 (89%), and five patients with histological grade 3 (6.8%).

In invasive breast carcinoma, the membranous positivity of E-cadherin immunohistochemically is typical in NST. Tumor cells with cytological loss of cohesion, generally forming scattered or "single file" aligned linear cords in a fibrous stroma or concentric placement around normal ducts,

Table 1. Demographic and Clinico-pathological Characteristics of the Patients

Age, years, mean ± SD, distribution	53,04±11,68 (28-81)
Side, n(%)	
Right	34 (%46,6)
Left	37 (%50,7)
Bilateral	2 (%2,7)
Tumor Localization, n(%)	
UOQ	38 (%44,3)
UİQ	6 (%55,6)
LOQ	11 (%15,1)
LİQ	5 (%6,8)
Central	8 (%11)
UOQ+Central	3 (%4,1)
Multifocal	2 (%2,7)
Tumor Type, n(%)	
İsolated Lobular Carcinoma	62 (%84,9)
Mixed Lobular Carcinoma	11 (%15,1)
Operation, n(%)	
Breast Conserving Surgery	42 (%57,5)
Mastectomy	31 (%42,5)
Axillary İnterference, n(%)	
SLNB	51 (%69,9)
ALND	22 (%30,1)
SLNB Lymph Node Dissection, number, mean±SD, distribution	3,82±1,42 (2-12)
ALND Lymph Node Dissection, number, mean±SD, distribution	14,82±4,79 (8-25)
ALND Lymph Node metastasis, number, mean±SD, distribution	2,86±1,39 (1-5)
N Stage, n(%)	
N0	46 (%63)
N1	17 (%23,3)
N2	10 (%13,7)
T Stage, n(%)	
T1	35 (%47,9)
T2	31 (%42,5)
T3	7 (%9,6)
Ki 67,percent, mean±SD, distribution	16,86±14,92 (1-70)
Nottingham grade, number, mean±SD, distribution	6,51±0,71 (5-8)
Histological grade, number, mean±SD, distribution	
Grade 1	3 (%4,1)
Grade 2	65 (%89)
Grade 3	5 (%6,8)
Menopause Status, n(%)	
Premenopausal	26 (%35,6)
Postmenopausal	47 (%64,4)

UOQ: Upper Outer Quadrant UİQ: Upper İnner Quadrant LOQ: Lower Outer Quadrant LİQ: Lower İnner Quadrant SLNB: Sentinel lymph node biopsy ALND: Axillary lymph node dissection

are common in ILC (Figure 1 and 2). The tumor consists of uniform cells with round or ovoid nuclei, narrow cytoplasm, low mitotic activity, and usually mild pleomorphism. Intracytoplasmic lumen formations or central mucoid inclusions can be observed in neoplastic cells. In ILC, the loss of E-cadherin protein causes a discohesive appearance in cells. Therefore, immunohistochemical loss of E-cadherin expression is observed in approximately 85% of cases. Nevertheless, E-cadherin expression can be observed in approximately 15% of the cases. In such cases, it is recommended to refer to the morphology (Figure 3).

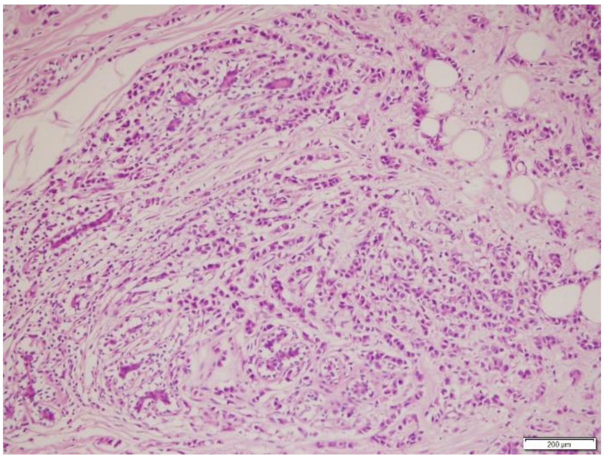

Figure 1. invasive lobular carcinoma, classical type

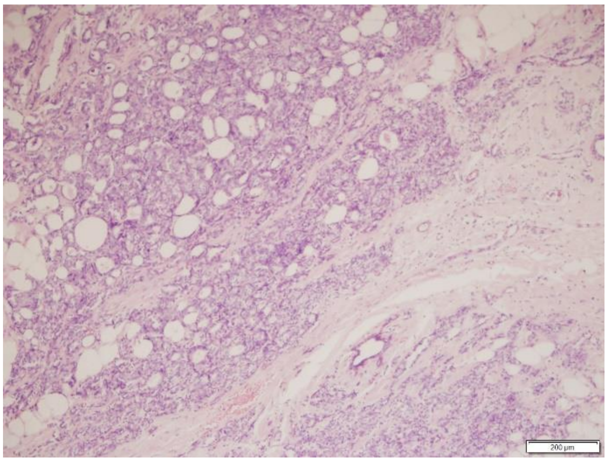

Figure 2. invasive breast carcinoma,NST

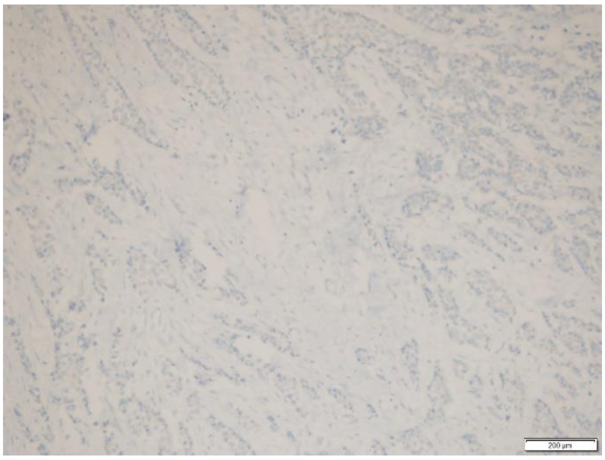

Figure 3: Immunohistochemical loss of e-cadherin in invasive lobular carcinoma

Discussion

Invasive lobular carcinoma is the second most common type of invasive breast cancer after IDC. ILC has unique clinical, pathological, and radiographic features, suggesting a separate clinical entity; however, it is treated with the same treatment paradigms as IDC. There is limited information about the specific treatment of ILC, including the response to standard therapy. In this study, 10.2% of the patients treated for breast cancer were determined to be of the ILC histological type, and this rate was found to be consistent with the literature.

Generally, women with ILC are slightly older compared to women with ICD at the time of diagnosis. The mean age of 53.04 was found to be compatible with the public health cancer statistics data of Turkey and the study conducted by Ozmen V (mean age 51.6) [12]. In the study of Enrico Orvieto et al., 36.8% of the patients were premenopausal and 63.2% were postmenopausal. Similar to the literature, 35.6% were premenopausal and 64.4% were postmenopausal in our study [13, 14].

ILC generally involves normal tissues without the intense desmoplastic response that usually accompanies IDC. The mass in the breast is not always a pronounced clinical feature, and sometimes it is difficult to distinguish it from the dense normal breast parenchyma. More than one-third is determined by asymmetric density, poorly defined opacity, and structural distortion in mammography. Microcalcifications screened on mammography are common symptoms of ductal carcinomas and are rarely detected in ILC. In ultrasonography (USG), the ILC appears as a heterogeneous hypoechoic mass with irregular margins and a posterior acoustic shadow. Some studies have demonstrated that USG has a higher sensitivity compared to mammography in detecting ILC and has the advantage of evaluating the presence of axillary lymph node metastasis. On the other hand, sensitivity in detecting ILC varies in the studies between 57-81% for mammography and 68-87% for

USG [15]. In the diagnosis of ILC and ICD, digital breast tomosynthesis and contrast-enhanced digital mammography are more sensitive compared to standard mammography [16, 17, 18]. USG is preferred as a complementary imaging method to standard mammography [19]. Greater multifocality and multicentricity in ILC is one of the factors causing the decrease in sensitivity in standard mammography compared to ICD. For all these reasons, breast magnetic resonance imaging (MRI) is recommended for all patients with ILC, unlike ICD. USG and breast MRI are recommended for both pre-operative evaluation and postoperative follow-up [19, 20].

Whether the prognosis in the ILC of the breast is different from the IDC is still a matter of discussion. Despite the controversy, factors affecting prognosis and treatment protocols are generally similar for both histological types. Nevertheless, ILC has been reported to be more frequently associated with factors such as advanced age at the time of diagnosis, large tumor size, multicentricity, multifocality, bilateralism, hormone receptor positivity, and HER2 negativity [11, 15].

ILC is almost always ER-positive and PR-positive. Excessive expression and/or amplification of HER2 is rare (3-13%). However, HER2 overexpression and/or amplification develop in a subset of pleomorphic ILCs. While 90-95% of patients with ILC have luminal A, this rate is 50% in ICD. Six studies analyzed ER, PR, and HER2 in detail and found that ICD was associated with triple-negative and HER2 with molecular subtypes, while ICL was associated with the luminal A subgroup. In this study, the ER receptor was positive in all patients, while 67 (91.8%) were PR positive and all were Cerb-B2 negative. These rates were consistent with the literature.

In terms of the location of the disease, ILC is more often multifocal. ILC is considered to have higher rates of bilateral disease; however, Pestalozzi et al. calculated similar rates of bilateral disease for IDC and ILC [22]. In our study, only two (2.7%) of the patients were bilateral.

Some studies in the literature observed the highest tumor size frequency in the T1 stage compared to the American Joint Committee on Cancer (AJCC) TNM staging criteria, while some studies observed it more frequently in the T2 stage. The percentage of T1 patients was found to be higher in our study, [21, 23, 24, 25, 26, 27]. In the literature, N0 has been demonstrated as the most common stage in terms of lymph node involvement, and it was followed by N1, N2, and N3, respectively. Pathological lymphatic stages were defined as pN0 by 50%, pN1 by 28%, pN2 by 15%, and pN3 by 7% [23, 24]. In our study, the lymph node status was pN0 by 63%, pN1 by 23.3%, and pN2 by 13.7%. In terms of distant metastasis, metastasis to bone and liver is frequent in both ILC and ICD. Unlike in ILC, the areas with greater metastatic spread are the abdominal cavity and the leptomeninges. Metastasis to the lung and central nervous system is less common compared to ICD [28, 29, 30, 31].

The general surgical treatment approach for breast cancer includes breast-conserving surgery (BCS) or mastectomy and systemic treatment depending on tumor characteristics such as tumor size, grade, lymph node, hormonal, and growth receptor status. One of the important points for the surgical treatment of invasive lobular cancer is the ability to choose the appropriate method among the BCS or mastectomy options due to the high rates of multifocality, multicentricity, and bilaterality. Fodor et al. investigated the long-term outcomes of BCS and mastectomy in ILC. For 15 years, they observed 235 patients with early-stage ILC who were prospectively treated with mastectomy or BCS. They found similar results for mastectomy and BCS in 15 years. Distant metastatic-free survival (62% vs. 70%; P= .2017), breast cancer-specific survival (62% vs. 70%; P= .1728), and regional recurrence-free survival (84% vs. 77%); P= .0644). Interestingly, better overall survival (OS) was observed in the BCS group compared to the mastectomy group (63% vs.

49% P= .0122) [32]. The fact that ILC is more multifocal and multicentric compared to IDC does not imply any contraindications for BCS. According to our patient data, 57.5% of the patients had undergone BCS, while 42.5% had undergone mastectomy. Our standard treatment policy is not based on the type of tumor histology. In their study, Biglia et al. concluded that a second surgery (conservative rejection/mastectomy) was necessary for a significantly higher percentage of patients with ILC to achieve negative limits. In general, there was no difference in the total number of mastectomies performed for ILC and IDC. In the multivariate analysis, only multifocality and tumor size (not histological type, grading, age, ER, and HER-2 status) were found to be independent predictors for re-excision or doubling the risk. In the first surgical approach, no significant difference was observed between the IDC and ILC groups, and BCS was the preferred treatment for most patients [21]. Recent studies have reported mastectomy rates ranging from 22% to 52% in patients with ILC (compared to 14% to 46% in patients with ICD). A positive surgical margin rate between 17% and 65% has been reported in patients with ILC undergoing BCS [33]. Similar to ICD, no improvement was observed in patients with ILC in terms of long-term survival after mastectomy compared to BCS with clear margins and the combination of radiotherapy [34].

Compared to the patients with ICD, patients with ILC appear to benefit less from neoadjuvant chemotherapy (NACT) administered to facilitate BCS and shrink the tumor. Low proliferation rate and high ER expression make ILC less susceptible to chemotherapy, as reflected by low pathological complete response (pCR) rates [36, 36, 37, 38]. There are conflicting results as to whether these low pCR rates can be attributed to differences in ER expression. Lips et al. found no difference between patients with ICD and ILC in response to chemotherapy [39]. Nevertheless, other studies have shown that the rate of pCR is still lower in patients with ILC when comparing ILC and ICD with a similar receptor status [40]. Although pCR appears to be a good prognostic factor for most breast cancers, this may not be the case for ILC, as low pCR rates do not lead to significantly worse outcomes in patients with ILC compared to ICD. Most patients with ILC still require mastectomy after NACT due to the lack of response to NACT [37, 41, 42].

Several studies have reported a higher nodal stage at diagnosis and a higher number of positive lymph nodes during surgery in ILC compared to ICD, leading to a higher rate of axillary lymph node dissection [22, 43, 44]. Since this is no longer seen in multivariate analysis, it can be attributed to larger tumor sizes and other misleading factors [45]. After sentinel lymph node biopsy, there is a 38% nodal positivity rate in node-negative patients, which highlights the challenges of clinical nodal evaluation in ILC [46].

Although ILC accounts for only a small percentage of invasive cancers, the pathogenesis, diagnosis, and clinical course of ILC have unique aspects and deserve special attention. Current analyses have demonstrated that the histology of ILC provides less benefit compared to NACT and tumors with ductal morphology. Despite the challenges in terms of radiological diagnosis and localization, BCS is preferred as an important treatment option for ILCs. While research on breast cancer is quite extensive, research on ILC is more limited. Further research is needed in this area, including providing an overview of ILC and treatment considerations that focus on early-stage treatment, particularly in the neoadjuvant setting.

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Corresponding author e-mail: girayakgul@hotmail.com

Orcid ID:
Gökhan Giray Akgül 0000-0002-0592-7521
Ebru Esen 0000-0003-3019-0872
Müjdat Turan 0000-0002-7854-4855
Sevket Barış Morkavuk 0000-0003-0441-0333
Simay Akyüz 0000-0002-0464-8934
Yasin Gülap 0000-0002-8983-3089
Pelin Seçken 0009-0007-5751-7907
Mehmet Ali Gülçelik 0000-0002-8967-7303

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Original Article

Comparison of Adjuvant Modified FOLFIRINOX with Other Adjuvant Chemotherapies in Resected Pancreatic Adenocarcinoma: Real-Life Data

Rezeke Edilmiş Pankreas Adenokarsinomda Adjuvan Modifiye FOLFİRİNOX'un Diğer Adjuvan Kemoterapilerle Karşılaştırılması: Gerçek Yaşam Verisi

Cihan Erol[1], Emre Hafızoğlu[2], Musa Barış Aykan[3], Deniz Can Güven[4], Bengü Dursun[5], Mutlu Hızal[2], Seda Kahraman[1], Didem Şener Dede[1], Muhammed Bülent Akıncı[1], Nuri Karadurmuş[3], Yüksel Ürün[5], Efnan Algın[2], Şuayib Yalçın[4], Bülent Yalçın[1], Mehmet Ali Nahit Şendur[1]

[1]Department of Medical Oncology, Faculty of Medicine,
Ankara Yıldırım Beyazıt University, Ankara, Turkey
[2]Department of Medical Oncology, Ankara City Hospital, Ankara, Turkey
[3]Department of Medical Oncology, Gülhane Education and Research Hospital, Ankara, Turkey
[4]Department of Medical Oncology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
[5]Department of Medical Oncology, Faculty of Medicine, Ankara University, Ankara, Turkey

ABSTRACT

Background: Pancreatic cancer is among the cancers with the worst prognosis and therefore adjuvant treatment is very important for reducing mortality. The aim of this study is to compare the gold standard mFolfirinox regimen with other treatment regimens in the adjuvant treatment of pancreatic cancer in real-world practice.

Materials and methods: Patients who underwent pancreatic cancer resection and received at least one dose of adjuvant chemotherapy were included in the study as two groups, mFolfirinox and Others (at a ratio of 1:2). The primary endpoint was disease-free survival (DFS). Secondary endpoints were determined as overall survival (OS), predictive factors, and safety.

Results: Data of 166 patients were collected from five oncology centers. With a median follow-up of 30.3 months (24.6-35.9), the estimated median DFS was detected 17.9 months (95% CI, 10.3-25.6) in the mFolfirinox group and 12.5 months (95% CI, 9.7-15.3) in the others group (p = 0.088). The estimated median OS was 30.7 months (95% CI, 15.7-45.7) in the mFolfirinox group and 22 months (95% CI, 16-27.9) in the others group (p=0.464). Better ECOG performance status, tumor location outside the head and ampulla, stage 1 and 2B, not receiving adjuvant chemoradiotherapy (CRT), and perineural invasion provide a disease-free survival advantage in favor of mFolfirinox.

Conclusion: In the adjuvant treatment of resected pancreatic cancer, the mFolfirinox regimen provided a statistically insignificant, but clinically significant DFS and OS benefit.

Keywords: Pancreatic adenocarcinoma, modified folfirinox, adjuvant chemotherapy, real-life experience

ÖZET

Amaç: Pankreas kanseri prognozu en kötü olan kanserler arasında yer alır ve bu nedenle adjuvan tedavi mortaliteyi azaltmak için çok önemlidir. Bu çalışmanın amacı, gerçek dünya pratiğinde pankreas kanserinin adjuvan tedavisinde altın standart mFolfirinox rejimini diğer tedavi rejimleriyle karşılaştırmaktır.

Gereç ve yöntem: Pankreas kanseri rezeksiyonu yapılan ve en az bir doz adjuvan kemoterapi alan hastalar mFolfirinox ve Diğerleri (1:2 oranında) olmak üzere iki grup olarak çalışmaya alındı. Birincil sonlanım noktası hastalıksız sağkalımdı (DFS). İkincil sonlanım noktaları, genel sağkalım (OS), prediktif faktörler ve güvenlik olarak belirlendi.

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Bulgular: Beş onkoloji merkezinden 166 hastanın verileri toplandı. Ortanca 30,3 aylık (24,6-35,9) takipte, tahmini ortanca DFS, mFolfirinox grubunda 17,9 ay (%95 GA, 10,3-25,6) ve diğerleri grubunda 12,5 ay (%95 GA, 9,7-15,3) olarak saptandı (p = 0.088). Tahmini ortanca OS, mFolfirinox grubunda 30,7 ay (%95 GA, 15,7-45,7), diğerleri grubunda 22 aydı (%95 GA, 16-27,9) (p=0,464). Daha iyi ECOG performans durumu, tümörün baş ve ampulla dışında yerleşimi, evre 1 ve 2B, adjuvan kemoradyoterapi (CRT) almama ve perinöral invazyon, mFolfirinox lehine hastalıksız sağkalım avantajı sağladı.
Sonuç: Rezeke edilmiş pankreas kanserinin adjuvan tedavisinde, mFolfirinox rejimi istatistiksel olarak önemsiz, ancak klinik olarak anlamlı bir DFS ve OS faydası sağladı.

Anahtar Kelimeler: Pankreas adenokarsinomu, modifiye folfirinox, adjuvan kemoterapi, gerçek yaşam deneyimi

Introduction

Pancreatic cancer is among the cancers with the worst prognosis and has an important place among cancer-related deaths [1, 2]. Minimal survival improvement has been achieved in the last few decades [3]. Although surgery is the only option for cure, 5-year survival rates are around 10% with surgery alone [4]. This low survival rate with surgery alone has led to the development of adjuvant treatment strategies. Gemcitabine was used in adjuvant therapy, which is an important drug in the treatment of metastatic pancreatic cancer, and in the landmark study phase-III CONKO-1, there was a significant improvement in median disease-free survival (DFS) with gemcitabine compared to surgery alone (13.4 months vs. 6.7 months $p<0.001$) [4]. With this study, gemcitabine remained the standard adjuvant therapy for a long time. The ESPAC-4 trial compared gemcitabine with the combination of gemcitabine and capecitabine in adjuvant therapy following the CONKO-1 trial. Median survival was 28 months to 25.5 months, with moderate significance in favor of combination therapy ($p = 0.032$) [5]. In the APACT trial which was recently presented, the adjuvant gemcitabine plus nab-paclitaxel study did not meet the primary endpoint of independently assessed DFS gemcitabine [6]. The combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (Folfirinox regimen) resulted in longer overall survival than gemcitabine when administered as first-line treatment in patients with metastatic pancreatic cancer [7]. Based on these results, the PRODIGE-24 phase III study was planned to investigate the efficacy of gemcitabine versus Folfirinox regimen in adjuvant treatment after pancreatic cancer resection [8]. In this study, the median disease-free survival was 21.6 months versus 12.8 months in favor of Folfirinox regimen, and the median survival was 54.4 months versus 35 months, respectively. Despite its apparent clinical efficacy, the Folfirinox chemotherapy regimen had high treatment toxicity. In this study, the efficacy was achieved by considering more toxicity. Because of this toxicity, the dose of irinotecan was reduced by removing the bolus 5-Fluorouracil, and this modified form (mFolfirinox) has become the gold standard for adjuvant therapy in patients with good performance in pancreatic adenocarcinoma. However, in real-life, patients are not treated with strict rules as in clinical trials [9]. There are many patient groups that were not included in the clinical trial. Therefore, real-life data are important to shed light on the treatment of these patient groups and also to confirm the results of clinical trials. We planned this retrospective real-life study to compare the gold standard mFolfirinox regimen with other treatment regimens in adjuvant treatment of pancreatic cancer.

Materials and Methods

Patients and design

This is a multi-center retrospective study. Study data were obtained retrospectively from patient files and hospital records. Ethical approval was obtained from the ethics committee of Ankara City Hospital, with the date of 08.06.2022 and number E2-22-1969, before starting study. The study was conducted in accordance with ethical rules, the Declaration of Helsinki and good clinical practice guidelines.

In our study, patient data were obtained from five high-volume tertiary oncology centers. Patients who underwent pancreatic cancer resection and received at least one dose of adjuvant chemotherapy were included in the study. All patients aged 18 years and older were included in the study. Patients who underwent R2 resection were allowed. Patients who received chemoradiotherapy in adjuvant treatment were also included in the study. The study was based on the comparison of two groups of patients, mFolfirinox and Others. In the study, which included patients at a ratio of 1:2, respectively, clinical, pathological and treatment information of the patients were collected. Data that are thought to be predictive factors were examined. The neutrophil to lymphocyte ratio (NLR), one of these factors, was calculated by dividing the neutrophil count by the lymphocyte count in complete blood count. The primary endpoint was disease-free survival. Secondary endpoints were determined as overall survival (OS), predictive factors, and safety. DFS was defined as the time from initiation of adjuvant treatment to recurrence/metastasis or death. OS was defined as the time from initiation of adjuvant treatment to death. The data of the patients who were not followed up were not used in the DFS analysis. The survival results of these patients were confirmed by checking the system of the Ministry of Health. Adverse events have been evaluated according to The Common Terminology Criteria for Adverse Events (CTCAE).

Statistical analysis

Statistical analysis was carried out using the IBM SPSS Statistics Version 25 program (SPSS Inc., Chicago, IL, USA). A median value and minimum-maximum values were used to determine continuous variables. Categorical variables were shown as numbers and percentages. The difference between the ages of the patients was evaluated with independent t-test, the difference of histologies and surgical margins between groups with the Fisher's exact test, and the differences of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) values between groups were evaluated with the Mann-Whitney U test. Differences between groups other than these were evaluated with the chi-square test. Survival was univariately analyzed by the Kaplan–Meier method with a log-rank test for the comparison of subgroups.

Results

Data of 166 patients were collected from 5 oncology centers at a ratio of 1:2 (mFolfirinox vs. others). The vast majority of patients in the others group received gemcitabine-based therapies as adjuvant treatment. 35.7% of patients (n= 40) were treated with gemcitabine plus capecitabine, 57.1% of patients (n = 64) were treated with single-agent gemcitabine, and 7.2% of patients (n = 8) were treated with other chemotherapy regimens. The median age at diagnosis of the patients was 57 (18-71) years and 63 (34-75) years for the mFolfirinox group and others group, respectively. The ≥ 65-year-old rate was 13% in the mFolfirinox group and 45% in the others group. There was no difference between the baseline characteristics of the patients, except for age, ECOG (Eastern cooperative oncology group) performance scores, whether or not they received adjuvant chemoradiotherapy, and postoperative CEA/CA19-9 values (Table 1).

Treatment and efficacy

The median duration of treatment was median 23.6 weeks (2 to 39.3) in the mFolfirinox group and 18.9 weeks (1 to 43.4) in the others group (p = 0.06). With a median follow-up of 30.3 months (24.6-35.9), 70% (n = 98) of all patients had an event for DFS, and 57.2% (n = 95) of patients died. The estimated median DFS was detected 17.9 months (95% CI, 10.3-25.6) in the mFolfirinox group and 12.5 months (95% CI, 9.7-15.3) in the others group (p = 0.088) (Figure 1). The estimated median OS was 30.7 months (95% CI, 15.7-45.7) in the mFolfirinox group and 22 months (95% CI, 16-27.9) in the others group (p = 0.464) (Figure 1). DFS rates at 12 months were

Table 1. Patient characteristics

	mFolfirinox group n= 54		Others group N=112		p value
Median age – years, *(range)*	57 (18 – 71)		63 (34 – 75)		< 0.001
≥ 65 years – n, (%)	7	*(13)*	49	*(45)*	< 0.001
Histology – n, (%)					0.55
Adenocarcinoma	54	*(100)*	109	*(97)*	
Other			3	*(3)*	
Stage – n, (%)					0.10
1	8	*(15)*	19	*(17)*	
2A	4	*(7)*	18	*(16)*	
2B	23	*(43)*	56	*(50)*	
3	17	*(32)*	19	*(17)*	
Missing	2	*(4)*			
Surgical margins – n, (%)					0.25
R0	41	*(76)*	88	*(79)*	
R1	10	*(19)*	18	*(16)*	
R2	0	*(0)*	6	*(5)*	
Missing	3	*(6)*			
Tumor location – n, (%)					0.15
Head	33	*(61)*	73	*(65)*	
Ampulla	14	*(26)*	16	*(14)*	
Other	7	*(13)*	22	*(21)*	
Lymphovascular invasion – n, (%)	36	*(67)*	72	*(64)*	0.81
Perineural invasion – n, (%)	46	*(85)*	93	*(83)*	0.61
ECOG performance status – n, (%)					0.002
0 - 1	48	*(89)*	87	*(78)*	
2	4	*(7)*	25	*(22)*	
Missing	2	*(4)*			
Adjuvant CRT – n, (%)					0.001
No	38	*(70)*	49	*(44)*	
Yes	16	*(30)*	63	*(56)*	
Median CEA – ng/mL,*(range)*	1.6 *(0.5-35.6)*		2.5 *(0.2-1123)*		0.002
Median CA19-9 – U/mL, (*range)*	32 *(1-3303)*		65 *(0.6-42010)*		0.004

mFolfirinox = Modified folfirinox, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, CEA = Carcinoembryonic antigen, CA19-9 = Carbohydrate antigen 19-9.

51.9% (n=27) and 53.4% (n=47) in the mFolfirinox group and in the others group (p = 0.502), respectively.

Predictive factors

In subgroup analysis, better ECOG performance status, tumor location outside the head and ampulla, stage 1 and 2B, not receiving adjuvant chemoradiotherapy (CRT), and perineural invasion provide a disease-free survival advantage in favor of mFolfirinox. In addition, in moderately differentiated histology and the NLR value being higher than the median value, a significant p value was found at the border. No difference was found between the groups in other subgroups (Table 2). In the overall survival analysis of the subgroups, no difference was found between mFolfirinox and other treatments in any group (Table 3).

Safety

Dose delay and dose reduction requirements were 67.9% (n=36) and 58.5% (n=31) in the mFolfirinox group, compared with 15.4% (n=16) and 12.6% (n = 13) in the others group, respectively (dose delay p<0.001, dose reduction p<0.001). Adverse events of any degree were seen in 92.3% in the mFolfirinox group, while 39.4% in the others group (p<0.001). Grade 3 or 4 adverse events were reported 51.9% in the mFolfirinox group, compared with 10.6% in the others group (p<0.001). The most common grade 3-4 adverse events in the mFolfirinox group were neutropenia (38.5%) and anemia (15.4%),

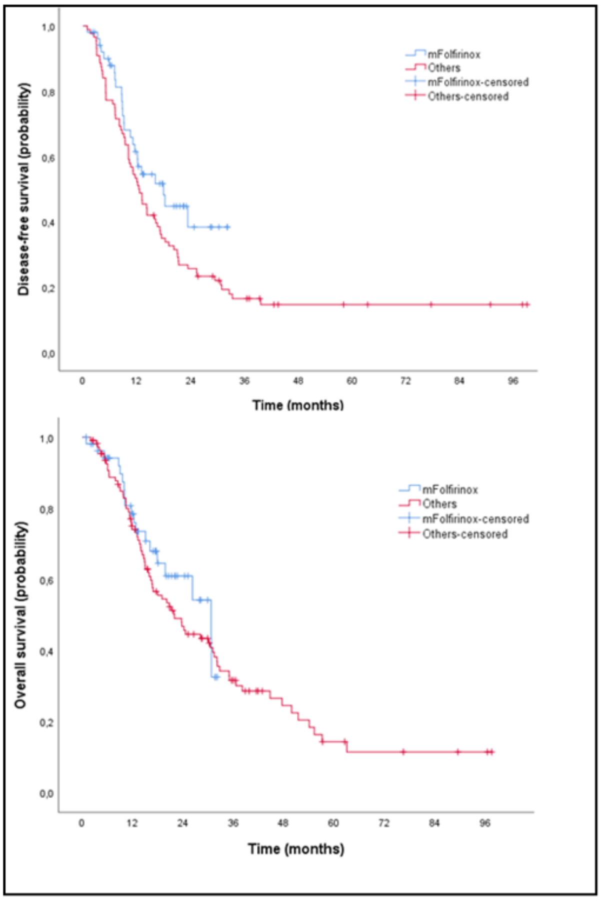

Figure 1. Kaplan-meier curves for disease-free survival and overall survival

compared with neutropenia (8.7%), anemia (3.8%) in the others group. One patient died in the mFolfirinox group due to treatment toxicity.

Discussion

The prognosis of pancreatic cancer is poor due to late diagnosis and aggressive nature [2, 10, 11]. Surgery remains the only curative treatment in resectable tumors. In addition to surgery, the cure rate is increased with adjuvant treatment [3, 12, 13]. Many clinical studies have investigated the results of various adjuvant treatment regimens [14]. However, the optimal multidisciplinary treatment strategy was controversial until the PRODIGE-24 phase 3 study, published in December 2018 [8]. Although there are still controversial points, with this study the mFolfirinox regimen became the gold standard in the adjuvant treatment of pancreatic cancer. In the adjuvant treatment of resected pancreatic cancer in our study, we found a clinically significant difference with the mFolfirinox regimen in median DFS of 17.9 months vs. 12.5 months compared to the other treatments, although it was not statistically significant. We also found a clinically significant, statistically insignificant difference in favor of mFolfirinox in overall survival of approximately 9 months. The mFolfirinox and other groups were generally well balanced, however, the mFolfirinox group consisted of younger, better ECOG performance scores, less treated with chemoradiotherapy, and had lower median CEA/CA 19-9 levels. The fact that fit patients, not exposed to chemoradiotherapy toxicity and had lower postoperative tumor markers were in the mFolfirinox group may have created a potential selection bias. However, the median DFS and OS of the others group were similar to both previous phase 3 studies [4, 5, 8, 15, 16] and real-life data [17, 18]. In the 5-year results of the recently published pivotal phase III trial, the median DFS was reported as 21.4 months and the median overall survival was 53.5 months [19]. In our study, DFS and especially OS in the mFolfirinox group were found to be lower than in the phase III pivotal clinical trial. Real-life data on the use of the mFolfirinox regimen in adjuvant treatment are very limited. In a small number of real-life studies, we see that very few patients use the mFolfirinox regimen for adjuvant treatment [20]. In our study, it is not surprising that the outcomes of patients in clinical practice were worse than in clinical trial. In the PRODIGE-24 study, all patients had an ECOG performance score of 0-1, while in our mFolfirinox group, 7% of patients had an ECOG performance score of 2. In addition, patients with stage III or CA 19-9 levels above 180 were excluded from the PRODIGE-24 study. In our study, 32% of the patients were stage III, and there were patients with high CA 19-9 levels. And we know that poor performance score, advanced stage and high CA 19-9 levels are associated with poor prognosis [17]. For this reasons, we can say that the differences in outcomes between mFolfirinox and the others group are not only

Table 2. Effects of treatments on disease-free survival in subgroup analysis

	mFolfirinox group	Others group	p value
	Median DFS (95% CI), months		
Age			
< 65 years	18.3 (6.7 to 29.8)	13.2 (11.2 to 15.1)	0.127
≥ 65 years	17.6 (13.2 to 22)	11.2 (6.5 to 15.7)	0.208
ECOG performance status			
0 - 1	23.3 (1 to 32.2)	13.2 (10.9 to 15.4)	0.023
2	8.6 (0.6 to 16.5)	11.6 (7.3 to 15.9)	0.908
Tumor grade			
Well differentiated	*	17.5 (4.6 to 30.3)	0.18
Moderately differentiated	18.3 (12 to 24.5)	12.4 (9.1 to 15.9)	0.055
Poorly differentiated	11.1 (8.1 to 14.2)	10.1 (6.7 to 13.4)	0.856
Tumor location			
Head	12.2 (5.1 to 19.1)	12.4 (8.9 to 15.9)	0.728
Ampulla	*	23.3 (7.5 to 39.2)	0.226
Other	*	10.3 (8.2 to 12.5)	0.045
Stage			
1	*	*	0.036
2A	*	14.2 (10.6 to 17.9)	0.512
2B	*	11.2 (8.6 to 13.8)	0.007
3	10.6 (7.7 to 13.5)	8.7 (3.5 to 13.9)	0.741
Surgical margins			
R0	23.3 (14.7 to 31.9)	14.2 (10.3 to 18.1)	0.082
R1	*	7.1 (2.8 to 11.4)	0.111
R2	N/A	8.1 (0.04 to 16.1)	N/A
Adjuvant CRT			
No	23.3 (*)	13.2 (9.1 to 17.3)	0.03
Yes	17.9 (8.9 to 26.9)	11.1 (7.8 to 14.5)	0.481
Body mass index			
< 18.5	11.5 (0.1 to 27.4)	12.2 (6.9 to 17.4)	0.364
18.5 - 24.9	16.1 (7.9 to 24.2)	13.1 (5.5 to 20.9)	0.545
≥ 25	*	12.6 (8.3 to 16.9)	0.104
Smoking history			
No	13.1 (6.6 to 19.4)	12 (5.9 to 18)	0.442
Yes	23.3 (7 to 39.6)	12.5 (10.3 to 14.6)	0.107
NLR			
≤ median	13.1 (5.4 to 20.7)	12 (7.9 to 16.1)	0.511
> median	23.3 (11.1 to 35.5)	13.2 (10.1 to 16.3)	0.06
Postoperative CA19-9 level			
≤ ULN**	*	17.1 (5.8 to 28.5)	0.129
> ULN	12.1 (6.6 to 17.8)	12.1 (9.8 to 14.5)	0.213
Lymphovascular invasion			
No	*	17.5 (5.6 to 29.4)	0.09
Yes	17.9 (6.5 to 29.3)	12 (9.7 to 14.3)	0.156
Perineural invasion			
No	*	39.6 (23.1 to 56.1)	0.466
Yes	17.9 (9 to 26.8)	11.6 (9.7 to 13.5)	0.016

*mFolfirinox = Modified folfirinox, DFS = Disease-free survival, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, NLR = Neutrophil to lymphocyte ratio, CA19-9 = Carbohydrate antigen 19-9, ULN = Upper limits of normal. * Statistical value could not be calculated due to the small number of patients. **The ULN is 30 U/mL.*

Table 3. Effects of treatments on overall survival in subgroup analysis

	mFolfirinox group	Others group	p value
	Median OS (95% CI), months		
Age			
< 65 years	30.7 (15.5 to 45.9)	20.7 (13 to 28.5)	0.28
≥ 65 years	*	23.7 (10.8 to 36.6)	0.627
ECOG performance status			
0 - 1	30.7 (16.6 to 44.7)	24.2 (14.3 to 34.1)	0.6
2	10.1 (*)	16.3 (10.8 to 21.6)	0.916
Tumor grade			
Well differentiated	*	44.7 (12.1 to 77.4)	0.494
Moderately differentiated	30.7 (11.9 to 49.5)	21.2 (15.9 to 26.5)	0.235
Poorly differentiated	12.3 (8.7 to 15.9)	14 (8.4 to 19.6)	0.284
Tumor location			
Head	26.3 (11 to 41.5)	20.7 (15.4 to 26.1)	0.506
Ampulla	*	36.6 (14.2 to 59)	0.249
Other	*	23.7 (12.4 to 34.9)	0.216
Stage			
1	*	32.1 (0.6 to 63.6)	0.252
2A	*	*	0.424
2B	30.7 (24.2 to 37.2)	21.2 (13.9 to 28.5)	0.288
3	15.1 (5.8 to 24.3)	12.8 (9.9 to 15.8)	0.936
Surgical margins			
R0	30.8 (18.2 to 43.4)	24.6 (15.1 to 34.1)	0.508
R1	*	23.7 (9.6 to 37.4)	0.847
R2	N/A	9.1 (2.7 to 15.3)	N/A
Adjuvant CRT			
No	30.7 (22.7 to 38.6)	31.1 (26.1 to 36.1)	0.57
Yes	30.1 (17.1 to 44.5)	16.6 (11.7 to 21.6)	0.317
Body mass index			
< 18.5	15.1 (*)	11.7 (*)	0.535
18.5 - 24.9	30.7 (14.4 to 47)	22 (13.3 to 30.6)	0.754
≥ 25	*	31.1 (12.5 to 49.6)	0.394
Smoking history			
No	*	20.1 (11.4 to 28.8)	0.335
Yes	30.7 (19.2 to 42.2)	30.1 (16.8 to 43.4)	0.918
NLR			
≤ median	30.8 (14.7 to 46.8)	23.7 (8.6 to 38.8)	0.929
> median	30.7 (15.1 to 46.2)	16.7 (10.7 to 22.7)	0.154
Postoperative CA19-9 level			
≤ ULN**	30.7 (*)	30.5 (16.3 to 44.7)	0.592
> ULN	26.3 (8.7 to 43.8)	16.7 (10.8 to 22.6)	0.622
Lymphovascular invasion			
No	*	30.1 (21.1 to 39.1)	0.517
Yes	30.7 (10.1 to 51.3)	19 (12.6 to 25.4)	0.626
Perineural invasion			
No	*	63 (35 to 91)	0.937
Yes	30.7 (16.3 to 45.1)	19 (12.4 to 25.6)	0.331

*mFolfirinox = Modified folfirinox, OS = Overall survival, ECOG = Eastern cooperative oncology group, CRT = Chemoradiotherapy, NLR = Neutrophil to lymphocyte ratio, CA19-9 = Carbohydrate antigen 19-9, ULN = Upper limits of normal. * Statistical value could not be calculated due to the small number of patients. **The ULN is 30 U/mL.*

due to selection bias, but are the effectiveness of mFolfirinox.

In subgroup analysis, it is predicted DFS advantage with mFolfirinox in the patients with ECOG performance status 0-1, tumors located in the pancreatic body and tail, stage I and IIB tumors, the patients who do not receive adjuvant chemoradiotherapy and tumors with perineural invasion. The efficacy of mFolfirinox in patients with an ECOG performance score of 2 compared to other regimens is not clear, as all patients in the PRODIGE-24 study were patients with an ECOG performance score of 0-1 [8]. Despite the small number of patients, we did not find any difference between treatment regimens in patients with an ECOG performance score of 2 in our study. These results suggest that this regimen should be considered in fit patients.

Chemotherapy is generally avoided in elderly patients [21]. However, elderly patients have been shown to benefit similarly from chemotherapy [22]. While patients ≥ 65 years of age benefited from mFolfirinox treatment in the pivotal trial, we found no difference between treatment regimens in patients ≥ 65 years of age in our real-life study. Based on these results, it may be a good option to consider less toxic regimens for elderly patients.

The use of adjuvant CRT, in the era of mFolfirinox, is controversial. It can generally be used in patients with positive surgical margins or lymph nodes. In our study, the outcomes of patients who did not receive adjuvant CRT were numerically higher than the patients who received it. This is the result of increasing treatment toxicity and adversely affecting survival. Also, there is no difference between the treatment regimens.

While we expect mFolfirinox, which is considered to be a more effective treatment, to have better survival in patients with poor prognostic factors (poorly differentiated, stage III, R1 resection, high NLR, postoperative high CA19-9 level, and lymphovascular invasion), unlike the pivotal study, no difference was found with other treatment regimens in our study. This may be due to the different patient population and treatment regimens.

As expected, the safety profile of the mFolfirinox regimen was less favorable than other adjuvant treatments. We found that we obtained this non-significant difference in survival outcomes in favor of mFolfirinox with higher treatment-related adverse events. In the PRODIGE-24 study, grade 3-4 adverse events were seen in 75.9% of patients, this rate was 51.9% in our study. Adverse events were lower than in the clinical trial, but slightly higher than in real-life data. In a retrospective study reported from China, dose reduction with mFolfirinox was found to be 41.2%, while in our study it was found to be 67.9% [23]. Toxicity is not only an important problem in the acute period. It may shorten the duration of treatment, leading to early discontinuation of adjuvant therapy. This may adversely affect long-term survival. In a study in which most patients received gemcitabine-based adjuvant treatment, median recurrence-free survival was found to be 22 months in patients who completed adjuvant therapy, and 9 months in patients whose therapy was discontinued early [20]. In our study, almost all patients (92.3%) had adverse events at any grade with mFolfirinox. Most of these were manageable adverse events. However, we would like to emphasize that 2% of patients (one patient) died of treatment-related adverse event in the mFolfirinox group. Therefore, patient selection for the mFolfirinox regimen in the adjuvant treatment of pancreatic cancer is very important. Treatment may be beneficial in patients who can tolerate treatment and experience minimal treatment toxicity.

We would like to highlight a few limitations of our study. The most important limitation is the retrospective nature of our study, and its natural consequences. The uneven distribution between groups and the potential selection bias were the result of this limitation. Second, adverse events may have been underestimated because the data were obtained from hospital records and patient files. Third, there was no granulocyte colonystimulating factor usage information available. Fourth, the treatment information at the time of recurrence of the patients was unknown. And finally, genetic factors (microsatellite instability and Breast cancer gene 1-2) that may affect the prognosis of patients were not known.

In conclusion, in the adjuvant treatment of resected pancreatic cancer, the mFolfirinox regimen provided a statistically insignificant, but clinically significant DFS and OS benefit. The mFolfirinox regimen was found to be more toxic than other adjuvant regimens, and mFolfirinox regimen should be considered in fit patients.

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Corresponding author e-mail: chan_erol@hotmail.com

Orcid ID:
Cihan Erol 0000-0003-3155-8798
Emre Hafızoğlu 0000-0001-6291-851X
Musa Barış Aykan 0000-0001-7538-9119
Deniz Can Güven 0000-0002-6924-9467
Bengü Dursun 0000-0002-1433-8446
Mutlu Hızal 0000-0001-5147-4431
Seda Kahraman 0000-0002-5328-6554
Didem Şener Dede 0000-0002-9756-5942
Muhammed Bülent Akıncı 0000-0001-7575-9925
Nuri Karadurmuş 0000-0003-3291-8062
Yüksel Ürün 0000-0002-9152-9887
Efnan Algın 0000-0002-8917-9267
Şuayib Yalçın 0000-0001-7850-6798
Bülent Yalçın 0000-0002-4431-8948
Mehmet Ali Nahit Şendur 0000-0001-7021-6139

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Case Report

Granulosa Cell Tumor of the Ovary in a Patient with Adjuvant Tamoxifen Use for Breast Cancer: An Extremely Rare Case Report

Meme Kanseri Tedavisinde Adjuvan Tamoksifen Kullanan Bir Hastada Ovaryan Granüloza Hücreli Tümör: Oldukça Nadir Görülen Bir Vaka

Hatice Tülüce Atlım[1], Yusuf İlhan[2], Anıl Alpsoy[3], Sema Sezgin Göksu[4], Gülgün Erdoğan[3],
Ali Murat Tatlı[4], Hasan Şenol Coşkun[5]

[1]Department of Internal Medicine, Akdeniz University, Antalya, Turkey
[2]Department of Medical Oncology, Tatvan State Hospital, Bitlis, Turkey
[3]Department of Pathology, Akdeniz University, Antalya
[4]Department of Medical Oncology, Akdeniz University, Antalya, Turkey
[5]Akdeniz Sağlık Vakfı Yaşam Hospital, Department of Medical Oncology, Antalya

ABSTRACT

Tamoxifen use can cause gynecologic tumors like uterine sarcomas. However, the relationship between tamoxifen use and adult granulosa cell tumors (AGCTs) is uncertain. Here we report a case of AGCT in a 57-year old patient with antecedent tamoxifen use for hormone-receptor positive breast cancer. After 22 months of tamoxifen use, the patient had diagnosed with a stage 1a granulosa tumor. To our knowledge, there are only four cases previously published about the relationship between the development of granulosa cell tumors and the use of tamoxifen. It is very difficult to say that there is a certain relationship between tamoxifen use and AGCT because of the rarity of the condition.

Keywords: Breast cancer, granulosa cell tumor, tamoxifen

ÖZET

Tamoksifen kullanımı uterin sarkomlar gibi jinekolojik tümörlere yol açabilir. Ancak tamoksifen kullanımının yetişkin granüloza hücreli tümör (AGCT) etiyolojisindeki yeri kesin değildir. Biz burada, hormon pozitif meme kanseri nedeniyle adjuvan tamoksifen tedavisi almakta olan 57 yaşındaki bir hastada gelişmiş olan AGCT vakasını bildirmek istiyoruz. Hastamız evre 1a AGCT tanısı aldığında 22 aydır tamoksifen kullanmaktaydı. Bildiğimiz kadarıyla, tamoksifen kullanımı altında gelişen AGCT' ler ile ilgili daha önce yayımlanmış 4 adet vaka bildirimi mevcuttur. Bu tip vakalarının çok nadir olması nedeniyle AGCT gelişimini tamoksifen kullanımı ile ilişkilendirmenin oldukça zor olduğunu söylemek isteriz.
Anahtar kelimeler: Meme kanseri, granüloza hücreli tümör, tamoksifen

Introduction

Breast cancer is the most common cancer type among women worldwide. Selective estrogen receptor modulators are widely used for treating hormone receptor-positive breast cancer. One of their mechanisms of action is that; it competes with estradiol for estrogen receptors. However, their pharmacodynamics are complex. They can also act as a partial estrogen agonist in certain tissues. So,

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sometimes detrimental effects can be developed with these drugs. For example, tamoxifen is known as an important risk factor for endometrial cancer [1].

Ovarian sex cord-stromal tumors (SCSTs) are a group of tumors that originates from the sex cord-stromal cells (Leydig, Sertoli and, Granulosa cells). They are less common when compared with epithelial and germinal origin ovarian tumors. According to Surveillance, Epidemiology and End Results United States national database, the incidence of SCSTs was 0.20 per 100,000 women [2]. Recent studies suggest that sex cord-stromal tumors might be associated with certain genetic syndromes like Peutz-Jeghers syndrome, Ollier Disease, Maffucci syndrome, and DICER1 syndrome [3]. However, the etiology of these tumors remains uncertain.

To our knowledge, they are only a few cases formerly reported about the relation of tamoxifen use and adult granulosa cell tumor (AGCT). Here, we report a case of AGCT with antecedent tamoxifen use for breast cancer.

Case Report

A 57-year-old postmenopausal woman with a history of breast cancer presented with abnormal uterine bleeding and an ovarian mass. Two years ago, the patient had undergone breast-conserving surgery due to intramammarian mass. Her pathology report was given as invasive ductal carcinoma, ER-positive, PR-positive, HER2-negative. Positron emission tomography/computed tomography scan had shown no distant metastasis. She had been diagnosed with hormone receptor-positive breast cancer. The patient was evaluated as T1N0M0, stage 1a breast cancer according to the TNM staging system. After breast-conserving surgery, she had received adjuvant radiotherapy. She has been receiving adjuvant tamoxifen for 22 months since her diagnosis. In June 2021, the patient was admitted to the hospital with abnormal uterine bleeding. Ultrasound showed a nodular mass in her left ovary. Therefore, she underwent an adnexal hysterectomy and salpingo-oophorectomy. On gross examination, 30x21x12 mm diameter of the left ovary with an intact capsule was seen. On the cut surface, an 18 mm yellow and nodular mass with a soft surface adjacent to ovarian stroma was observed. Microscopically, at small magnification, a moderately cellular tumor characterized by solid, microfollicular, insular and trabecular patterns localized at the ovarian stroma was observed. At high magnification, tumor cells showed pale to eosinophilic

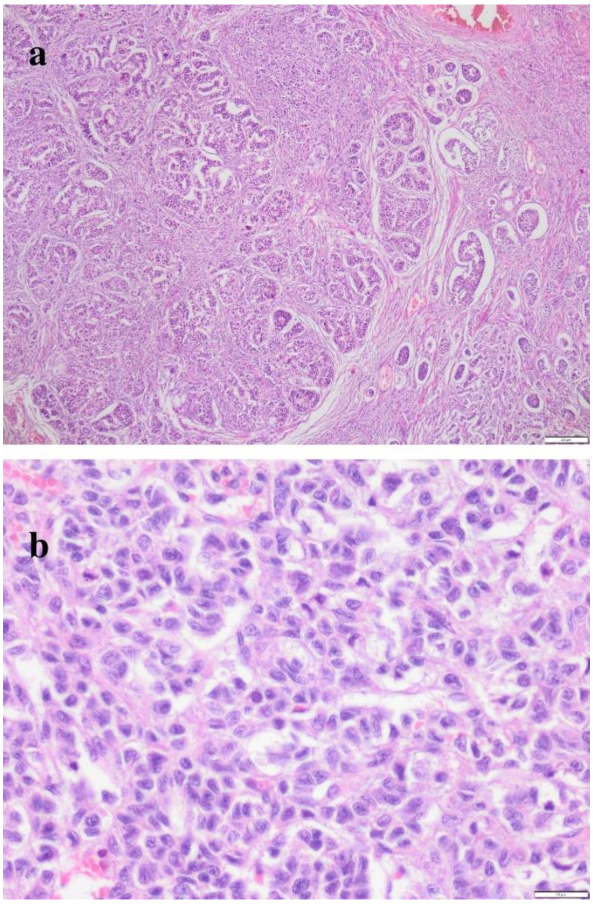

Figure 1a. Trabecular pattern of the tumor can be observed, especially at the right side of the image (HE x40). 1b. Trabecular pattern of the tumor can be observed (HE x100).

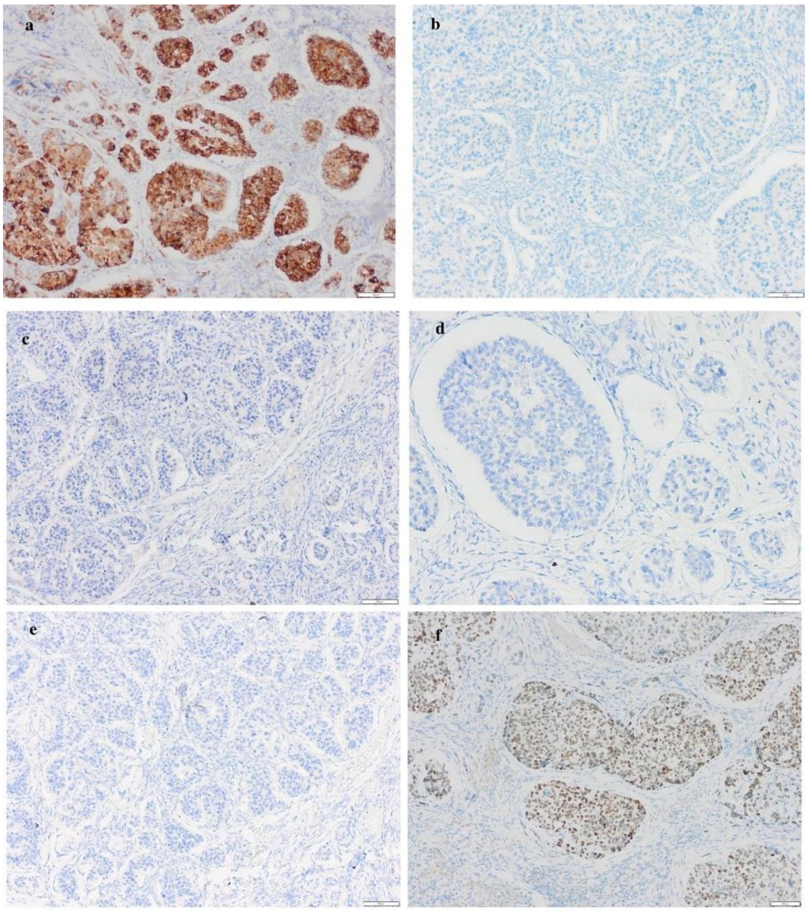

Figure 2a. Tumor cells showed cytoplasmic positivity for Inhibin (x100). b. Tumor cells stained negative for CK7 (x100). c. Tumor cells stained negative for PAX8 (x100). d. Tumor cells stained negative for GCDFP15 (x200).e. Tumor cells stained negative for Mammoglobulin (x100). f. Tumor nuclei stained positive for PR (x100).

cytoplasm and pale, oval nuclei with an irregular border. Some tumor cells had nuclear grooves (Figure 1). On 10 high magnification fields, 13 mitoses were counted. Immunohistochemically tumor cells stained positive for inhibin whereas they stained negative for CK7and PAX8. Since the patient had a breast cancer history differential diagnosis was made with negative staining for GCDFP15, Mammoglobulin, ER, and Cerb B2. PR showed immunopositivity with tumor cells (Figure 2). Inhibin positivity and pale cytoplasm ruled out poorly differentiated adenocarcinoma and small cell carcinoma. A final diagnosis of adult granulosa cell tumor was rendered based on morphology and immunohistochemical stains. The peritoneal washing cytology was negative. The stage of disease was classified as 1A according to FIGO. No adjuvant therapy was suggested. Keeping her on a close follow-up is decided. Tamoxifen therapy is continued since there is no clarity about the relation between tamoxifen use and AGCT. The patient is still in remission for both breast cancer and AGCT. An informed consent form was obtained from the patient.

Discussion

The adult granulosa cell tumor is relatively uncommon cancer type among women cancers [2,4]. Based on a few cases in the literature, it is considered that tamoxifen might play a role in the pathogenesis of AGCT. The studies designed to prove the relationship between tamoxifen use and

Table 1. The clinical and pathological characteristics of the patients

References	Age	Duration of Treatment	FIGO Classification	Mitotic index	ER	PR
Gherman et al.	52	11 months	1c	5	Unknown	Unknown
Arnould et al.	63	4 years	1c	2	-	+
Abhassian et al.	47	5 years	1c	3-5	Unknown	Unknown
Tanaka et al.	58	5 years*	1c	5	-	+
Our current case	57	22 months	1a	13	-	+

*2 years of torefemine use after 5 years of tamoxifen theraphy

uterine sarcomas are first failed due to the rarity of cases [5]. But recently, tamoxifen is known to be a risk factor for uterine sarcomas [1].

To our knowledge, AGCT with antecedent tamoxifen use has been described in only four cases previously. The first case of all was reported by Gherman et al in 1994. It was a 52-old woman with liver disfunction. The authors concluded that the hepatic failure may have resulted in changes in tamoxifen metabolism, therefore AGCT may be developed [6]. The second case was a case of breast carcinoma metastasis within AGCT, reported by Arnould et al in 2002. This time the patient had no signs of hepatic failure [7]. Then in 2010 Abahssain et al reported the third case of AGCT with antecedent tamoxifen use. They presumed that considering worldwide tamoxifen use among women AGCT development might be random [8]. Finally, in 2020, Tanaka et al reported AGCT in a 58-year old female patient with long-term tamoxifen use [9]. We report the fifth case of AGCT in a 57-year old patient after 22 months of tamoxifen use. We also emphasize that the AGCT cases may be incidental. The clinical and pathological characteristics of these patients are summarized in Table 1.

At least in the cases in which we can reach the hormone receptor information, we can see that ER was negative in ovarian GCTs. If tamoxifen acted through only hormone receptors, ER-receptor would have been positive in these GCTs. On the other hand, in 2009 Merglen et al represented that, the risk of death from breast cancer significantly increases in patients with ER-negative breast cancer who were treated with tamoxifen. And they also concluded that, besides its remarkable impact on ER-positive breast cancer, tamoxifen may cause carcinogenesis of ER-negative tumors [10]. Some of the studies demonstrated that tamoxifen's impact on the hormone receptors is not its only mechanism of action. Tamoxifen also can act on growth factor signaling pathways, therefore it can be detrimental effects [11]. Moreover, metabolites like metabolite E and bisphenol derived from tamoxifen can have alternative mechanisms of action for ER-negative cells. For example, Wiebe et al identified metabolite E and bisphenol in tamoxifen resistance MCF-7 human breast tumor implanted in athymic nude mice, as well as tumors from patients with tamoxifen resistance [12]. Due to the multifocal effects of tamoxifen, we think that it may be related to cancers such as AGCT, although it is not certain.

Considering the widespread use of tamoxifen all around the world, among women with breast carcinoma, the development of AGCT seems to be incidental, but these results show the importance of proper surveillance especially for women on tamoxifen and the early diagnosis of gynecological tumors. Our current case and these results show that it is very difficult to say there is a certain relationship between tamoxifen use and AGCT because of the rarity of the condition

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Corresponding author e-mail: dryusufilhan@gmail.com

Orcid ID:
Hatice Tülüce Atlım 0000-0002-6676-2847
Yusuf İlhan 0000-0002-2875-6876
Anıl Alpsoy 0000-0003-4978-7652
Sema Sezgin Göksu 0000-0002-1222-0444
Gülgün Erdoğan 0000-0003-3518-2142
Ali Murat Tatlı 0000-0001-9696-1102
Hasan Şenol Coşkun 0000-0003-2969-7561

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Case Report

A Giant Metastatic Adrenal Cortical Carcinoma Case Presented with Rapid Progression

Hızlı İlerleyen Dev Metastatik Adrenal Kortikal Karsinom Olgusu

Merve Durna[1], Atakan Topçu[2], İsmail Yurtsever[3], Melih Şimşek[2], Mehmet Aydın[4], Mesut Şeker[2]

[1]Department of Internal Medicine, Bezmialem Vakif University, Istanbul, Turkey
[2]Department of Medical Oncology, Bezmialem Vakif University, Istanbul, Turkey
[3]Department of Radiology, Bezmialem Vakif University, Istanbul, Turkey
[4]Department of Nuclear Medicine, Bezmialem Vakif University, Istanbul, Turkey

ABSTRACT

Adrenocortical carcinoma (ACC) is an uncommon and aggressive tumor. Despite the current treatment options commonly used in ACC, the prognosis is poor. No risk factors have been identified except for genetic predisposition. The most important factors affecting the prognosis are the stage at the time of diagnosis and the resectability of the primary tumor. Here, we present a metastatic ACC case of a 29-year-old woman presented with symptoms of swelling in her feet, abdominal striae, and mild abdominal pain for three months. The abdominal computed tomography scan revealed a 14 cm mass in the right adrenal gland, indistinguishable from the liver and right kidney. Clinicians should consider primary ACC, which has limited treatment options, in the differential diagnosis in the presence of findings such as edema, obesity, and striae.

Keywords: Adrenocortical carcinoma, case study, chemotherapy, metastatic, mitotane

ÖZET

Adrenokortikal karsinom (AKK) nadir görülen, agresif bir tümördür. AKK’de yaygın olarak kullanılan mevcut tedavi seçeneklerine rağmen prognoz kötüdür. Genetik yatkınlık dışında herhangi bir risk faktörü tanımlanmamıştır. Prognozu etkileyen en önemli faktörler, tanı anındaki evre ve primer tümörün rezektabilitesidir. Bu yazıda, üç aydır ayaklarda şişlik, karında çizgilenme ve hafif karın ağrısı şikayetleri ile başvuran 29 yaşındaki kadın hastada metastatik AKK olgusu sunulmaktadır. Bilgisayarlı tomografide sağ böbreküstü bezinde karaciğer ve sağ böbrekten ayırt edilemeyen 14 cm'lik kitle saptandı. Tedavi seçenekleri kısıtlı olan primer AKK; ödem, obezite, stria gibi bulguların varlığında ayırıcı tanıda düşünülmelidir.

Anahtar kelimeler: Adrenokortikal karsinom, olgu sunumu, kemoterapi, metastatik, mitotan

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Introduction

Adrenocortical carcinoma (ACC) is an uncommon and agressive tumor. The annual incidence is reported as 0.5-2 cases per million, and it is more common in women than men. A bimodal age distribution is seen, as under the age of five years and in the fifth decade[1]. Currently, except for genetic predisposition, no risk factors have been identified. While most of the patients present with symptoms related to excessive hormone production; the remaining cases are detected incidentally or as a result of complaints related to tumor size. In adrenocortical carcinomas, computed tomography (CT) and magnetic resonance imaging (MRI) are the preferred imaging modalities both for the localization of the tumor and detection of distant metastases. 25% of the cases has metastatic disease at the time of diagnosis, mostly to liver, lung, lymph nodes, and bone [2]. While 5-year survival rate is 60-80% in tumors confined to the adrenal gland, it is decreased to 0-28% in metastatic stage [3]. The most important factors affecting the prognosis are stage at the time of diagnosis and the resectability of primary tumor. In addition, advanced age, tumor size, presence of hormone-secreting tumor, high Ki-67 index (>10%) and mitotic activity, and tumor necrosis may be related to poor prognosis in ACC. Currently, the only curative approach is surgical resection. Palliative therapy is just limited to patients with unresectable or metastatic ACC [4]. Here, it was aimed to present a metastatic ACC case that passed away rapidly after the initiation of systemic treatment.

Case Report

A 29-year-old woman referred to our clinic with symptoms of swelling in her feet, abdominal striae, and mild abdominal pain that has begun three months ago. Medical history of the patient was remarkable for obesity (BMI: 43), type-2 diabetes mellitus, hypothyroidism, and thalassemia minor. The medications were levothyroxine sodium, metformin, and insulin aspart. Alopecia, acne, aphthous stomatitis, striae on the abdomen and feet, and bilateral pretibial edema were found in the physical examination at referral. Initial laboratory findings showed hyperglycemia, elevated liver function tests including total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, gamma glutamyl transferase, aspartate transaminase, alanine transaminase, and INR (international normalized ratio) levels. Ejection fraction was more than 60% without significant pathology in Echochardiography. No thrombus formation was detected with bilateral lower extremity doppler ultrasound screening. Further investigation was planned due to the Cushingoid appearance and abnormal laboratory results.

After consultation with department of endocrinology, hypercortisolemia (midnight level: 46,6 µg/dL), and low ACTH levels (5 pg/mL) were detected. 1 mg dexamethasone suppression test was compatible with hypercortisolemia. Aldosterone to renin ratio, cathecolamine and sex-hormone levels were in normal range. The Pituitary MRI showed no significant finding. Abdominal CT scan revealed a 14 cm mass in the right adrenal gland, indistinguishable from the liver and right kidney, and multiple parenchymal liver masses with the largest diamater 10 cm. (Figure 1, 2, 3). No pathological lesion was detected in thorax CT. The histopathological and immunohisto-chemical analysis of liver tru-cut biopsy was reported as the metastasis of primary adrenal cortex carcinoma. And, positive staining for synaptophysin, inhibin, melan A, vimentin and p53 was detected in the patohology specimen. A hypermetabolic mass with intense 18-FDG (18-fluorodeo-xyglucose) uptake in the right surrenal region with tendency to coalesce in the liver was detected in 18-FDG positron emission tomography-computerized tomography (18-FDG PET-CT). A similarly heterogeneous

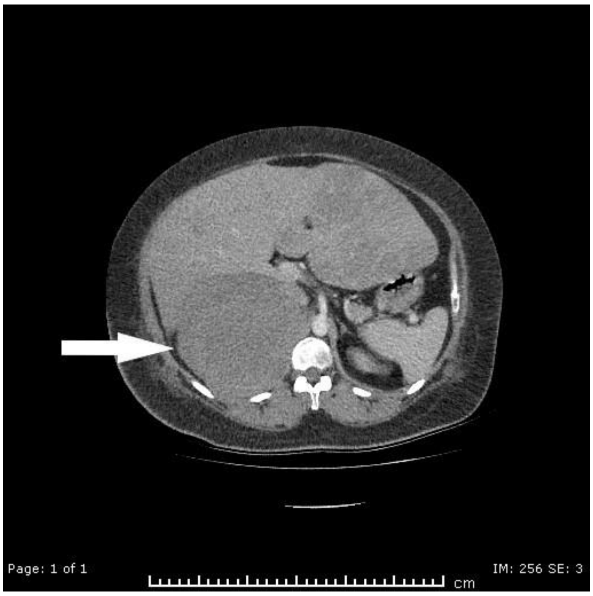

Figure 1. Contrast-enhanced CT image in the axial plane: Hypodense mass filling the right adrenal lodge and indenting the liver. Heterogeneously enhancing hypodense mass lesions in the liver parenchyma.

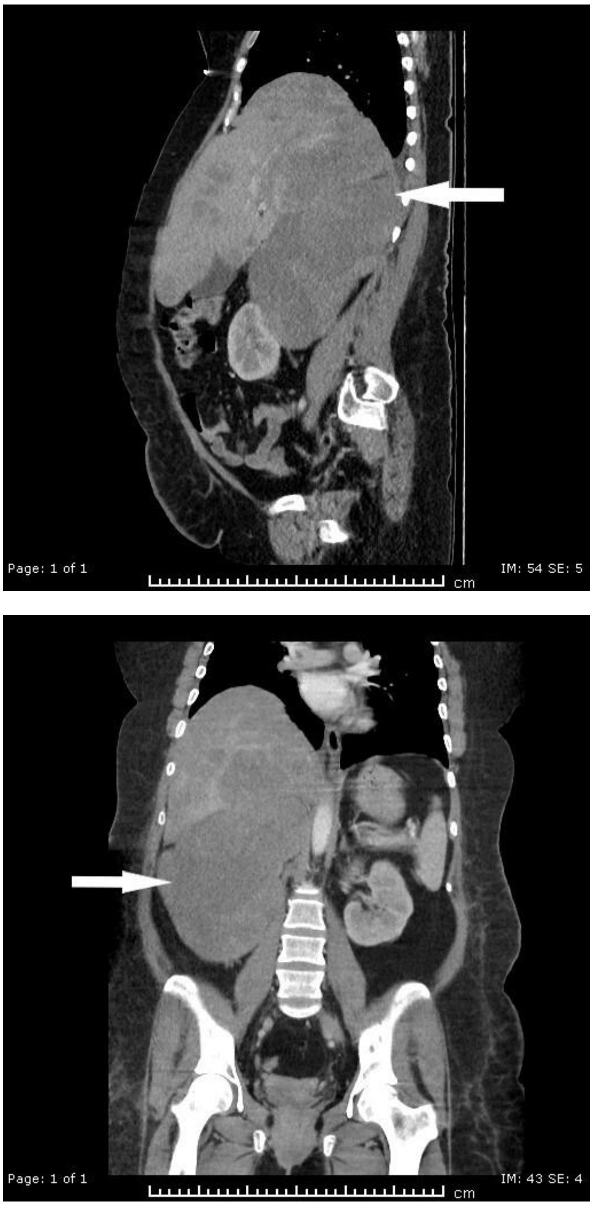

Figure 2 and 3. Contrast-enhanced CT image, coronal and sagittal section: A lobulated contoured hypodense mass filling the right adrenal lodge and extending inferior. The mass has a component on the superior part that erases the liver contours and invades the liver. It is seen that the mass depresses the right kidney downwards.

pattern of 18-FDG uptake was also demonstrated in the liver metastases. (Figure 4).

Surgery was not considered due to widespread liver metastasis, and systemic chemotherapy consisted of cisplatin and etoposide was immediately initiated with daily mitotane therapy. However, neutropenic sepsis occurred four days after the completion of first-cycle of chemotherapy, and no further chemotherapy could be given. The patient had hepatic failure and was in a state of visceral crisis at the time of admission and presented with serious signs and symptoms. In the follow-up, severe renal and liver impairment developed. Moreover, the mental status of the patient worsened progressively, and status epilepticus occurred. General condition of the patient deteriorated rapidly due to high disease burden, visceral crisis and sepsis. It was a chain of events that resulted in infectious manifestations and multiorgan failure on the basis of uncontrolled aggressive malignancy in the patient. The patient passed away on the 23rd day of the diagnosis. Hence, informed consent was obtained from the next kin of the patient for publication of this case report and related images.

Discussion

ACC is an uncommon tumor with a five-year overall survival (OS) rate less than 50%. The well-established prognostic factors are age, disease stage, distant metastasis, Ki-67 index,

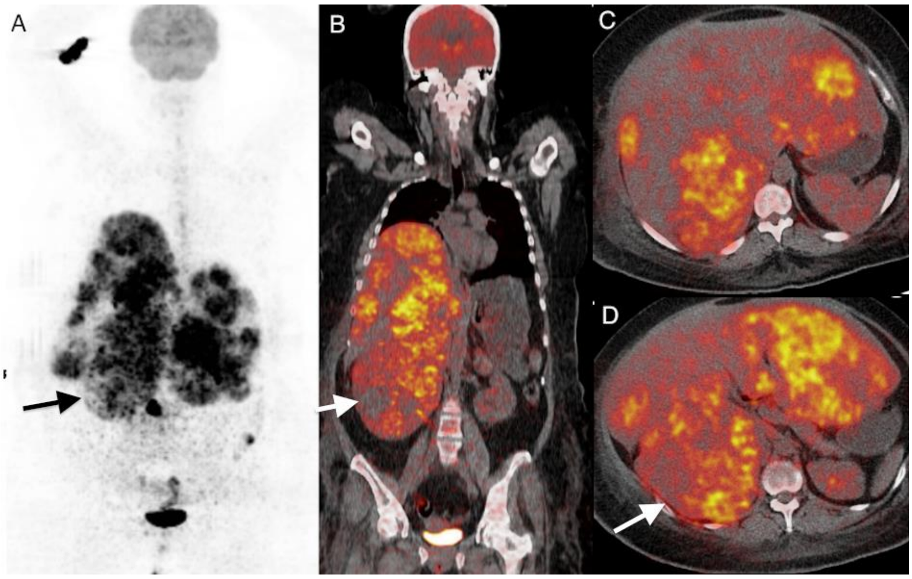

Figure 4. The primary mass was indicated with an arrow on maximum intensity projection (MIP) PET scan (figure A), coronal fusion image (figure B), axial fusion images (figure C and D).

hormone production status, and complete resection of the mass [5]. Surgery is the preferred treatment option and is recommended even in the presence of distant metastasis [6]. Despite resection, recurrence and metastasis rates are high for ACC. ACC can be functional or non-functional depending on hormone secretion. While functional carcinomas are usually detected early because of the symptoms related to excessive hormone production; nonfunctional carcinomas may not be diagnosed until the tumor has compression on adjacent tissue and organs or it may be detected incidentally in imaging [2].

For functional ACC; obesity, hypertension, Cushing's syndrome can be seen in cortisol-secreting masses; virilization in androgen-secreting masses; hypertension, muscle weakness, and hypokalemia due to aldosterone secreting tumors; gynecomastia in tumors that secrete estrogen [6]. In the present case, there were not any complaints due to the hormone excess despite hypercortisolism. Abdomen CT scan findings were consistent with typical characteristics of ACC. Furthermore, 18-FDG PET-CT showed high uptake in the right adrenal primary mass and in liver metastases.

Chemotherapy regimen consisting of cisplatin, doxorubicin, and etoposide in combination with mitotane therapy is usually given in the adjuvant, unresectable, and metastatic settings [7,8]. Moreover, radiotherapy can be applied for symptom palliation in patients with metastatic ACC [9].

Despite the current treatment options commonly used in ACC, the prognosis is poor. A rapid progression of the disease is also common in this patient group. Therefore, more effective and less toxic new treatment options such as immunotherapy and multi-kinase inhibitors are needed for advanced disease [10]. In our case, despite administration of one cycle of cisplatin and etoposide in combination with daily mitotane therapy, the disease progressed rapidly and the patient passed away in a few weeks.

Conclusion

In conclusion, we aimed to present a young patient with diagnosis of metastatic ACC with aggressive clinical course and mortal outcome. The presence of long-standing nonspecific symptoms precluded suspicion for clinical diagnosis, and the patient who lost the chance of early diagnosis was diagnosed in the metastatic stage. Rapidly initiated systemic treatments did not yield results and the patient passed away in a short time. Clinicians should consider primary ACC, which has limited treatment options, in the differential diagnosis in the presence of findings such as edema, obesity, and striae in the lower extremities.

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Corresponding author e-mail: mervedurna@hotmail.com

Orcid ID:
Merve Durna 0000-0002-3000-6708
Atakan Topçu 0000-0002-3634-4820
İsmail Yurtsever 0000-0001-7482-668X
Melih Şimşek 0000-0003-0633-8558
Mehmet Aydın 0000-0001-5349-8752
Mesut Şeker 0000-0002-3721-5406

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