Original Article

Incidence of Nucleophosmin (NPM1) and FMS-like Tyrosine Kinase (FLT3) Mutation in Adult Patients with Acute Myeloid Leukaemia (AML) and Its Influence on Survival; A Single Centre Study

Akut Myeloid Lösemi (AML) Tanılı Erişkin Hastalarda Nükleofosmin (NPM1) ve FMS Like Tirozin Kinaz (FLT3) Mutasyonun İnsidansı ve Sağ Kalıma Etkisi; Tek Merkez Deneyimi

Abdullah Karakuş[1], Vehbi Demircan[1], Mehmet Sinan Dal[2], Mehmet Ayyıldız[1]
[1]Department of Hematology, Dicle University School of Medicine, Diyarbakır, Turkey
[2]University of Health Sciences, Ankara Oncology Training and Research Hospital, Department of Hematology and Bone Marrow Transplantation Center, Ankara Turkey,

ABSTRACT

Introduction: Acute Myeloid Leukaemia (AML) is a disease characterized by bone marrow failure due to increased proliferation resulting from the protection of myeloid precursor cells from differentiation and apoptosis control in the bone marrow. Nucleophosmin (NPM1) and FMS-like tyrosine kinase (FLT3) are mutations frequently seen in AML, which has heterogeneous genetics. The present study aimed to evaluate the clinical characteristics and lifespan of the patients with NPM1 and FLT3 in AML.
Materials and Methods: The study retrospectively investigated the clinical, immunophenotypical, and genetic parameters of the patients diagnosed with AML between 1 January 2012 and 31 June 2019 in the haematology clinic of Dicle University following WHO 2016 criteria. The study primarily focused on the patients' response to the disease, genetic characteristics, and the relationship of NPM1 and FLT3 mutations with their lifespan
Results: The study was performed 107 cytogenetically normal patients were investigated using RT-PCR (Real-Time Polymerase Chain Reaction) in NMP1 and FLT3 mutations in 269 AML patients. While the median survival time in the NPM1-positive patient group was 12.3 months (95% confidence interval (C.I.): 0.1-32 months), it was 10.6 months (%95 C.I: 4,9-16,3 months) in the NPM1-negative group. On the other hand, the median survival time in the FLT3-positive patient group was 8,4 months (95% C.I: 1,2-15,6 months), and it was 12,3 months (95% C.I: 3,8-20,8 months) in the FLT3-negative group. While the number of NPM1-positive patients was 31 (29%), one of the FLT3-positive patients was 19 (17.8%)
Discussion: The study found that while the NPM1 positivity rate in AML cytogenetically normal patients was 29%, the FLT3 positivity rate was 17.8%, representing the first-ever data in this respect in our country. The results indicate that overall survival was better in cases with NPM1 and worse in those with FLT3.

Keywords: AML, NPM1, FLT3, survival

ÖZET

Giriş: Akut Myeloid Lösemi (AML) kemik iliğinde myeloid öncü hücrelerin diferansiyasyon ve apoptozis kontrolünden korunup proliferasyon hızının artması sonucu kemik iliği yetmezliği ile giden bir hastalıktır. Nükleofosmin (NPM1) ve FMS like tirozin kinaz (FLT3), heterojen bir genetiğe sahip olan AML'de sık görülen mutasyonlardır. Bu çalışmamızda AML'de NPM1 ve FLT3 tespit edilen hastaların klinik özelikleri ve yaşam sürelerini değerlendirmeyi amaçladık.
Gereç ve yöntemler: Çalışmaya 01 Ocak 2012-31 Haziran 2019 tarihleri arasında Dicle Üniversitesi hematoloji kliniğinde WHO 2016 kriterlerine göre AML teşhisi konan hastaların klinik, immünofenotipik ve genetik parametreleri retrospektif olarak incelendi. Hastaların tedaviye cevapları,

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yaşam süreleri, genetik özelikleri ve NPM1 ve FLT3 mutasyonlarının yaşam süresi ile ilişkisi incelenmiştir.
Bulgular: Allojenik hematopoietik hücre naklinden sonra akut GVHH'li 59 hasta ve akut GVHH'si olmayan Çalışmamızda 269 AML tanısı alan hastalardan 'sitogenetik olarak normal 107 hasta RT-PCR (Gerçek Zamanlı Polimeraz Zincir Reaksiyonu) kullanılarak NMP1 ve FLT3 mutasyonlarında araştırıldı. NPM1 pozitif hasta grubunda ortanca sağkalım 12,3 ay (% 95 confidence interval(C.I.): 0,1-32 ay) tespit edildi, NPM1 negatif hasta grubunda ise 10,6 ay (% 95 C.I: 4,9-16,3 ay) olarak tespit edildi. FLT3 pozitif hasta grubunda ortanca sağkalım süresi 8,4 ay (%95 C.I: 1,2-15,6 ay) olup FLT3 negatif grupta ise 12,3 ay (%95 C.I: 3,8-20,8 ay) olarak tespit edildi. NPM1 pozitif hasta sayısı 31 (%29), FLT3 pozitif hasta sayısı 19(%17,8) izlendi
Tartışma: Ülkemizin ilk verisi olarak AML sitogenetik normal hastalarda NPM1 pozitiflik oranı %29, FLT3 pozitiflik oranı %17,8 bulundu. NPM1 ile genel sağkalım daha iyi, FLT3 ile genel sağkalım daha kötü olarak izlendi.

Anahtar kelimeler: AML, NPM1, FLT3, sağkalım

Introduction

AML is a malignant haematological disease that causes bone marrow failure and the related symptoms and signs resulting from the abnormal accumulation of myeloblasts from hematopoietic precursor cells in the bone marrow. It is a disease with heterogeneous genetic characteristics. In its 2016 AML criteria, the World Health Organization (WHO) defines it as a condition where the myeloblast ratio detected in the bone marrow or peripheral blood is at least 20% by multi-parameter flow cytometry. An exception to this is that AML diagnosis can be made even if the myeloblast rate is below 20% in the presence of cytogenetic or molecular AML-specific mutations. [1]

It is essential to detect genetic mutations before treatment in AML patients. Genetic mutations determine the prognosis and play a role in defining the treatment process to be performed. The detected mutation also provides information about the minimal residual disease, which is essential in monitoring it [2].

Previous research demonstrates that molecular translocations and genetic mutations in AML can differ between societies. Some translocations seen in AML are RUNX1 / RUNX1T1 t (8; 21), CBFB / MYH11 inv (16), KMT2A / MLLT3 t (9; 11), PML-RARA t (15; 17) and BCR-ABL t (9 ; 22). PML-RARA mutation is a cause of acute promyelocytic leukaemia and is associated with a good prognosis. RUNX1 / RUNX1T1 t (8; 21), CBFB / MYH11 inv (16) mutations are also frequent translocations associated with a good prognosis. Apart from these, other chromosomal anomalies are associated with poor prognosis, and the absence of any chromosomal anomalies constitutes the intermediate-risk group. [3]

While nucleophosmin-1 (NPM-1) presence is associated with a good prognosis, the presence of FMS-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD) causes a poor prognosis. Establishing these mutations in AML patients provides direction for treatment decisions and predicts the response to induction and consolidation chemotherapy and the risk of relapse and overall survival. [2]

Nucleophosmin (NPM1) is a ubiquitously expressed phosphoprotein generally located between the nucleus and the cytoplasm. It plays a role in the ribosomal protein assembly and transport and regulation of tumour suppressor ARF (cyclin-dependent kinase inhibitor 2A). When an NPM1 mutation exists in AML, transportation of such proteins and enzymes from the cytoplasm to the nucleus is reduced [4, 5].

FMS-like tyrosine kinase 3 (FLT-3) regulates the differentiation, proliferation, and survival

of hematopoietic progenitor cells and is also required for normal haematopoiesis. Mutations such as those of the Juxta-membrane domain of FLT3 receptor tyrosine kinase and those of internal tandem duplication lead to uncontrolled proliferation of myeloblasts [6,7].

The present study aimed to determine the frequency of NPM1 and FLT3 in cytogenetic negative AML patients and determine the prognostic difference between the NPM1 positive and NPM1 negative patient groups and the one between the FLT3 positive and FLT3 negative patient groups.

Material and Method

The sample of the present study consisted of the patients presented to the clinic of our university between 1 January 2012 and 31 June 2019 and were diagnosed with peripheral smear, flow cytometry, bone marrow smear, and AML according to 2008 -2016 WHO classification. Translocation analyses of the patients were performed on RT-PCR on LightCycler 480 (Roche, Germany) device with t (15; 17), t (8; 21), inv 16, and t (9; 22). Of this patient group, the patients with negative translocation and analyzed using EZ1 Blood mini kit (Qiagen, Germany) and FLT3 ITD Toolset (Teknigen Biyoteknoloji, Istanbul, Turkey) and Lightmix FLT D835 kit (TıbmolBiol, Berlin, Germany) kit NPM1 ve FLT3-ITD and FLT3 D895 RT- PCR were included in the study. The study compared the overall survival of the NPM1 positive and the NPM1 negative patient groups. In the same patient group, survival was compared in the FLT3-ITD and FLT3-D895 positive patient group and the FLT3-ITD and FLT3-D895 negative patient group.

Characteristics of the Patients: Cytogenetic and molecular mutations were screened in 269 patients diagnosed with AML, and the lifespan of the patients and its relationship with the genetic mutation were examined.

Treatment: The standard "7 + 3" treatment was administered to the patients. Cytosine arabinoside 100mg / m² was given for seven days (24 hours continuous infusion), and idarubicin treatment of 12 mg/m² was administered for three days. Bone marrow evaluation was performed on day 28 of the treatment. In patients in remission, high-dose cytosine arabinoside was administered 3 or 4 times, once in 28 days in a dosage of 3 g/m² twice a day on days 1, 3, and 5. Allogeneic stem cell transplantation was planned for patients with a poor prognosis or those who did not complete remission. Patients who were not suitable for standard treatment received 5 + 2 treatment or the patients whose performance score was low and could not tolerate these two treatments received 5-azacitidine, decitabine, and supportive treatment.

NPM1 Screening: Genomic DNA was obtained from blood samples using an EZ1 Blood mini kit (Qiagen, Germany). The screening was initiated using the ipsogen NPM MutaScreen (Qiagen, Hilden) Kit in patient samples whose DNA concentrations were adjusted. Final reaction volume: Using 12.5µl TaqMan Universal PZR Master mix, 1.0 µl Primer and probe mix separately (PPM-Total NPM1, PPM-Mut NPM1, PPM-NPM1 MutA, PPM-NPM1 MutB or PPM-NPM1 MutD), 6.5µlNuclease-free PZR-grade water was calculated to yield 5.0µlDNA, 2x 25 µl.

FLT3 Screening: DNA isolation was performed on the MagnaPure LC 2.0 device (Roche Diagnostics GmBH, Mannheim, Germany) in line with the instructions of the manufacturer company using the Magna Pure LC DNA isolation kit from blood tubes with EDTA taken from the patients. To specify the FLT3-ITD mutations in the DNAs thus obtained, an analysis was performed on the device LightCycler 480 in line with the manufacturer's instructions using the toolset (Teknigen Biyoteknoloji, Istanbul, Turkey) and Lightmix FLT-D835 kit (TıbmolBiol,

Table 1: General characteristics of the patients diagnosed with AML

	Disease Variables	Number – Rate
Cytogenetic Distribution of the Patients with AML	Number of Patients	269
	t(15;17)	61(%22,7)
	t(8;21)	17(%6,3)
	inv 16	12(%4,5)
	Patients with cytogenetics normal	169
	Patients who could not undergo cytogenetic evaluation	10
	NPM1 and FLT3 evaluated patient group	107
General Characteristics of the Patients with Cytogenetic Normal AML Examined for NPM1, FLT3-ITD, and FLT3-D895 mutations	Age	51,5 (17-91)
	Haemoglobin	8,9(3,5-16) gr/dl
	White Blood Cells	27 900(1 600-388 000) /mm³
	platelet	53 000(7 000-452 000) /mm³
	CD34 +	41(38,3%)
	NPM1+	31(29%)
	FLT3 +	17(17, 8%)
Treatments Administered to Patients with Cytogenetic Normal:	7+3 [a]	79(73,8%)
	5+2 [b]	6(5,6%)
	5- azacitidine	15(14%)
	decitabine	3(2,8%)
	Supportive Treatment	4(3,7%)

a: 7+3 ARA-C 100 mg/m^2 1 to 7 day, İdarabucin 12 mg/m^2 1 to 3 day
b: 5+2 ARA-C 100 mg/m^2 1 to 5 day, İdarabucin 12 mg/m^2 1 to 2 day
nucleophosmin-1 (NPM-1), FMS-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD)

Table 2. Median survival time and the survival rates over five years concerning cyto-negative AML patients

	NPM1(+)	NPM1(-)	FLT3 (+)	FLT(-)
Median Survival Time (months)	12,3	10,6	8,4	12,3
Survival Rates over a 5-Year Period	37%	20%	19%	29%

Berlin, Germany). The results emerging from the FLT3-ITD detection were analyzed using the high-resolution melting method, and the Tm calling analysis was used to analyze the results obtained in the one for FLT-D835, both following the instructions of the manufacturing company.

Statistics: The data were analyzed using IBM SPSS v. 24 (IBM Corp., Armonk, USA). The descriptive analysis-explore test was used to define the normal distribution of the continuous variables. The continuous variables with normal and non-normal distribution were presented using mean, standard variation, and median values. P value of <0.05 was considered statistically significant. On the other hand, numbers and percentages were used for categorical variables. Kaplan-Meier survival curve was performed using the log-rank test.

Results

The study sample consisted of 269 patients diagnosed with AML, of whom 146 (54.3%) were men and 123 (45.7%) were women. The cases were examined with the RT-PCR method in terms of three cytogenetic parameters frequently detected through this method, as a result of which 61 patients were detected as t(15; 17) positive (22.7%), 17 as

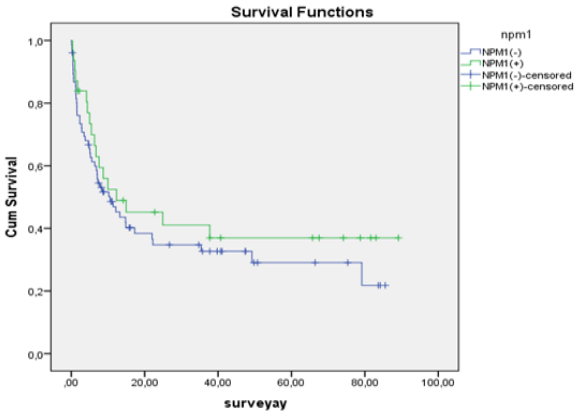

Figure 1: The overall survival (months) in NPM1 (+) and NPM1 (-) patients

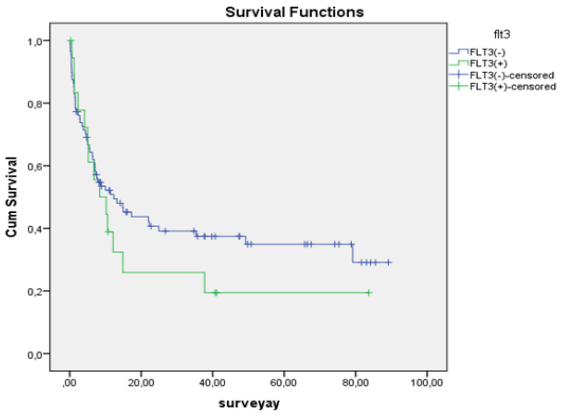

Figure 2: The overall survival (months) in FLT3 (+) and FLT3 (-) patients

t(8;21) positive (6.3%) and 12 as inv16 positive (4.5%). The patients diagnosed with AML who had had positive translocation were not included in the study. 107 patients examined for NPM1, FLT3-ITD, and FLT3-D895 mutations were evaluated.

Of the patients with normal cytogenetic, 60 (56.1%) were men, and 47 (43.9%) were women. The mean age of the patients was 51.5 (17-91) years. The haemogram values of the patients at the time they presented to the clinic were as follows: WBC mean value was 27 900/mm³ (1 600-388 000), haemoglobin mean value 8.9 gr/dl (3.5-16gr/dl), platelet mean value 53 000 (7 000-452000/mm³). AML molecular mutations were NPM1 31(29%), FLT3-ITD 19 (17.8%) FLT3-D895 2 (1.9%). NPM1 mutation and FLT3 mutation positive only 1(0.9%). (Table 1)

While the standard 7+3 treatment was administered to 79 patients (73.8%), 15 (14%) patients received 5- azacitidine treatment, six patients (5.6%) 5 + 2 treatment, three patients (2.8) decitabine treatment and four patients (3.7%) supportive treatment. While 40 (37.8%) patients moved on with their lives during the monitoring period, 67 (62.6%) patients died. While 42 (39.3%) of the patients were refractory to treatment, 34 (31.8%) patients had a recurrence in the later periods.

Based on the analysis of the cases with normal cytogenetic, the present study found that the rate of NPM1 positive incidence was 29% and FLT 3 positivity rate of 17.9%.

The median survival time of the patients was 10.6 months, which was found to be 12.3 months in NPM1 positive patients and 10.6 months in NPM1 negative patients. Even though the patients with NPM1-positive AML seemed advantageous in terms of a longer survival time, the result was not statistically significant ($p>0.05$). (Table 2, Figure 1))

The median survival time in patients with FLT3-ITD-positive AML was 8.4 months, 12.3 months in the FLT3-ITD negative patients. Another statistically non-significant result was that the patients with FLT3-positive AML had a shorter survival time ($p>0.05$). The survival rate over five years in NPM1 positive patients was 37%, 19% in FLT3 positive patients. (Table 2., Figure 2.)

Discussion

The FLT3-ITD and NPM1 mutations in patients with AML play an essential role in prognostic risk classification. Defining the correct mutation can therefore help optimize the therapeutic approaches in AML. Past research suggests that the presence of an

NPM1 mutation might indicate a good prognosis [2]. In the present study, we investigated the overall survival time of 107 cytogenetically normal patients with those with positive NPM1 mutation and compared the results with the NPM1 negative patient group. The group with NPM1 positive AML had a median survival time of 12.3 months; the rate of the median overall survival time over five years was 37%. The overall survival in patients with NPM1 negative AML, on the other hand, was 10.6 months. The analysis of the NPM1 mutation regardless of FLT3 mutation indicated a relationship between NPM1 positivity and a longer survival time. Though observed as an advantage in clinical practice in terms of a longer survival time, it was not found to be statistically significant p (0,374). The lack of a statistically significant difference may be attributed to the retrospective structure of the study, the study sample consisting of a small number of patients, and the non-inclusion of other prognostic parameters in the evaluation.

Patients with FLT3-positive AML have a higher risk of prognosis and a possibility of recurrence after achieving remission. The patient group with FLT3 positive AML had a mean survival time of 8.4 months, 12.3 months in the group with FLT3 negative AML. Even though the mean survival time was longer in patients in FLT3-negative patients, the results indicate no statistically significant difference in this respect p (0.34). Since FLT3 TKD is in 2(1.9) patients, survival analysis is not performed. Although there have been no survey studies investigating FLT3 cases in our society, the results should be interpreted with caution due to the retrospective structure and the small sample size of the study, and the difference between consolidated treatment options. The survival rate over five years was 19% in FLT3-positive patients and 29% in patients with FLT3-negative AML. Much of the previous research reports that FLT3 positivity is related to a shorter survival time. Similarly, our study results also indicate that the FLT 3 positivity is related to a shorter survival time in our society [8, 9].

Many parameters influence the prognosis in patients with AML, one of the most critical genetic mutations. Previous research on the frequency of genetic mutations suggests that it might vary from one society to another. Based on the analysis of the cases with normal cytogenetic, the present study found that the rate of NPM1 positive incidence was 29%. While WHO reports an NPM1 positivity rate between 45 to 64% in the patient group with adverse cytogenetic in its statistics for 2016, research reports that it is 28.3% in Egypt, 24.9% in Japan, and lower than 10% in South Africa [10-13].

The FLT3-ITD mutation is frequently observed in AML, and the FLT3-D895 mutation can be observed in some patients. Its incidence, like the NPM1 mutation, may differ from one society to another. According to WHO, its incidence has been reported to be between 20 and 40% [14]. Research reports a lower positivity rate between 10 and 20% in India and China [15, 16]. The present study, on the other hand, found an FLT 3 positivity rate of 17.9%.

The frequency of NPM1 and FLT3 mutations in our patients, which was observed not to be very high in the present study, is lower than the one observed in western countries (such as the USA, England, Germany, etc.) but similar to the one observed in eastern countries (such as India, China, Japan, etc.).

In conclusion, some limitations that partially limited the present study need to be considered, such as the retrospective structure and the small sample size of the study, as a study on a heterogeneous disease like AML, and differences in treatment options. Previous studies report that frequency of mutation may differ between societies. As there has been no

research investigating the frequency of genetic and molecular mutations and their effect on survival time in our country, we believe that the present study will provide essential insights into the current literature. Further research should be performed in more centres and larger samples.

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Corresponding author e-mail: abdullahkarakus10@gmail.com

Orcid ID:
Abdullah Karakuş 0000-0003-2090-4392
Vehbi Demircan 0000-0002-0378-8687
Mehmet Sinan Dal 0000-0002-5994-2735
Mehmet Ayyıldız 0000-0003-3411-6215

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Original Article

Gynecologic Clinicopathological Evaluation of Women with Breast Cancer Using Tamoxifen

Tamoksifen Kullanan Meme Kanserli Kadınların Jinekolojik Açıdan Klinikopatolojik Değerlendirilmesi

Anıl Turhan Çakır[1], Rıfat Şener[1], Muhammet Atay Özten[2], Görker Sel[2], Müge Harma[1], Mehmet İbrahim Harma[1]

[1]Department of Obstetrics and Gynecology, Department of Gynecological Oncology, Bülent Ecevit University, Zonguldak
[2]Department of Obstetrics and Gynecology, Bülent Ecevit University, Zonguldak

ABSTRACT

Introduction: Tamoxifen is a selective estrogen modulator agent used in breast cancer women. While it has an antiestrogenic effect in the breast, it has estrogenic and antiestrogenic effects in the genital system. It has side effects such as endometrial polyps, hyperplasia, cancer, and ovarian cysts in the uterus and ovaries. In our study, we examined the gynecological clinical and pathological features of patients using tamoxifen

Materials and Methods: In this retrospective study, 183 women's, using tamoxifen for breast cancer, demographic data, comorbidities, menopausal status, admission symptoms, ultrasound findings, endometrial sampling results, tamoxifen duration of use were obtained from patient files and evaluated.

Results: The mean age of 183 patients included in our study was 53.86±10.04. Ovarian cysts were detected in 22 (12%) patients, 15.6% of premenopausal and 8.6% of postmenopausal patients. 13.7% of all patients, 17.8% of premenopausal, and 9.7% of postmenopausal patients had abnormal uterine bleeding. Endometrial sampling was performed in 54.1% of the patients. Endometrial biopsy results were unsatisfactory in 18.6% of the patients, benign findings in 15.3%, atrophy in 6.6%, polyps in 9.3%, hyperplasia without atypia in 2.2%, hyperplasia with atypia in 1.1%, and cancer in 1.1%. Abnormal uterine bleeding rates were statistically higher in those who received treatment at 60 months or more than under 60 months.

Discussion and Conclusion: Tamoxifen is associated with pathologies such as polyps, hyperplasia, cancer, and ovarian cyst. Uterine pathologies usually present with abnormal uterine bleeding. As the duration of tamoxifen use increases, the rate of abnormal uterine bleeding also increases.

Keywords: Breast Cancer, Tamoxifen, Ovarian Cysts, Endometrium, Polyps, Endometrial Hyperplasia

ÖZET

Giriş: Tamoksifen, meme kanserli kadınlarda kullanılan bir selektif östrojen modülatör ajandır. Memede antiöstrojenik etkiye sahipken, genital sistemde östrojenik ve antiöstrojenik etkileri vardır. Uterus ve overlerde; endometrial polip, hiperplazi, kanser, over kistleri gibi yan etkileri vardır. Çalışmamızda tamoksifen kullanan hastaların jinekolojik açıdan klinik ve patolojik özelliklerini inceledik.

Gereç ve Yöntem: Bu retrospektif çalışmada, meme kanseri için tamoksifen kullanan 183 kadının demografik verileri, komorbiditeleri, menopoz durumu, başvuru semptomları, ultrason bulguları, endometriyal örnekleme sonuçları, tamoksifen kullanım süreleri hasta dosyalarından elde edilerek değerlendirildi.

Bulgular: Çalışmamıza dâhil edilen 183 hastanın yaş ortalaması 53,86±10,04 idi. Toplam 22 (%12) hastada over kisti saptandı. Premenopozal hastaların %15,6'sında ve postmenopozal hastaların %8,6'sında kist tespit edildi. Tüm hastaların %13,7'sinde, premenopozal hastaların %17,8'inde ve postmenopozal hastaların %9,7'sinde anormal uterin kanama görüldü. Hastaların %54,1'inde

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endometriyal örnekleme yapıldı. Hastaların %18,6'sında endometriyal biyopsi sonuçları yetersiz, %15,3'ünde benign bulgular, %6,6'sında atrofi, %9,3'ünde polip, %2,2'sinde atipisiz hiperplazi, %1,1'inde atipili hiperplazi ve %1,1'inde kanser saptandı. Anormal uterin kanama oranları, 60 ay veya üzerinde tedavi görenlerde, 60 ayın altında tedavi görenlere göre istatistiksel olarak daha yüksekti.
Tartışma ve Sonuç: Tamoksifen, polip, hiperplazi, kanser ve over kisti gibi patolojilerle ilişkilidir. Uterus patolojileri genellikle anormal uterin kanama ile kendini gösterir. Tamoksifen kullanım süresi arttıkça anormal uterin kanama oranı da artmaktadır.

Anahtar kelimeler: Meme Kanseri, Tamoksifen, Over Kistleri, Endometriyum, Polipler, Endometriyal Hiperplazi

Introduction

Tamoxifen is an aromatase inhibitor that has been used for over 40 years in the prevention and treatment of breast cancer. Tamoxifen reduces epithelial cell proliferation by antiestrogenic activity in breast tissue [1].

Tamoxifen is a non-steroidal selective estrogen receptor modulator (SERM). It can act as an estrogen agonist or antagonist in the female genital tract at different periods and different tissues. The spectrum of side effects of tamoxifen on the genital tract is variable and broad. It increases the risk of endometrial polyp, endometrial hyperplasia, endometrial carcinoma, uterine sarcoma and carcinoma, ovarian cyst [2,3].

In this study, we aimed to evaluate pathological findings such as endometrial sampling results and clinical findings such as age, ultrasound findings, presence of vaginal bleeding symptoms, duration of drug use, co-morbidities, and determine the relationship between them in women with breast cancer using tamoxifen.

Material and Method

This study was approved by the ethics committee for clinical studies (approval number: 2021/01) of Zonguldak Bülent Ecevit University, Turkey. and was conducted in accordance with the Declaration of Helsinki. The study was planned retrospectively. Patients who used 20 mg tamoxifen daily for breast cancer and applied to the Gynecology and Obstetrics Clinic of Zonguldak Bülent Ecevit University Faculty of Medicine between April 2012 and December 2020 were included in the study. Demographic data, co-morbidities (Hypertension, diabetes mellitus and others such as hypothyroidism, hyperthyroidism, coronary artery disease, heart failure, asthma), menopausal status, admission symptoms, ultrasound findings, endometrial sampling results, tamoxifen duration of use were obtained from patient files. We excluded patients who had a history of endometrial pathology before tamoxifen use, underwent a hysterectomy, with a history of cancer other than breast cancer, and missing data for clinical characteristics or ultrasonography.

Endometrial biopsy was performed on the patients with the clinician's decision. Pipelle aspiration, dilatation and curettage or hysteroscopy methods were preferred. Pathology results of the endometrial biopsy were classified as ınsufficient, atrophy, benign findings, polyp, hyperplasia without atypia, hyperplasia with atypia, and cancer.

SPSS 22 program (Version 22.0. Armonk, NY: IBM Corp) was used in the analysis of the Kolmogorov Smirnov test was used as the normal distribution test. Data are presented as mean (standard deviation), median (min-max/IQR), number and percentage. Mann-Whitney U test, t-test, and Chi-square test were used in the analysis. A value of $p<0.05$ was considered statistically significant.

Table-1: The clinical features of the patients

	n (%)
Co-morbidities	
None	107 (58.5)
HT	21 (11.5)
DM	2 (1.1)
HT+DM	13 (7.1)
Other	40 (21.9)
Menopausal Status	
Premenopause	90 (49.2)
Postmenopause	93 (50.8)
Abnormal Uterine Bleeding	
(-)	158 (86.3)
(+)	25 (13.7)
Ovarian Cyst	
(-)	161 (88)
(+)	22 (12)
Endometrial Sampling	
(-)	84 (45.9)
(+)	99 (54.1)
Total	183 (100)

HT: Hypertension, DM: Diabetes Mellitus

Table-2: Pathology results of endometrial biopsy

	n (%)
Insufficient	34 (18.6)
Atrophy	12 (6.6)
Benign Findings	28 (15.3)
Polyp	17 (9.3)
Hyperplasia without atypia	4 (2.2)
Hyperplasia with atypia	2 (1.1)
Cancer	2 (1.1)

Results

The mean age of 183 patients included in our study was 53.86±10.04 (min=34-max=86). Ninty (49.2%) of the patients were in the premenopausal period, and 93 (50.8%) were in the postmenopausal period. The clinical features of the patients are shown in Table-1. The pathology results of the endometrial biopsy are given in Table-2. The distribution of the presence of abnormal uterine bleeding, ovarian cyst, and endometrial biopsy results according to menopausal status are shown in Table-3.

In all patients, endometrial thickness, presence of an ovarian cyst, cyst size, and endometrial sampling results were compared according to the duration of tamoxifen use (under 60 months and above), and no significant difference was found between the groups (respectively p= 0.817, p=0.144, p=0.217, p=0.077). In both premenopausal and postmenopausal patient groups, again, there was no significant difference between the groups (for the premenopausal patient group respectively p=0.782, p=0.171, p=0.429, p=0.199 and for the postmenopausal patient group respectively, p=0.757, p=0.710, p=0.286, p=0.294). In all patients and both premenopausal and postmenopausal patient groups, the relationship between tamoxifen duration and vaginal bleeding was examined, and there was a statistically significant difference. It was found that bleeding rates were higher in the group that received treatment for 60 months or more (p=0.001, p=0.009 and p=0.008, respectively) (Table-4).

Discussion

Tamoxifen is an anti-cancer drug with low toxicity, high efficacy, easily accessible and applicable, used in the treatment of breast cancer. In 1977, the Food and Drug Administration (FDA) approved the use of tamoxifen in the adjuvant treatment of breast cancer [4]. In 1998, it was used in prophylactic treatment in patients with a high risk of breast cancer [5]. In 2013, it was shown that increasing the treatment period from 5 years to 10 years provides a life advantage [6].

Tamoxifen is a selective estrogen modulator agent used in women with estrogen receptor-positive breast cancer. It exerts different effects in different tissues. Tamoxifen inhibits estrogen by binding to the estrogen receptor in breast tissue, thus preventing tumor proliferation. It can act as an agonist or antagonist in different sites of the female genital tract [7,8]. Therefore it has various side effects in different systems. It is associated with sexual dysfunction, vaginal discharge, hot flashes, blood clots, and menstrual irregularities.

Table-3: Distribution of presence of abnormal uterine bleeding, ovarian cyst, and endometrial biopsy results according to menopausal status

	Menopausal Status	
	Premenopause	Postmenopause
Abnormal Uterine Bleeding		
(-)	74 (82.2)	84 (90.3)
(+)	16 (17.8)	9 (9.7)
Ovarian Cyst		
(-)	76 (84.4)	85 (91.4)
(+)	14 (15.6)	8 (8.6)
Endometrial Sampling		
(-)	41 (45.6)	43 (46.2)
(+)	49 (54.4)	50 (53.8)
Endometrial Biopsy Results		
Insufficient	12 (13.3)	22 (23.7)
Atrophy	4 (4.4)	8 (8.6)
Benign Findings	15 (16.7)	13 (14)
Polyp	13 (14.4)	4 (4.3)
Hyperplasia without atypia	3 (3.3)	1 (1.1)
Hyperplasia with atypia	1 (1.1)	1 (1.1)
Cancer	1 (1.1)	1 (1.1)
Total	90 (100)	93 (100)

Table-4: Tamoxifen duration and vaginal bleeding

		Tamoxifen duration		
		0-59 months	60 months<	P
All patients				
Vaginal bleeding				
	(-)	115 (92)	37 (71.2)	0.001*
	(+)	10 (8)	15 (28.8)	
Premenopause Vaginal bleeding				
	(-)	58 (87.9)	12 (60)	0.009*
	(+)	8 (12.1)	8 (40)	
Postmenopause Vaginal bleeding				
	(-)	57 (96.6)	25 (78.1)	0.008*
	(+)	2 (3.4)	7 (21.9)	

p<0.005 was regarded as statistically significant

Uterine pathology usually presents with abnormal uterine bleeding in patients using tamoxifen. Abnormal uterine bleeding requires further investigation. Ultrasonography and/or endometrial sampling is performed. Surveillance with ultrasonography and/or endometrial biopsy to detect endometrial cancer is not recommended for asymptomatic patients using tamoxifen, as it increases unnecessary intervention and is not cost-effective. The American College of Obstetricians and Gynecologists (ACOG) stated that "Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and as such require no additional monitoring beyond routine gynecologic care" but ACOG also advised that patients on tamoxifen should report any abnormal vaginal symptoms, including staining, leukorrhea, spotting, bloody discharge [9].

Abnormal uterine bleeding is seen in 50% of premenopausal patients and 25% of postmenopausal patients using tamoxifen [10-12]. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-2 study, it was reported that 24.4% of 4693 postmenopausal patients receiving tamoxifen treatment

experienced some degree of vaginal bleeding [12]. A total of 75,170 pre- or postmenopausal breast cancer cases who received adjuvant endocrine therapy in a study evaluated; in premenopausal – using tamoxifen frequency of gynecological symptoms is 20%, while the probability of gynecological intervention is 34%, for postmenopausal patients the rates were 12% and 11%, respectively [13]. In our study, 13.7% of all patients, 17.8% of pre-menopausal and 9.7% of postmenopausal patients using tamoxifen had abnormal uterine bleeding.

Abnormal uterine bleeding in patients using tamoxifen is more associated with endometrial pathologies such as endometrial polyps, hyperplasia, and cancer [11]. Endometrial polyps are the most common endometrial pathology. Polyps occur in 11% of postmenopausal cases using tamoxifen for more than four years. Polyp rate is 7% in patients using premenopausal tamoxifen, not different from the general population. The risk of endometrial hyperplasia and cancer increases for postmenopausal patients [14]. Tamoxifen results in a two- to threefold increased risk of endometrial cancer in postmenopausal patients at five years. In our study, endometrial sampling was performed in 54.1% of the patients. Endometrial biopsy results were unsatisfactory in 18.6% of the patients, benign findings in 15.3%, atrophy in 6.6%, polyps in 9.3%, hyperplasia without atypia in 2.2%, hyperplasia with atypia in 1.1%, and cancer in 1.1%. In the study in which the endometrial biopsy results of 821 patients who used tamoxifen for breast cancer were examined, 77.2% normal histological findings, 21% endometrial polyps, 7% endometrial hyperplasia, 7% endometrial cancer were found [15]. In their study of AlZaabi et al., 10.3% of 204 patients with breast cancer using tamoxifen underwent endometrial biopsy. Two (0.98%) endometrial cancer, one (0.50%) serous carcinoma, three (1.47%) atrophic endometrium, one (0.50%) chronic endometritis and three (1.47%) inactive endometrium was detected in the pathological examination of endometrial biopsies [16]. In our study, polyps were observed in 4.3% of postmenopausal patients and 14.4% of premenopausal patients using tamoxifen. Although the incidence of polyps in postmenopausal patients seems to be low, there are also studies that found a low rate of 4.1%, similar to our study [17].

Screening of an asymptomatic patient using tamoxifen with routine gynecological ultrasonography is not recommended. Ultra-sonography in asymptomatic postmeno-pausal patients has high false positives and results in many unnecessary additional interventions [14]. In our study, 13.7% of all patients, 17.8% of premenopausal and 9.7% of postmenopausal patients using tamoxifen had abnormal uterine bleeding, but endometrial sampling was performed in 54.1% of the patients. Although the rate of abnormal uterine bleeding is similar or less than the literature, the rate of endometrial sampling is high. However, pathological findings rates detected in endometrial sampling are similar to the literature. As self-criticism, we can say that we have made unnecessary gynecological interventions.

Until 2013, the recommended duration for tamoxifen use was five years. However, after it was observed that increasing the treatment to 10 years decreased the deaths due to breast cancer, the treatment period was extended in eligible patients. Of course, this led to an increase in side effects. The risk of endometrial cancer is associated with the duration of tamoxifen use. In the Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) trial (n = 12,894), the risk of endometrial cancer was significantly higher at ten years compared with five years (RR 1.74, 95% CI 1.30- 2.34) [18,19].

In our study, endometrial sampling results were compared according to the duration of

tamoxifen use (under 60 months and above), and no significant difference was found between the groups, but it was found that abnormal uterine bleeding rates were statistically higher in the group who received treatment at 60 months or more than under 60 months. While we observed an increase in abnormal uterine bleeding rates according to the duration of tamoxifen use in our study, we could not detect a difference between the endometrial sample results. This may be due to the low number of patients.

Tamoxifen can affect the ovary. Tamoxifen exposure can be related to the development of ovarian cysts or an increased risk of ovarian cancer [20,21]. Metindir et al. stated that ovarian cysts were seen in 19.3% of the patients using tamoxifen. Cyst was observed in 49.1% of premenopausal women and 1.1% of postmenopausal women [22]. In the study of Kim et al., the prevalence of ovarian cyst in women using tamoxifen was 19.4% for pre and 6.3% for postmenopausal patients [23]. These ratios were 16.3% and 4.6%, respectively, in the study of Lee et al. [17]. Similar to other studies, in our study, ovarian cyst was detected in 22 (12%) patients, 15.6% of premenopausal patients, and 8.6% of postmenopausal patients.

Conclusion

Tamoxifen has some effects on the female genital tract. Uterine pathologies usually present with abnormal uterine bleeding. While it is generally associated with pathologies such as polyps, hyperplasia, and cancer in the uterus, it also increases the incidence of cysts in the ovary. Intervention should not be performed on patients without symptoms to prevent unnecessary intervention in patients using tamoxifen.

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Corresponding author e-mail: dranilturhan@hotmail.com

Orcid ID:
Anıl Turhan Çakır 0000-0001-7976-4123
Rıfat Şener 0000-0002-7297-5486
Muhammet Atay Özten 0000-0003-2000-3818
Görker Sel 0000-0001-8653-5687
Müge Harma 0000-0002-4327-674X
Mehmet İbrahim Harma 0000-0002-9734-5253

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Original Article

Transformed Lymphomas: Is It Really Rare?

Transforme Lenfomalar: Gerçekten Nadir mi?

Ersin Bozan[1], Semih Başcı[1], Samet Yaman[1], Gökcen Bozan[2], Sema Seçilmiş[1], Burcu Aslan Candır[1], Tuğçe Nur Yiğenoğlu[1], Merih Kızıl Çakar[1], Mehmet Sinan Dal[1], Fevzi Altuntaş[1]

[1]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Hematology and Bone Marrow Transplantation Center
[2]Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Internal Medicine

ABSTRACT

Objective: In our study, we aimed to evaluate the factors that affect the prognosis of patients with transformed lymphoma who are followed up in our clinic.
Materials and Methods: Forty-five patients with transformed lymphoma who were eligible for our study were retrospectively analyzed. The preparations of the patients were confirmed by experienced pathologists with second look.
Results: The majority of the primary diagnosis of the patients was follicular lymphoma. The most common type of transformed lymphoma was diffuse large B-cell lymphoma (DLBCL). The time to transformation was measured as 31 months (2-312). The number of patients who responded to the first rescue treatment after transformation was 32 (71%), and the number of refractory patients was 9 (20%). Median survival in transformed patients was 4.5 months (1-102).
Conclusion: The time to transformation was measured as 31 months. In addition, heterogeneity in the diagnosis type of primary diseases and the treatments received are other reasons that may explain the difference in transformation times between studies. More studies are needed for more accurate prognostic assessment.

Keywords: Clinical response, Prognostic factors, Targeting Therapy, Survival

ÖZET

Giriş ve Amaç: Çalışmamızda kliniğimizde takipli olan transforme lenfoma hastalarının prognozunda etkili olan faktörleri değerlendirmeyi amaçladık.
Yöntem ve Gereçler: Çalışmamıza uygun olan 45 transforme lenfoma hastası retrospektif olarak incelendi. Hastaların preparatları deneyimli patologlar tarafından yeniden değerlendirilerek doğrulandı.
Bulgular: Hastaların primer tanısının büyük çoğunluğunu folliküler lenfoma oluşturmaktaydı. En sık transforme lenfoma çeşidi diffüz büyük B hücreli lenfoma (DBBHL) olarak gözlendi. Transformasyona kadar geçen süre 31 ay (2-312) olarak ölçüldü. Hastalarda transformasyon sonrası ilk kurtarma tedavisine yanıt veren kişi sayısı 32 (%71), refrakter hasta sayısı ise 9 (%20)'du. Transforme hastalarda median sağ kalım 4,5 ay (1-102) olarak ölçüldü.
Tartışma ve Sonuç: Transformasyona kadar geçen süre 31 ay olarak ölçüldü. Primer hastalıkların tanılarındaki heterojenlik ve alınan tedavilerdeki farklılıklar çalışmalar arası transformasyon sürelerinin farklılığını açıklayabilecek nedenlerden olabilir. Daha sağlıklı prognostik değerlendirme için daha fazla çalışmaya ihtiyaç duyulmaktadır.

Anahtar Kelimeler: Klinik yanıt, Prognostik faktörler, Hedefe Yönelik Tedavi, Sağkalım

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Introduction

Lymphomas are the most common hematological malignancies. In classification, lymphomas are divided into two as Hodgkin lymphomas (HL) and non-Hodgkin lymphomas (NHL). Hodgkin lymphomas are most common between the ages of 20 and 40, but after the age of 55, there is a second increased incidence. The incidence of Hodgkin lymphomas in the community is 2.3/100,000. NHL is the 7th most common malignancy and accounts for 4.3% of all cancer cases. NHL ranks 5th in cancer-related deaths. Its incidence is 19.6 per 100,000 [1-3]. Advanced age and stage are among the factors thought to affect prognosis in DLBCL, which is one of the most frequently transformed lymphoma types [4,5].

In addition to standard conventional chemotherapy and radiotherapy, targeted therapy agents improved prognosis. Especially with the initiation of rituximab treatment, great progress has been made in the treatment of lymphoma. With the improvement of both treatment and care conditions, the life expectancy after treatment was prolonged and contributed to the occurrence of transformed lymphomas in patients [6]. In some studies, it has been shown that a bulky mass, which is thought to have a poor prognostic effect in the pre-rituximab period, is not as effective as thought on the prognosis in the post-rituximab period [7]. Rescue treatments used in patients with transformed lymphoma vary by center, and inter-clinical response rates vary according to treatment regimens [8].

Autologous transplantation is among the treatment options for suitable lymphoma patients who are considered to be at high risk after transformation. Considering the effects of the preparation regimens used before autologous transplantation on the prognosis, it may be necessary to perform autologous transplantation with a preparation regimen that is thought to be suitable for the patient profile [9].

There are various publications on the incidence of transformed lymphoma in patients with relapsed/refractory lymphoma. In their study, Bolanle Gbadamosi et al. reported that 73 of 617 patients examined between 2007 and 2015 were diagnosed with transformed lymphoma [10]. In other studies, the rate of transformation in lymphomas varies between 10 and 70% [11]. In addition, the rate of transformation varies according to the type of primary lymphoma [12]. Risk scoring used in lymphomas can be useful in predicting the formation of transformation. For example, there are studies showing that disease stage, FLIPI score at diagnosis, presence of lactate dehydrogenase (LDH) and B symptoms are associated with the risk of transformation in follicular lymphoma [13,14]. One reason why the rate of transformed lymphoma varies so much in the literature is that there are few studies. In addition, the incidence of lymphomas may vary depending on gender, race, age, some infectious factors (HHV-8, HIV, HCV, HBC, EBV, H.Pylori, Chlamydia, Borrelia, etc.).

The factors that cause the formation of transformed lymphomas are not yet fully understood. It is thought that radiotherapy and chemotherapeutic agents exposed during the treatment process contribute to the process. Unfortunately, the clinical course is worse in transformed lymphomas than in de novo lymphoma, and the response to treatment is worse [10,15-17]. While making the treatment decision in transformed lymphomas, the type of transformed lymphoma, its stage and the general clinical condition of the patient are important parameters that determine the treatment decision. There are studies in the literature suggesting that post-transformation rescue chemotherapy should be given in patients with a diagnosis of primary follicular lymphoma, considering the patient's anthracycline exposure, and then autologous

stem cell transplantation should be performed [18]. In lymphoma patients, both in primary diagnosis and after transformation, follow-up can be life-saving by providing early diagnosis of relapsed, refractory or newly developed transformed lymphoma. Therefore, patients should be followed up in routine follow-up. Periodic laboratory and imaging examinations should be performed, and if suspicious lesion is encountered, biopsy should be performed again [19].

In our study, we aimed to evaluate the factors contributing to prognosis, risk factors, clinical features and response to treatment, considering the data gap in the literature in transformed lymphomas. Transformed lymphomas are often an exclusion criteria when conducting randomized controlled trials. Therefore, there are insufficient data on this patient group. Our research aims to close this information gap.

Materials and Methods

This study by Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital ethics committee approval was obtained. (Ethics committee no: 2021-12/16). This study was conducted under the ethical principles of Helsinki.

The records of all lymphoma patients admitted to the lymphoma outpatient clinic were reviewed retrospectively. Patients admitted to the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Hematology clinic between March 2002 and April 2021 were evaluated.

In the study, in which approximately 600 patients were evaluated, 45 patients who met the criteria were included in the study. Transformed lymphoma diagnosis of the patients was confirmed histopathologically by hematopathologists.

The primary and transformed lymphoma diagnoses of the patients were made by experienced pathologists and confirmed by second look.

Patients older than 18 years of age with a diagnosis of transformed lymphoma were included in the study. Transformed lymphoma was not proven by second look and patients under the age of 18 were not included in the study. The primary diagnoses of the patients were DLBCL, Mantle cell lymphoma, Hodgkin lymphoma, Chronic lymphocytic leukemia (CLL), Burkitt lymphoma, Marginal zone lymphoma, Follicular lymphoma, Peripheral T-cell lymphoma (PTCL), Angioimmunoblastic T-cell lymphoma.

Patients with low-grade lymphoma with no indication for treatment were followed up using a wait-and-see strategy. Patients with indications for treatment were treated in line with the recommendations of current guidelines. After the primary diagnosis, patients were screened with PET-CT to evaluate treatment response or when recurrence was suspected. Histopathological sampling was performed from the patients with suspicious lesions.

Statistical analyzes were performed using the IBM Statistical Package for the Social Sciences (SPSS) V26 (Armonk, NY). The general characteristics of the patients were presented with descriptive statistics. Numerical data were given as median (min.-max.), categorical data as ran. Factors predicting treatment response were analyzed by logistic regression, and factors predicting survival were analyzed by cox regression. $P<0.05$ was considered statistically significant.

Results

The median age of the patients was 54.5 (18-85). The number of women was 20 (44.4%) and the number of men was 25 (55.6). The incidence, stages of primary diagnoses and laboratory datas are shown in Table-1.

Table 1. Demographics and clinical data of the patients

Parameters	N, %
Age (median, min-max)	54,5 (18-85)
Gender (M/F)	25 (55.6%) / 20 (44.4%)
Initial Diagnosis	
Follicular lymphoma	16 (35.6%)
Hodgkin lymphoma	11 (24.4%)
Chronic lymphocytic leukemia	5 (11.1%)
Marginal zone lymphoma	5 (11.1%)
Diffuse large B cell lymphoma	4 (8.9%)
Mantle cell lymphoma	1 (2.2%)
Burkitt lymphoma	1 (2.2%)
Peripheral T cell lymphoma	1 (2.2%)
Angioimmunoblastic T cell lymphoma	1 (2.2%)
Stage (early/late)	15 (33.3%) / 30 (66.7%)
Laboratory	Median (min-max)
LDH (u/L)	228 (144-821)
Uric acid (mg/dL)	5,7 (2,7-10,7)
Albumin (g/L)	4,1 (2,6-5)
WBC (cells/uL)	5210 (3500-59320)
Hb (g/dL)	12,8 (5,9-16)
Plt (cells/uL)	220.000 (46.000-485.000)
Initial Treatment	
R-CHOP	17 (37.8)
ABVD	11(24,4%)
WATCH&WAIT	9 (20%)
CHOEP	2(4,4%)
CHOP	1 (2,2%)
CODOX M	1 (2,2%)
CVP	1 (2,2%)
R-EPOCH	1 (2,2%)
R-HYPER CVAD	1 (2,2%)
R-FC	1 (2,2%)
RT (received)	13 (28.9)

LDH: lactate dehydrogenase; WBC: white blood cells; Hb: Hemoglobin; Plt: Platelets.
R: Rituximab, CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone,
ABVD: Adriamycin Bleomycin Vinblastine Dacarbazine, CHOEP: Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisolone, CODOX M: Cyclophosphamide, Doxorubicin, Vincristine, Methotrexate, Cytarabine, CVP: Cyclophosphamide, Vincristine,
Prednisolone, EPOCH: Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin, HYPER CVAD: Cyclophosphamide, Vincristine, Doxorubicin, Dexamethasone, FC: Fludarabine, Cyclophosphamide, RT: Radiotherapy

Table 2. Histological Transformed Lymphoma Clinical Data

Parameters	N, %
Time to histologic transformation (median, min-max)	31 (2-312) months
Stage (early/late)	11 (24.4%) / 34 (75.6%)
Ki67 (median, min-max)	80 (7-95)
HTL Diagnosis	
Diffuse large B cell lymphoma	31 (68.9%)
Hodgkin Lymphoma	4 (8.9%)
Marginal zone lymphoma	4 (8.9%)
Follicular lymphoma	3 (6.7%)
Angioimmunoblastic T cell lymphoma	1 (2.2%)
Peripheral T cell lymphoma	1 (2.2%)
Chronic lymphocytic leukemia	1 (2.2%)
HTL first treatment	
R-CHOP	20 (44,4%)
Watch&Wait	8 (17,8%)
R-GDP	4 (8,9%)
GDP	3 (6,7%)
ABVD	2 (4,4%)
ASHAP	1 (2,2%)
CVP	1 (2,2%)
Obinutuzumab+lenalidomid	1 (2,2%)
Rituksimab+bendamustin	1 (2,2%)
Rituksimab+CHOEP	1 (2,2%)
Rituksimab+deksametazon	1 (2,2%)
Missing	1 (2,2%)
Salvage CT line ≥2	7 (15.6%)
RT	8 (7.8%)
HTL first salvage treatment response	
Chemosensitive	32(71%)
Chemorefractory	9(20%)
N/A	4(8,9%)
Mortality	9 (20%)
Time from HTL diagnosis to mortality (median, min-max)	4,5 (1-102) months

HTL, histologically transformed lymphoma; CT: chemotherapy RT: radiotherapy
N/A: not applicable.R: Rituximab, CHOP: Cyclophosphamide, Doxorubicin, Vincristine, Prednisolone, GDP: Gemcitabine, Dexamethasone, Cisplatin, ABVD: Adriamycin Bleomycin Vinblastine Dacarbazine, CHOEP: Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisolone, ASHAP: Adriamycin, Solumedrol, High-dose Ara-C, cisplatinum, CVP: Cyclophosphamide, Vincristine, Prednisolone

Table 3- Factors Affecting Response- Refractory to Initial Rescue Therapy Evaluated*.

Parameters	Univariate Analysis	
	HR (%95-CI)	P Value
Age	1,02 (0,98-1,06)	0,29
Gender (female based)	0,6 (0,16-2,16)	0,43
1. Lymphoma Stage	2,06 (0,97-4,38)	0,06
Kİ-67	1,02 (0,99-1,05)	0,20
Time to histologic transformation	0,99 (0,98-1,01)	0,39
LDH (u/L)	1 (0,99-1,01)	0,96
Uric acid (mg/dL)	1,25 (0,83-1,88)	0,28
Albumin (g/L)	2,13 (0,46-9,94)	0,33
Hb (g/dL)	0,94 (0,70-1,26)	0,68

LDH: lactate dehydrogenase; Hb: Hemoglobin
*In the parameters examined, no parameter that had a significant relationship with the response was found.

Table 4- Factors Affecting Survival After Transformation*

Parameters	Univariate Analysis	
	HR (%95-CI)	P Value
Age	1,04 (0,99-1,08)	0,12
Gender (female based)	1,14 (0,57-2,29)	0,70
2. Lymphoma Stage	4,93 (0,76-31,88)	0,09
Kİ-67	1 (0,97-1,03)	0,95
Time to histologic transformation	0,99 (0,98-1,01)	0,54
LDH (u/L)	0,99 (0,99-1,01)	0,65
Uric acid (mg/dL)	1,27 (0,85-1,91)	0,25
Albumin (g/L)	0,95 (0,20-4,56)	0,95
Hb (g/dL)	0,90 (0,67-1,22)	0,52

LDH: lactate dehydrogenase; Hb: Hemoglobin
*Parameters thought to be associated with survival after transformation were examined by Cox regression analysis, but again, no significant difference was found due to diagnostic heterogeneity and the limitation of the study population.

While 36 (80%) of the primary diagnosed patients received active chemotherapy, 9 (20%) were followed without medication. The initial treatments of the patients are shown in Table-1.

The median time to transformation was observed as 31 months (2-312). The majority of the transformed patients, such as 31 (68.9%), were diagnosed with DLBCL (Table 2). When the patient was restaged after transformation, the number of early stage patients was 11 (24.4%), while the number of late stage patients was 34 (75.6%). The median Ki67 proliferation index value of the transformed patients was 80% (7-95%).

The treatments given in patients with transformed lymphoma are shown in Table-2. The number of patients who received more than two lines of treatment was seven (15.6%). In the post-treatment evaluation, 32 (71%) of the patients transformed in PET-CT were responsive to treatment. nine (21%) were considered as refractory. Treatment response of four (8.9%) patients could not be reached. Mortality was observed in nine (20%) patients. Post-transformation mortality time was 4.5 months (1-102).

Cases refractory to first salvage therapy in logistic regression analysis are analyzed in Table 3. In the parameters examined, no parameter that had a significant relationship with the response was found. The limited number of cases examined here and the lack of a homogeneous diagnosis group seem to play a role.

In Table 4, parameters thought to be associated with survival after transformation were examined by Cox regression analysis, but again, no significant difference was found due to diagnostic heterogeneity and the limitation of the study population.

Discussion

Although it is clinically rare, high-grade and low-grade lymphomas can transform into each other after treatment. However, due to the large number of lymphoma types, a heterogeneous study group is formed, making it difficult to obtain meaningful statistical data. However, limited studies have shown that the prognosis in transformed lymphomas is worse than in de novo lymphomas. Addition of additional mutations to primary lymphoma and previous treatment agents play a role in this. In addition, the fact that the treatments given differ according to the centers and years makes it difficult to make comparisons between studies. For example, pre-rituximab data and current stem cell transplant

preparation regimens are just some of the reasons for these differences.

Especially since many studies were conducted in the pre-rituximab period, different results can be obtained in terms of treatment responses and overall survival. In the study of Link BK et al., OS was worse in patients who were transformed before 18 months than those with late transformation, and additionally, it was seen that taking rituximab beforehand did not make a difference in terms of survival with de novo DLBCL [18]. No significant difference was found in our study.

When the literature is examined, follicular lymphoma is the most common first diagnosis in transformed lymphomas in many studies [11,12,15]. In our study, we observed that 16 (35.6%) of our patients had a diagnosis of follicular lymphoma, consistent with the literature.

The time to transformation was measured as 31 months. During this time Villa et al. 44 months, Gbadamosi et al. In his study, it was shown as 40 months [10,20]. The type of diagnosis of the primary diseases and the treatments received are among the reasons that may explain the difference in transformation times between studies.

Conclusion

Despite new treatment agents such as rituximab, immunomodulators, Bruton tyrosine kinase inhibitors, BCL-2 inhibitors and CAR-T cell therapy, desired curative treatment responses still have not been achieved in transformed lymphomas. For this reason, many clinical studies are still ongoing. Due to the heterogeneous nature of transformed lymphomas, reaching a sufficient number of patients and conducting randomized controlled studies create difficulties.

Improvement of treatment success in transformed lymphomas can be achieved by conducting extensive studies including new treatment agents in this area.

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Corresponding author e-mail: ersinbozan87@gmail.com

Orcid ID:
Ersin Bozan 0000-0002-3307-3121
Semih Başcı 0000-0003-4304-9245
Samet Yaman 0000-0003-4081-1070
Gökçen Bozan 0000-0002-5064-9102
Sema Seçilmiş 0000-0003-2957-2339
Burcu Aslan Candır 0000-0003-3386-8984
Tuğçe Nur Yiğenoğlu 0000-0001-9962-8882
Merih Kızıl Çakar 0000-0003-0978-0923
Mehmet Sinan Dal 0000-0002-5994-2735
Fevzi Altuntaş 0000-0001-6872-3780

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Original Article

The Prognostic Significance of Preoperative Cancer Antigen-125 Levels in Uterine Papillary Serous Carcinomas

Uterin Papiller Seröz Karsinomlarda Preoperatif Kanser Antijen-125 Düzeylerinin Prognostik Önemi

İlker Çakır[1], Volkan Karataşlı[1], Varol Gülseren[2], Duygu Ayaz[3], Barış Sever[1], Zübeyde Emiralioğlu Çakır[1], Gökşen Görgülü[1], Oğuzhan Kuru[1], Muzaffer Sancı[1], Mehmet Gökcü[1]

[1]Departmant of Gynecology and Obstetrics, Tepecik Education and Research Hospital, İzmir, Turkey
[2]Departmant of Gynecology and Obstetrics, Erciyes University, Kayseri, Turkey
[3]Departmant of Pathology, Tepecik Education and Research Hospital, İzmir, Turkey

ABSTRACT

Introduction: This study aimed to determine the relationship between preoperative cancer antigen(CA)-125 levels and clinicopathologic prognostic factors as well as appropriate cut-off levels for pure uterine papillary serous carcinoma.

Materials and Methods: Study data were collected from the documents and electronic medical records of patients who were diagnosed with pure uterine papillary serous carcinoma between 2005 and 2020 in our institution. The association between clinicopathological variables and CA-125 were analyzed. The accuracy of the preoperative serum CA-125 value in predicting metastasis sites was evaluated by the receiving operating characteristic curve analysis and the most appropriate cut-off values available were selected.

Results: Seventy-eight patients met the study criteria. Median value of preoperative serum CA-125 level was higher in patients with omental (P<0.001), ovarian (P<0.001), cervical involvement (P=0.017) and deep myometrial invasion (≥50%) (P= 0.001). According to the receiving operating characteristic curve, the optimal cut-off value of preoperative CA-125 level for predicting omental involvement was 35.5 U/mL (sensitivity: 93.8%, specificity: 79.3%), cervical involvement was 15.0 U/mL (sensivity: 86.8%, specificity: 44.7%) and ovarian involvement was 32.5 U/mL (sensivity: 77.3%, specificity: 72.2%).

Discussion: An elevated level of preoperative serum CA-125 is a marker for omental, ovarian, cervical involvement and deep myometrial invasion. The value for cervical involvement may be a guide that radical hysterectomy should be considered in the foreground in patients undergoing surgery. There is a need for future studies to evaluate the role of CA-125 in predicting recurrence and survival in uterine papillary serous carcinoma.

Keywords: Biomarkers, cervix uteri, endometrial cancer, hysterectomy

ÖZET

Giriş: Bu çalışmada, pür uterin papiller seröz karsinomda preoperatif kanser antijeni(CA)-125 düzeylerinin çeşitli klinikopatolojik değişkenlerle ilişkisinin ve metastaz bölgesini öngörmede optimal cut-off değerlerinin belirlenmesi amaçlanmıştır

Gereç ve Yöntemler: Çalışma verileri, kurumumuzda 2005-2020 yılları arasında pür uterin papiller seröz karsinom tanısı alan hastaların belgelerinden ve elektronik tıbbi kayıtlarından toplandı. Klinikopatolojik değişkenler ile CA-125 arasındaki ilişki analiz edildi. Preoperatif serum CA-125 değerinin metastaz bölgelerini tahmin etmedeki doğruluğu, ROC(receiving operating characteristic) eğrisi analizi ile değerlendirildi ve mevcut en uygun cut-off değerleri seçildi.

Bulgular: Yetmiş sekiz hasta çalışma kriterlerini karşıladı. Ameliyat öncesi serum CA-125 düzeyi ortanca değeri omental (P<0,001), over (P<0,001), servikal tutulum (P=0,017) ve derin miyometriyal invazyon (≥%50) (P = 0,001) olan hastalarda daha yüksekti. ROC eğrisine göre, omental tutulumu öngörmek için preoperatif CA-125 seviyesinin optimal cut-off değeri 35.5 U/mL (duyarlılık: %93,8,

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özgüllük: %79,3), servikal tutulum için 15.0 U/mL (duyarlılık: %86,8, özgüllük: %44,7) ve over tutulumu için 32,5 U/mL (duyarlılık: %77,3, özgüllük: %72,2) idi.
Tartışma: Preoperatif serum CA-125'in yüksek seviyesi omental, over, servikal tutulum ve derin myometrial invazyon için bir belirteçtir. Servikal tutulum için cut-off değeri, cerrahi uygulanacak hastalarda radikal histerektominin ön planda düşünülmesi gerektiğine dair bir rehber olabilir. Uterus papiller seröz karsinomunda CA-125'in nüks ve sağkalımı öngörmedeki rolünü değerlendirecek ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Biomarker, endometrial kanser, histerektomi, serviks uteri

Introduction

Endometrial cancer is the most common gynecologic malignancy in women[1]. The prognosis of endometrioid type tumors is excellent, but there are high grade tumors such as uterine papillary serous carcinoma (UPSC) [2,3]. UPSC has a poorer prognosis even if diagnosed at an early stage[2]. Although UPSC accounts for 10% of endometrial cancer cases, it is responsible for about half of deaths and recurrences[2–4]. UPSC has a higher propensity for deep myometrial invasion, cervical involvement and metastasis to omentum, ovaries and lymph nodes[3–5]. At the time of diagnosis approximately 55% to 85% of women with UPSC will have extrauterine spread [2,3,6].

Sensitivity of preoperative radiological imaging for detecting extrauterine spread is limited[7,8]. Due to the high frequency of extrauterine spread, patients with UPSC require a more extensive surgical procedure [3,9]. This surgical procedure should include hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissection and omentectomy. However, this surgical procedure is associated with higher complication rates[10]. For these reasons, a preoperative test or tumor marker that can predict extrauterine spread in the early period can contribute to determining the clinical approach and treatment plan.

Today, the use of preoperative measurement of cancer antigen (CA) 125 level for the diagnosis of endometrial cancer and post-treatment follow-up is increasing. Many studies have demonstrated the role of CA-125 level in endometrial cancer and its relationship with deep myometrial invasion, extrauterine spread, positive peritoneal cytology, lymph node metastasis, recurrence, advanced stages, and reduced survival [11–14]. The studies have included different histological types of tumors and suitable cut-off levels of CA-125 as a predictor and also have shown its relationship with various prognostic factors[15–17].

This study aimed to determine the relationship between preoperative CA-125 levels and clinicopathologic prognostic factors as well as appropriate cut-off levels for pure UPSC.

Material and Methods

Study data were collected from the documents and electronic medical records of patients who underwent surgery for endometrial cancer between 2005 and 2020 at a tertiary cancer center. The study was approved by the institutional ethics committee. All procedures performed in studies involving human participants were under the national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All patients were operated by gynecologic oncologists and all surgical specimens were evaluated by gynecological pathologists.

The inclusion criteria were histopathological confirmation of pure UPSC and patients who had CA-125 levels measured (chemiluminescence microparticle immunoassay 91 technique-Architect i2000 SR Immunoassay

Analyzers/ Abbott Laboratory, 92 Diagnostics Division, Abbott Park, IL, USA) at most 10 days prior to operation.

The exclusion criteria were patients who received primary radiotherapy and neo-adjuvant chemotherapy, had mixed histology, had synchronous cancers of the ovary, fallopian tube, or peritoneum, who did not have preoperative CA-125 levels, and in-complete medical records and follow-ups. Thus, the study included a total of 78 patients who met the inclusion criteria.

Treatment

In the preoperative period, UPSC was diagnosed by pipelle biopsy or fractional dilation and curettage. All patients were evaluated by computed tomography or magnetic resonance imaging. Comprehensive surgery was attempted to perform in all patients according to National Comprehensive Cancer Network (NCCN) guidelines. A vertical midline incision was preferred in all patients for ease of access during abdominal exploration and organ resection. After entering the peritoneal cavity, a peritoneal wash was obtained for cytology. Exploration of the abdominal cavity included a systematic examination of the peritoneal surfaces, omentum, colon and small intestine, and para-colic, pelvic, mesenteric and para-aortic sites, as well as palpation to locate suspicious lesions. Optimal surgery (cytoreduction) included hysterectomy, bilateral salpingo-oophorectomy(BSO), pelvic and para-aortic lymph node dissection, omentectomy and excision of lesions suspected to be a metastasis, if any. Suboptimal surgery included at least hysterectomy, BSO and/or pelvic lymph node sampling and/or omentum biopsy. Lymphadenectomy was defined as simultaneous pelvic and para-aortic lymph node dissection. Pelvic lymphadenectomy was defined as the removal of lymphatic tissue in the external, internal, and common iliac and obturator regions. Para-aortic lymph-adenectomy was defined as removal of the lymphatic tissue over the inferior vena cava and aorta, beginning at the level of the aortic bifurcation and up to the left renal vessels. Radical hysterectomy was performed on patients suspected of having cervical involvement on preoperative imaging. Stage was defined as according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) surgical staging criteria for uterine cancer[18]. Patients who were diagnosed before 2009 revised according to the 2009 FIGO criteria. Adjuvant therapy decisions were made by multidisciplinary tumor boards according to NCCN guidelines.

Follow-up

The follow-up intervals of the patients were every 3 months for the first 2 years, every 6 months up to 5 years and annually after 5 years. Follow-up visits consisted of clinical examination, ultrasonography of pelvis and abdomen, CA-125 testing in the case of high preoperative levels. Computed tomography or magnetic resonance imaging was used for the suspected presence of metastases. A biopsy procedure was performed in the case of accessible suspicious metastases. Recurrence was confirmed by gynecological pathologists or experienced radiologists in the multi-disciplinary tumor board.

Statistical Analysis

Clinicopathological and demographic data including age, parity, FIGO stage, type of surgery, recurrence, presence of extrauterine disease, the involvement of ovary, lymph node, cervix and omentum, lymphovascular space invasion (LVSI), deep myometrial invasion were collected. Their association with preoperative CA-125 levels was evaluated. The level of preoperative CA-125 was considered elevated if they were equal to or greater than 35 U/mL. A statistically significant logistic regression model (enter) was created using age, tumor size, preoperative serum CA-125 value, myomet-

Table 1. Characteristics of the study group

Variables	Mean±SD	Median (min-max)
Age (years) (n=78)	64.9±8.4	65.0 (45.0-82.0)
Parity (n=78)	2.9±1.2	3.0 (0.0-7.0)
		n (%)
FIGO stage (n=78)		
1A		11 (14.1)
1B		8 (10.3)
2		11 (14.1)
3A		9 (11.5)
3B		2 (2.5)
3C1		6 (7.7)
3C2		13 (16.7)
4		18 (23.1)
Extrauterine involvement (n=78)		
No		30 (38.5)
Yes		48 (61.5)
Cytoreduction *(n=78)*		
Optimal		59 (75.6)
Suboptimal		19 (24.4)
Lymph node involvement (n=60)		
Negative		33 (55.0)
Positive		27 (45.0)
Depth of myometrial invasion (n=78)		
<50%		25 (32.1)
≥50%		53 (67.9)
Cervical involvement (n=78)		
Negative		38 (48.7)
Positive		40 (51.3)
Omental involvement (n=76)		
Negative		59 (77.6)
Positive		17 (22.4)
LVSI (n=78)		
Negative		25 (32.1)
Positive		53 (67.9)
Preoperative serum CA-125 (U/mL) (n=76)		
<35		46 (60.5)
≥35		30 (39.5)
Recurrence (n=77)		
No		56 (72.7)
Yes		21 (27.3)

CA-125: Cancer antigen-125, FIGO: International federation of gynecologists and obstetrics, LVSI: Lymphovascular space invasion, SD: Standard deviation.

rial invasion, lymphovascular space invasion status as independent variables and extrauterine involvement as dependent variable. The association of extrauterine disease with preoperative CA-125 level, age, tumor diameter, myometrial invasion, and LVSI were investigated and an appropriate cut-off value was determined.

Study data were analyzed using the SPSS (statistical software package) version 20.0 (IBM Corp., Armonk, NY, USA). Number, percentage, mean, standard deviation, median, minimum and maximum values were used to present the data. The t-test was used as a parametric test, while the Mann-Whitney U test was used as nonparametric test according

to results of conformity to normal distribution test. The chi-square test was used in the analysis of categorical data. The Hosmer-Lemeshow statistical fit test was used to examine the suitability of the logistic regression analysis (Enter method). The accuracy of the preoperative serum CA-125 value in predicting metastasis sites was evaluated by the receiving operating characteristic (ROC) curve analysis and the most appropriate cuttoff values available were selected. A p-value <0.05 was considered statistically significant.

Results

The study population consisted of 78 women. The characteristics of the study group are shown in Table 1. In order to achieve optimal cytoreduction, rectosigmoid colon resection was performed on six patients, total colectomy on one patient, segmenter transverse colon resection on one patient, and peritonectomy on five patients (not shown in the table).

Preoperative serum CA-125 values were compared with univariate analyses according to clinicopathological features. There was a statistically significant difference between preoperative serum CA-125 values and omental involvement (P <0.001), ovarian involvement (P <0.001), cervical involvement (P = 0.017), myometrial invasion (P = 0.001). The median value of preoperative serum CA-125 level was higher in patients with omental, ovarian, cervical involvement and myometrial invasion depth equal to or greater than 50%. When preoperative serum CA-125 values were compared according to lymph node involvement, LVSI and recurrence, no statistically significant difference was found(P>0.05) (Table 2).

Percentage of patients with levels of preoperative CA- 125 greater than and less than 35 U/mL, according to clinicopathologic characteristics, are shown in Table 3.

Preoperative CA-125 value (P=0.001) and LVSI (P=0.029) were significantly associated with the presence of extrauterine involvement in univariate analysis. Extrauterine involvement was present in 86.7% of those with preoperative serum CA-125 value of 35 U/mL and above and in 69.8% of those with positive LVSI (Table 4). However in multivariate analysis only serum CA-125 value of 35 U/mL and above was associated with the presence of extrauterine involvement. Logistic regression model revealed that a preoperative serum CA-125 value of 35 U/mL and above increased extrauterine involvement risk 8.255 (95% confidence interval, 2.271-29.999) times(not shown in the table).

ROC curves were determined for the predictive value of preoperative serum CA-125 values for cervical, omental and ovarian involvement (Figure 1). Preoperative serum CA125 value was found to be the best cut-off point of 15.0 U/mL in estimating cervical involvement, 35.5 U/mL in estimating omental involvement, and 32.5 U/mL in estimating ovarian involvement (Table 5).

Discussion

Our study is the one of the largest studies in the literature evaluating preoperative CA-125 levels in patients with pure UPSC. CA-125 elevation is not a common condition in endometrioid type of endometrial cancer, but it is used in diagnosis and follow-up in epithelial serous ovarian cancer cases[19]. Although UPSC is a type of endometrial cancer, it is more similar to serous cancer of the ovary because of its spread into the peritoneal cavity and histological patterns[15]. For this reason, CA-125 elevation is more common in UPSC compared to endometrioid type of endometrial cancer. In our study preoperative CA-125 levels were significantly associated with omental, ovarian, cervical involvement and deep myometrial invasion but not with the recurrence, LVSI, lymph node involvement.

Table 2. Preoperative CA-125 values of women with UPSC

Variables	Preoperative serum CA125 (U/mL)		*P* value
	Mean±SD	Median (min-max)	
Omental involvement			
Negative	59.4±226.9	19.5 (3.0-1743.0)	**<.001***
Positive	253.5±227.5	205.0 (34.0-862.0)	
Ovarian involvement			
Negative	33.3±33.9	19.5 (3.0-141.0)	**<.001***
Positive	381.7±648.7	79.5 (4.0-2687.0)	
Lymph node involvement			
Negative	53.0±91.5	25.0 (4.0-454.0)	.136
Positive	188.9±514.4	34.0 (3.0-2687.0)	
Cervical involvement			
Negative	179.0±521.9	16.5 (3.0-2687.0)	**.017***
Positive	89.3±123.5	32.5 (7.0-454.0)	
LVSI			
Negative	131.6±375.5	25.0 (3.0-1743.0)	.309
Positive	135.4±385.0	26.0 (4.0-2687.0)	
Depth of myometrial invasion			
<50%	103.3±354.3	14.0 (3.0-1743.0)	**.001***
≥50%	148.4±393.0	34.0 (4.0-2687.0)	
Recurrence			
No	156.6±440.1	26.0 (3.0-2687.0)	.801
Yes	73.2±110.8	24.5 (4.0-400.0)	

P -values were calculated with Mann-Whitney U test. CA-125: Cancer antigen-125,
LVSI: Lymphovascular space invasion, SD: Standard deviation, UPSC: Uterine papillary serous carcinoma.
* *P* -value < .05.

Table 3. Preoperative CA-125 level according to clinicopathological features

Variables	Preoperative serum CA125 (U/mL)		*P* value
	<35	≥35	
	n (%)	n (%)	
FIGO stage			
1	18 (94.7)	1 (5.3)	**<.001***
2	7 (70.0)	3 (30.0)	
3	20 (66.7)	10 (33.3)	
4	1 (5.9)	16 (94.1)	
Extrauterine involvement			
Negative	25 (86.2)	4 (13.8)	**.001***
Positive	21 (44.7)	26 (55.3)	
Depth of myometrial invasion			
<50%	19 (79.2)	5 (20.8)	**.045***
≥50%	27 (51.9)	25 (48.1)	
Cervical involvement			
Negative	26 (68.4)	12 (31.6)	.241
Positive	20 (52.6)	18 (47.4)	
Omental involvement			
Negative	44 (75.9)	14 (24.1)	**<.001***
Positive	1 (6.2)	15 (93.8)	
Ovarian involvement			
Negative	39 (72.2)	15 (27.8)	**.003***
Positive	7 (31.8)	15 (68.2)	
Lymph node involvement			
Negative	21 (67.7)	10 (32.3)	.335
Positive	14 (51.9)	13 (48.1)	
LVSI			
Negative	17 (68.0)	8 (32.0)	.494
Positive	29 (56.9)	22 (43.1)	
Recurrence			
No	34 (61.8)	21 (38.2)	.886
Yes	12 (60.0)	8 (40.0)	

P -values were calculated with Chi-square test. CA-125: Cancer antigen-125,
FIGO: International federation of gynecologists and obstetrics, LVSI: Lymphovascular space invasion.
* *P* -value < .05.

Table 4. Factors affecting extrauterine involvement, univariate analysis

Variables	Extrauterine involvement				*P* value
	Negative		Positive		
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age (years)	65.0±9.5	64.5 (45.0-82.0)	64.9±7.7	65.5 (45.0-82.0)	.958[a]
	n (%)		n (%)		
Tumor size (cm)					
≤2	7 (50.0)		7 (50.0)		.499
>2	23 (35.9)		41 (64.1)		
Preoperative serum CA-125 (U/mL)					
<35	25 (54.3)		21 (45.7)		**.001***
≥35	4 (13.3)		26 (86.7)		
Depth of myometrial invasion					
<50%	12 (48.0)		13 (52.0)		.347
≥50%	18 (34.0)		35 (66.0)		
LVSI					
Negative	14 (56.0)		11 (44.0)		**.029***
Positive	16 (30.2)		37 (69.8)		

P -values were calculated with Chi-square test. CA-125: Cancer antigen-125,
LVSI: Lymphovascular space invasion, SD: Standard deviation. * *P* -value < .05.
a: *P* value was calculated with t test.

Table 5. AUC values, sensitivity, and specificity of CA-125 for metastasis site

Preoperative serum CA-125 (U/mL), Cutoff Value	***Metastasis site***	***AUC***	***Sensitivity (%)***	***Specificity (%)***
15.0	Serviks	.659	86.8	44.7
35.5	Omentum	.919	93.8	79.3
32.5	Over	.803	77.3	72.2

AUC: area under the curve, CA-125: Cancer antigen-125.
Statistical significance level was found to be <.05 in receiving operating characteristic curve analysis.

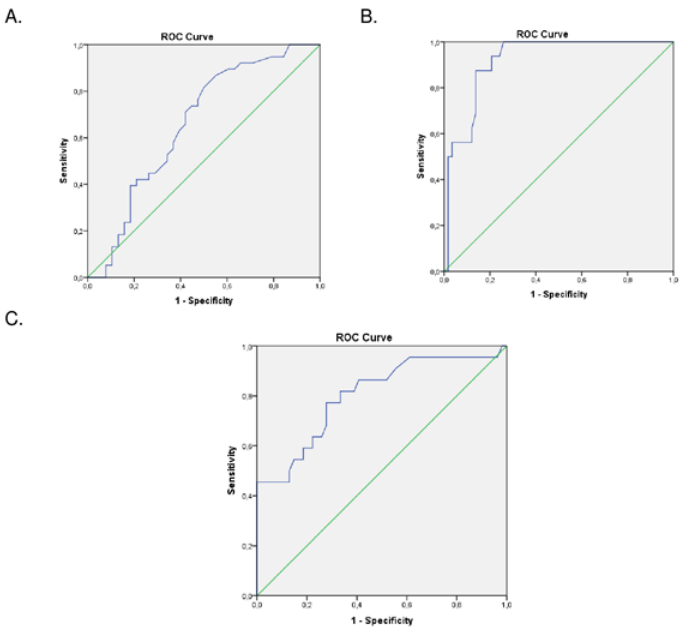

Figure 1. Receiving operating characteristic (ROC) curves for metastasis site in relation with preoperative CA-125 levels in uterin papillary serous carcinoma; A,cervical involvement, area under the curve(AUC)=0.659; B, Omental involvement, AUC=0.919; C, Ovarian involvement, AUC=0.803.

These results were consistent with the prior studies[15,16,19,20].

Schmidt et al. found that CA-125 level, LVSI, and depth of myometrial invasion were associated with extrauterine involvement in univariate analyses, while the depth of myometrial invasion was insignificant in multivariate analyses[15]. In line with our study, Roelofsen et al. found that CA-125 level and LVSI were associated with extrauterine involvement in univariate analyses, but only CA-125 level remained significant in multivariate analyses[21].

Many previous studies have shown various sensitivity and specificity levels of preoperative serum CA-125 values for extra-uterine metastasis [15,16,19,21]. Never-theless, there was no consensus on the reference cut-off value of preoperative CA-125 level in UPSC. Schmidt et al. found a cut-off value of 57.5U/mL with 68.8% sensitivity and 95.6% specificity for omental involvement, 41.8U/mL with 72.2% sensitivity and 85.7% specificity for ovarian involvement. In our study, we determined cut-off values with higher sensitivity for omental and ovarian involvement. An additional issue not reported in previous studies was what the best cut-off level of CA-125 for predicting cervical involvement. A level of 15.0 U/mL was the best cut-off value for predicting cervical involvement. Although according to the results of ESMO-ESGO-ESTRO 2016 Endometrial cancer consensus conference, radical hysterectomy is not recommended for stage II endometrial cancer, modified (type B) or type A radical hysterectomy should be considered only if required for obtaining free margins[22]. This value may be a guide that radical hysterectomy should be considered in the foreground in patients undergoing surgery.

The fact that CA-125 elevation is associated with ovarian and omental involvement but not with LVSI and lymph node involvement may be an evidence that metastatic cells spread to serous surfaces, just as in serous cancer of the ovary. Moreover only the CA-125 level was significant in the multivariate analyses of the factors affecting extrauterine involvement supports our hypothesis.

The major limitation of our study is its single-center retrospective design. Although the statistical analyses were carried out in a small patient population, our study included one of the largest number of patients in the literature. The strength of the study is that it included pure UPSC patients, all surgeries were performed by the gynecologic oncologists, and the histological diagnosis was confirmed by the gynecological pathologists.

In conclusion, this study contributes to the growing evidence on the use of preoperative serum CA-125 in patients with UPSC. Our data clearly show that an elevated level of preoperative CA-125 is a marker for omental, ovarian, cervical involvement and deep myometrial invasion. Although the relationship between CA-125 elevation and extrauterine involvement has been demonstrated, there is a need for future studies to evaluate the role of CA-125 in predicting recurrence and survival in UPSC.

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

Orcid ID:
İlker Çakır 0000-0003-0245-5298
Volkan Karataşlı 0000-0002-4015-6494
Varol Gülseren 0000-0002-0779-8305
Duygu Ayaz 0000-0002-2202-2732
Barış Sever 0000-0002-9690-8819
Zübeyde Emiralioğlu Çakır 0000-0001-8298-8363
Gökşen Görgülü 0000-0003-2837-8497
Oğuzhan Kuru 0000-0002-4497-7222
Muzaffer Sancı 0000-0002-8494-4302
Mehmet Gökcü 0000-0002-3187-2317

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Original Article

Which is The Best Strategy in Local Advanced Larynx Cancer? Total Laryngectomy Plus Radiotherapy or Larynx Preservation with Chemoradiotherapy: Single Center Experience

Lokal İleri Evre Larinks Kanserinde Hangi Strateji En İyisi? Total Larenjektomiye Radyoterapi Eklenmesi mi Organ Koruyucu Kemoradyoterapi mi? Tek Merkez Deneyimi

Mete Gündoğ[1], Hatice Başaran[1], Alperen Vural[2], Esin Kiraz[1], Celalettin Eroğlu[1], Imdat Yüce[2], Sedat Çağlı[2]

[1] Erciyes University, Department of Radiation Oncology, Kayseri, Turkey
[2] Erciyes University, Department of Otorhinolaryngology, Kayseri, Turkey.

ABSTRACT

Objectives: The treatment of locally advanced laryngeal cancer (LALC) is very challenging. In the last few decades there has been a shift from total laryngectomy towards organ-sparing approaches. The aim of the current study is to compare oncological outcomes between surgery (total laryngectomy) followed by radiotherapy and larynx preservation with chemoradiotherapy (CRT).

Materials and Methods: 114 patients with stage III-IV laryngeal cancer were included in the study, between 2009 and 2018. Thirty-six patients (31.6%) were performed total laryngectomy followed by radiotherapy and 78 (68.4%) underwent the larynx preservation approach. Survival differences between the groups were examined with the Kaplan-Meier test and cox-regression tests for factors affecting survival.

Results: 5-year overall survival (OS) was found 66.3 months and 74.1 months, in the larynx preservation and the surgical groups, respectively (p=0.29). There was no statistically difference between groups for OS in the patients with T3/N0-N1 (p=0.76), but surgical groups had longer OS in the patients with T3/N2-N3 (p=0.04). There was no statistically difference between groups for OS in the patients with T4/N0-N1 (p=0.47), however CRT groups had longer OS in the patients with T4/N2-N3 (p=0.02). The N2-N3 was the factor associated with poor progression-free survival and distant metastasis free survival in multivariate analysis (p<0.01). Age (≥65) was associated with a 2.1-fold increased risk of death (p=0.01). The trans-glottis tumors were associated with a 3.6-fold increased risk of tracheostomy (p<0.01).

Conclusion: The N0-N1 and N2-N3 should also be considered as well as advanced T-category for the treatment of LALC.

Keyword: larynx-preservation, chemoradiotherapy, cisplatin, cetuximab, survival

ÖZET

Amaç: Lokal ileri larinks kanserinin tedavisi çok zordur. Son birkaç on yılda total larenjektomiden organ koruyucu yaklaşımlara, yani kemoradyoterapiye doğru bir kayma olmuştur. Bu çalışmanın amacı, cerrahi (total larenjektomi) ardından radyoterapi ve kemoradyoterapi ile larinksin korunması arasındaki onkolojik sonuçları karşılaştırmaktır.

Gereç ve Yöntem: 2009-2018 yılları arasında evre III-IVa-b larinks kanserli 114 hasta çalışmaya dahil edildi. 36 hastaya (%31,6) radyoterapi ve 78 hastaya (%68,4) larinks koruyucu yaklaşım uygulandı. Larinks koruma yaklaşımları, indüksiyon kemoterapisi sonrası kemoradyoterapi veya eş zamanlı kemoradyoterapi idi. Gruplar arasındaki sağkalım farklılıkları Kaplan-Meier testi ve sağkalıma etki eden faktörler cox-regresyon testi ile değerlendirildi.

Bulgular: 5 yıllık genel sağkalım larinks koruma ve cerrahi gruplarda sırasıyla 66,3 ay ve 74,1 ay olarak bulundu (p=0.29). Evre III hastalarda 5 yıllık hastalık spesifik sağkalım (HSS) oranı cerrahi grupta

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%63,3 iken kemoradyoterapi grubunda %66,2 idi (p=0,83). Evre IV hastalarda 5 yıllık HSS oranları cerrahide %68,6, kemoradyoterapi grubunda %46,2 bulundu (p=0,22). İleri N kategorisi (N2-N3), çok değişkenli analizde kötü progresyonsuz sağkalım ile ilişkili faktör olarak bulundu (p<0.01). Yaş (≥65) 2,1 kat (p=0,01), ileri T kategorisi (T4) 2 kat artmış ölüm riski (p=0,03) ile ilişkili bulundu. Trans-glottik tümörler 3.6 kat artmış trakeostomi riski ile ilişkili bulundu (p<0.01).
Sonuç: T3/N0-N1 ve T3/N2-N3 alt grupları ayrı ayrı değerlendirildiğinde, T3/N0-N1 hastalarda, kemoradyoterapi yüksek düzeyde larinks koruması sağlayan bir tedavi seçeneğidir.

Anahtar kelimeler: larinks koruma, kemoradyoterapi, sisplatin, setuksimab, sağkalım

Introduction

Larynx cancer causes 2% of all malignancies in the world. Also, it is the 2nd most common cancer in the head and neck region [1]. The standard treatment of locally advanced laryngeal cancer is unclear. In the last decades there, significant changes have evolved in locally advanced laryngeal cancer treatment. Until the 1980s, total laryngectomy (TL) was the main treatment modality and post-operative radiotherapy according to poor prognostic features was a possible treatment strategy. Besides the morbidity of the organ loss, the cosmetic discomfort of permanent stoma causes physiological and psychological problems in patients. The idea of organ protection treatment includes the possibility of treatment with a combination of radio-therapy and chemotherapy without compro-mising oncological outcomes. The studies that compare the outcomes between the TL plus postoperative radiotherapy with induction chemotherapy that consists of 5-fluorouracil and cisplatin followed by radiotherapy showed no different outcomes according to disease control or overall survival [2-4]. A subsequent study showed that concomitant chemoradiotherapy had good outcomes than induction chemotherapy followed by radiotherapy, in terms of local control and rate of larynx preserving and there were no differences in late adverse effects [5,6]. However, some studies in recent years have suggested that survival rates in locally advanced larynx cancer are reduced. They thought that the shift from surgical to organ-sparing approaches might cause these reduced survival times. They claim that the reason for this reduced survival was a shift from surgery to organ-sparing approaches [1,7]. Therefore, in recent years, articles advocating the re-emergence of surgical approaches in locally advanced diseases have been published [8]. Currently, it is recognized that the best oncologic outcome in patients who has locally advanced tumors (T4a) been usually achieved by surgical treatment involving organ resection. But, deciding the method of treatment is quite challenging both for the physician, as well as the patient. In case of moderately extensive tumors suitable for TL (T3 and selected T4a), oncological outcomes of organ protection protocols should be kept in mind [9]. With this study, comparison of the treatment outcomes of surgical and non-surgical approaches are aimed.

Materials and Method

Patients

The trial was carried out by department of radiation oncology and Department of Otorhinolaryngology-Head and Neck Surgery together. 114 patients with locally advanced laryngeal cancer were included in this retrospective study, between March 2009 and December 2018. TNM staging was determined by clinical examination, endo-scopy, computed tomography, and positron emission computed tomography, according to AJCC 7th staging [10]. All patients had been evaluated by the tumor board which consisted of head and neck surgeons, pathologists, radiation oncologists, medical oncologists, radiologists, and nuclear medicine specialists.

After the evaluation for each case, the appropriate treatment modalities are presented to the patient by describing meticulously the pros and cons of each treatment both in terms of oncological outcomes as well as potential effects. For this study group with T3-4 laryngeal cancers, the suggested treatment options were either surgery or organ-preserving approach. Groups were then created according to the patient's treatment choice for this cohort. The patients who underwent partial laryngectomy, the ones with previous treatment to the head and neck area, the ones with poor Karnofsky Performance Scales (<70) and patients with surgically unresectable tumors were excluded from the study. Both induction chemotherapy followed by chemoradiotherapy and concomitant chemoradiotherapy was accepted as larynx preservation approaches. The written informed consent was obtained from all participants. The trial was approved by the local ethics committee (Number 2020/395).

Surgical Approach

The surgical approach was resection of the primary tumor plus bilateral modified radical neck dissection. Thirty-six patients (31.6%) underwent total laryngectomy plus adjuvant radiotherapy. Post-operative adjuvant radiotherapy was started four weeks after surgery and it was applied 2.0 Gy per fraction per day with five fractions per week. 60 Gy dose was applied to the tumor bed for patients with R0 resection. Uninvolved lymph nodes and supraclavicular nodes were applied 50-60 Gy.

Non-surgical approach

We considered the treatment of organ protection as induction chemotherapy followed by chemoradiotherapy, concurrent radiotherapy combined with cisplatin, or concurrent radiotherapy combined with cetuximab (bio-radiotherapy). For these patients, it was accepted as an organ loss that total laryngectomy performed after recurrence or tracheostomy performed for any reason. 78 of 114 patients (68.4%) were treated with the intent of larynx preservation. 71 (92%) of 78 patients had cisplatin as concurrent chemotherapy (100 mg/m^2 every 3 weeks or 50mg/m^2 a week). Cetuximab was administered to seven patients (8%) according to published protocols [11]. Induction chemotherapy was administered to 16 of 78 patients (20.5%) and 62 of 78 patients (79.5%) received concurrent chemotherapy for the organ-preserving protocol. High-risk planning target volume (PTV) (primary tumor volume and associated nodes), intermediated-risk PTV, and low-risk PTV received the prescribed dose as 70Gy, 60Gy, and 54Gy respectively.

Statistical analysis

IBM SPSS Statistics software (Version, 21, Armonk;NY: IBM Corp) was used to analyze the data of the study. Evaluation of normality was performed by using the Shapiro-Wilk test. To compare categorical variables Chi-square or Fisher's exact tests were used. The survival time between groups was compared with Kaplan-Meier analysis and log-rank tests. The effective factors on survival such as gender, T category, N category, treatment modalities were determined with the in the univariate test. $p < 0.05$ was accepted as statistically significant. Variables with p values <.05 were entered into a backward stepwise regression in multivariate analysis.

Results

The median age was 60 (range: 31-79). 12 (10.5%) of the patients were female and 102 (89.5%) were male. In the non-surgical group, 63 patients (79.5%) had a complete response, while 11 patients (14.1%) had a partial response. There was a stable response for 2 patients (2.6%) and progression for 3 patients (3.8%). In the non-surgical group, 17 of 78 patients (21.8%) underwent salvage surgery.

Table 1. The general characteristics of the patients

		Total	Total laryngectomy plus radiotherapy		Larynx preservation		p
			n	(%)	n	(%)	
Gender	Female	12	0	0	12	15.4	0,01
	male	102	36	100	66	84.6	
Age	<65	72	22	61.1	50	64.1	0.83
	>65	42	14	38.9	28	35.9	
Tumor site	Glottis	21	1	2.8	20	25,6	<0,01
	Supra-glottis	59	14	38.9	45	57.7	0,05
	Sub-glottis	7	6	16.7	1	1.3	<0,01
	Trans-glottis	27	15	41.7	12	15.4	<0,01
T category	T3	85	21	58.3	65	82.3	0,01
	T4	29	15	41.7	14	17.7	
N category	N0-1	89	27	75.0	63	79.7	0,62
	N2-3	25	9	25.0	16	20.3	
Stage	III	66	12	33.3	53	67.1	<0,01
	IVA	48	24	66.7	26	32.9	
Tracheostomy		56	36	100	20	25.3	<0,01
Local recurrence	-	91	32	88.9	62	78.5	0,20
	+	23	4	11.1	17	21.5	
Death	alive	66	25	69.4	42	53.2	0.10
	ex	48	11	30.6	37	46.8	

p: Fisher's Exact Test value

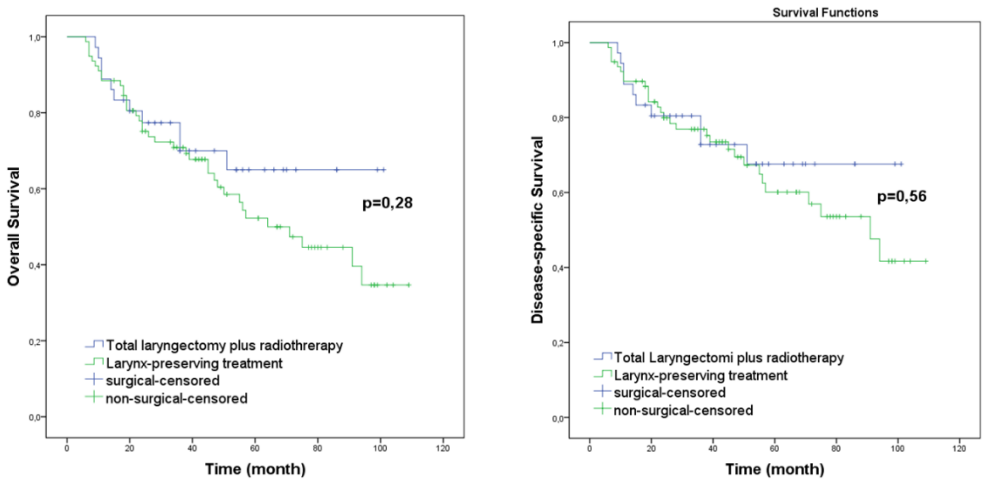

Figure 1: Kaplan-Meier survival curves between total laryngectomy plus radiotherapy and larynx preserving.

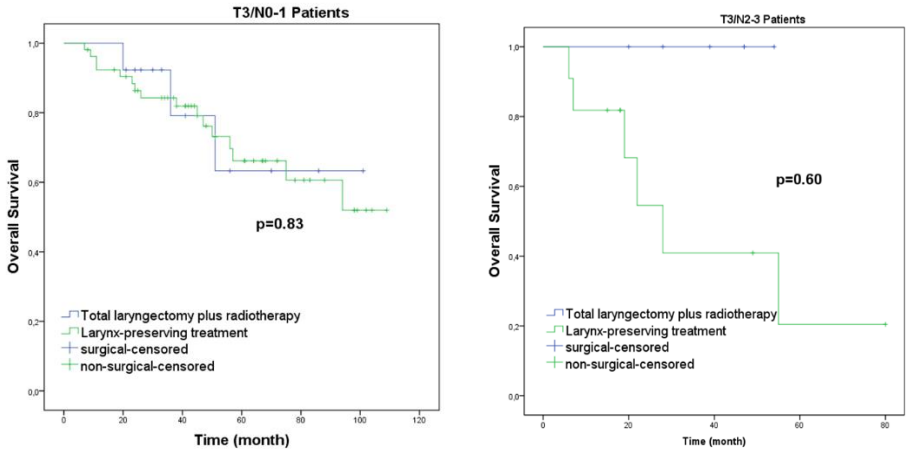

Figure 2: Intergroup survival curves according to N stage in T3 patients

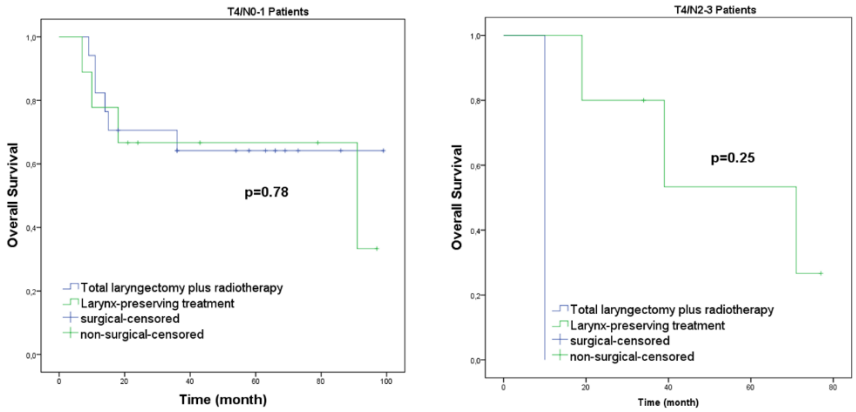

Figure 3: Intergroup survival curves according to N stage in T4 patients.

In the last visit, 66 patients (57.9%) were alive at last examination. 39 patients (34.2%) died from cancer and nine patients (7.9%) died from non-cancer related causes. The patient's characteristics are summarized in Table 1.

Survival

The median overall survival (OS) was 75 months for all the patients, with a median follow-up of 41 months. The 5-year OS rates were found 60% in the surgical group and 52.3% in the non-surgical group. The differences between groups were not found statically significant (p=0.28). Disease-specific survival (DSS) was 76.2 months in the surgical group, while it was 73.1 months in the non-surgical group (p=0.56)(Figure 1). Additionally, progression-free survival (PFS) was 75.2 months in the surgical group and it was 71.0 months in the non-surgical group (p=0.27). In patients with stage III, 5-year OS rate was 57,5% in the surgical group, while that's the rate was 57,4% in the non-surgical group. However, there was no significant statistical difference between the groups (p=0.76). Also, in patients with stage IV, 5-year OS rates were found 68.6% in the surgical group and 40,4% in the non-surgical group, respectively. The difference didn't achieve to statistically significant value (p=0.11). When the outcomes were evaluated in terms of T-category, 5-year OS rate was 73,8% in the surgical group in patients with T3, while that's the rate was 51,7% in the non-surgical group (p=0.08). When the subgroups of T3 cases were examined; 5-year OS rate was 57,5% in total laryngectomy + RT arm and 57,4% in chemoradiotherapy arm in the T3N0-1 cases (p = 0.76). However, in T3N2-N3 cases, this ratio was 100% in the total laryngectomy + RT arm and 17,9% in the chemoradiotherapy arm (p=0.04) (Figure 2). Also, in patients with the T4 category, the 5-year OS rates were found 52.5% and 54,4% for surgical and non-surgical groups, respectively (p=0.83). No difference in survival was found between groups in terms of T4-category. When the subgroups were examined in terms of T4, in the T4N0-1 patients the 5-year OS rate was 64,2% in the surgical group while this rate was 53,3% in the non-surgical group (p:0,47). But, in the T4N2-3 patients the 5-year OS rate was 26,7% in the non-surgical group while this rate was 0% in the surgical group (There was one patient and he died at the tenth month) (p:0,02) (Figure 3).

In 58 of the 78 patients (74.4%), the larynx was preserved. Larynx preservation rates were found 76.8% and 71.8% at the 2nd and 5th years, respectively. While the 5-year larynx preservation rate of patients treated with induction chemotherapy and sequential radiotherapy was 71.8%, it was 72.9% in patients receiving only chemoradiotherapy. There were no statistically significant differences between groups (p=0.97). Also, 5-year larynx preservation rates were found 74.3% in patients with T3 and 60.6% in patients with T4 (p=0.17). In patients receiving cetuximab during radiotherapy, 5-year larynx-preservation rates were found as 51.4%, while in patients receiving cisplatin this rate was found 73.9%, but differences between groups were not found statistically significant (p=0.13). However, in terms of OS, between patients receiving cetuximab and patients receiving cisplatin, the difference was statistically significant (33 months versus 77.2 months, respectively, p<0.01).

Univariate and multivariate analyses

In univariate and multivariate analysis, the advanced age (>65) was found as factor affecting OS (HR:2.17, 95%CI: 1.154-4.100, p<0.01) and advanced T status (T4) was found as factor affecting OS (HR:2.05, 95%CI: 1.061-3.964, p=0.03). The treatment approach (surgical versus non-surgical) was not detected as a factor affecting OS (HR: 1.43, 95%CI: 0.732-2.820, p=0.29) (Table 2). The advanced stage (stage-IVA-B) and N-category (N2-N3) were the factors associated with poor progression-free survival, in univa-

Table 2. Univariate and multivariate analysis

		Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p
Overall Survival							
Gender	Female	1.04	0.376-2.919	0.93			
	Male						
Age	≤65						
	>65	2.18	1.234-3.851	<0.01	2.17	1.154-4.100	0.01
T category	T-3						
	T-4	1.96	1.021-3.798	0.04	2.05	1.061-3.964	0.03
N category	N0-N1						
	N2-N3	1.26	0.643-2.481	0.49			
TNM Stage	III						
	IVA-B	1,55	0.881-2.747	0.12			
Treatment	Surgery plus radiotherapy						
	Larynx-preserving	1.43	0.730-2.812	0.29			
Tumor sub-site	Glottis						
	Supra-glottis	0.38	0.137-1.064	0.26			
	Sub-glottis	0.86	0.451-1.643				
	Trans-glottis	0.57	0.131-2.552				
Progression-free Survival							
Gender	Female	0.95	0.337-2.674	0.92			
	Male						
Age	≤65						
	>65	1.18	0.619-2.254	0.61			
T category	T3	1,57	0.795-3.104	0.19			
	T4						
N category	N0-N1						
	N2-N3	2.65	1.379-5.127	<0.01	2.65	1.379-5.124	<0.01
TNM Stage	III						
	IVA-B	2.24	1.193-4.242	0.01			
Treatment	Surgery plus radiotherapy						
	Larynx-preserving	1,21	0.576-1.182	0.29			
Tumor sub-site	Glottis						
	Supra-glottis	2.44	0.846-7.079	0.22			
	Sub-glottis	0.81	0.091-7.253				
	Trans-glottis	2.61	0.834-8.227				

a value of p<0.05 was considered statistically significant

Table 3. Univariate and multivariate analysis for larynx-preserving survival

		Univariate			Multivariate		
		HR	95% CI	p	HR	95% CI	p
Gender	Female						
	Male	3.19	0.427-23.865	0.23			
Age	<65						
	≥65	1.52	0.421-1.024	0.06			
T category	T3						
	T4	1.84	0.721-5.499	0.18			
N category	N negative						
	N positive	1,29	0.498-1.199	0.24			
TNM Stage	III						
	IVA-B	2,75	1.142-6.660	0.02	1.97	0.753-5.157	0.16
Tumor sub-site	Glottis						
	Supra-glottis	0.197	0.068-0.574				
	Sub-glottis	0.309	0.134-0.716				
	Trans-glottis	15.160	2.482-92.598	<0.01	3.66	1.461-9.205	<0.01
Treatment	ICT followed by CRT						
	Concurrent bio/chemo-radiotherapy	0.98	0.592-1.651	0.96			
Concomitant drug	Cisplatin (chemo-therapy)						
	Cetuximab (bio-therapy)	2.49	0.724-8.560	0.14			

ICT; Induction chemotherapy, CRT; concurrent chemoradiotherapy, a value of p<0.05 was considered statistically significant

riate analysis (HR:2.24, 95%CI:1.193-4.242, p=0.01 and HR:2.65, 95%CI:1.379-5.127, p<0.01, respectively) (Table 2). N-category (N2-N3) was associated with an approximately 2.6-fold increased risk of progression (HR:2.65, 95%CI:1.379-5.127, p<0.01) (Table 2). In univariate analysis, N-category (N0-N1 v N2-N3), and stage (stage III v IVA-B) were associated with distant metastasis. (HR:3.76, 95%CI:1.623-8.731, p<0.01 and HR:2.51, 95%CI:1.073-5.898, p=0.02). In multivariate analysis, only N-category (N2-N3) was associated with distant metastasis (HR:3.76, 95%CI: 1.623-8.731, p<0.01) (Table 2).

When the patients were evaluated in terms of larynx preservation; in univariate analysis, trans-glottic tumor and stage were found as factors affecting larynx-preservation survival (HR:3.667, 95%CI: 1.461-9.205, p<0.01 and HR:2.75, 95%CI:1.142-6.660, p=0.02, respectively). Multivariate analysis showed that trans-glottis tumors were associated with a 3.6-fold increased risk of tracheostomy (HR: 3.66, 95%CI: 1.461-9.205, p<0.01) (Table 3).

Discussion

Organ preservative approaches for advanced laryngeal cancer have been well established in the literature in terms of effectiveness and safety [2,5,6]. According to the results of the Veterans Affairs Laryngeal Cancer Study Group and RTOG91-11 study, there has been a shift from surgical approaches to chemo-radiotherapy in the last few decades, in locally advanced larynx cancer treatment. In the cohort of this study, approximately 70% of patients have organ-protective approaches. This current study confirmed that there has

been a shift from surgical treatments to larynx protection treatments. Especially, all of the female patients preferred the organ-protective approaches. In this respect, it is compatible with literature. However, in recent years, the authors have begun to advocate surgical priority over chemoradiotherapy. In the study based on SEER data, Carvalho et al., first announced a reduction in survival times in patients with larynx cancer. They suggested that organ protection protocols increased from 37.4% to 50.6%, which led to a decrease in survival [12]. Similarly, Chen et al., argued that the risk of death for 4-year overall survival increased by 13% in patients treated with CRT, due to the increased use of CRT in the treatment of locally advanced diseases [13]. This relationship has been replicated in subsequent studies [14-16]. However, the oncological results of treatment selection are still debated in studies in the literature. Rades et al., found that tumor size and histologic grade were affecting OS. They did not find any differences between surgery plus adjuvant treatment and larynx-preserving treatment in terms of survivals [17]. Similarly, Timme et al., found that the 5-year overall survival rate was 45% and %46 in patients receiving chemoradiotherapy and in patients undergoing surgery, respectively, and it was not statistically significant [18]. In this current study, we didn't find a significant statistical difference between the laryngeal-preservation and non-preservation approaches, both overall survival and disease-specific survival. Additionally, when patients were evaluated for T-category, we found that there was a tendency towards larynx-protection protocol in patients with T3 tumors, whereas there was a tendency towards surgery in patients with T4a tumors. This situation coincides with studies in the literature [7]. Many authors agree that oncological outcomes are similar in patients with T3 tumors, whether total laryngectomy or larynx protection therapy is selected [7,19]. However, some studies have shown that total laryngectomy plus radiotherapy is superior to non-surgical approaches in patients with T4A tumors [20-23]. In this study, T3 patients who underwent total laryngectomy tended to have longer OS than non-surgical patients, although this did not reach statistical significance. It can be thought that the association of N2-3 lymph node metastasis is more effective in this trend than the effect of the T category alone. The results of patients with T4 tumors were also very close between the non-surgical approach and surgical approach. In this current study; T4/N2-3 patients who were initially treated with the organ preservation protocol had longer OS than patients who underwent surgery. Whether with chemoradiotherapy or induction chemotherapy, the initial effect of systemic chemotherapy might have led to this result. While local control could achieve with radiotherapy in this group of patients, distant metastasis might be reduced with systemic chemotherapy. Because in multivariate analysis, N2-3 status was associated with distant metastasis. In the GORTEC trial, 3-year OS rates were found as 60% and larynx preservation rates were found %66 [24]. Also, in the TAX-324 study, the 3-year OS rate was 60% and the larynx preservation rate was 70.3% [25]. In the study of EORTC, the 3-year OS rate was found 48.5% for laryngeal cancer, and the 3-year larynx-free survival rate was 52% [3]. In the long-term results of RTOG 91-11 study, they upgraded their results that 10-year OS rate was found 38.8% for patients treated with induction chemotherapy plus radiotherapy (ICT+RT), while it was 27.5% for patients treated with concurrent chemoradiotherapy (CRT) [6]. Additionally, they showed that the 10-year laryngectomy-free survival rate was found as 28.9% in patients with treated ICT+RT and 23.5% in patients with treated CRT. We found in this current work that 5-year OS rate was 55% for patients treated with ICT+RT and was 52% for patients treated with CRT. In this current study, the 5-year larynx protection rates were found as 71.8% in patients

receiving ICT+RT and 73.1% in patients receiving CRT. These results are comparable to the results of the RTOG 91-11 study which a cornerstone of larynx protection strategies.

Bonner et al., had demonstrated the efficacy of cetuximab in patients with head and neck cancer and then the TREMPLIN study was designed [11,26]. This study investigated that after three cycles of induction chemotherapy (consist of taxan, cisplatin, and 5-fluorouracil), compare between concurrent radiotherapy with cisplatin and concurrent radiotherapy with cetuximab. They reported that larynx preservation rates were 87% in the cisplatin arm and 82% in the cetuximab arm, at 18 months. And also, the 3-year OS rate did not differ between groups. In this current study, the larynx-preservation rate did not differ between patients receiving cetuximab and receiving cisplatin, but the OS of patients with cisplatin had better than those receiving cetuximab. However, it should not be ignored that cetuximab treatment was used in patients with comorbid diseases who were not suitable for chemotherapy in this study. The limitations of this study are as follows: there is a limited number of patients and the follow-up time is also short. It is a non-randomized study, so data were obtained from different sources (partly from patient cards, partly from electronic files and national database). In this study, acute and late side effects related to treatment and quality of life analysis were not evaluated.

Conclusion

Our results show that chemoradiotherapy remains a successful method in patients who want laryngeal protection. However, T3/N0-N1 and T3/N2-N3 subgroups should be evaluated differently and different treatment strategies should be considered. Excellent results are obtained with chemoradiotherapy for T3/N0-N1 patients. However, especially in T3/N2-N3 patients, total laryngectomy should also be kept in mind, despite the patient's desire to protect the larynx. In very advanced disease such as T4/N2-3, it may be necessary to consider the control of systemic disease rather than the treatment of local disease.

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Corresponding author e-mail: mgundog@erciyes.edu.tr

Orcid ID:
Mete Gündoğ 0000-0001-9195-2442
Hatice Başaran 0000-0003-3093-0738
Alperen Vural 0000-0003-1969-7760
Esin Kiraz 0000-0002-7867-3227
Celalettin Eroğlu 0000-0002-5743-2440
İmdat Yüce 0000-0003-0938-4437
Sedat Çağlı 0000-0003-4913-8687

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Original Article

Efficacy of Pazopanib in Patients with Pretreated Advanced Stage Soft Tissue Sarcomas

Önceden Tedavi Edilmiş İleri Evre Yumuşak Doku Sarkomlu Hastalarda Pazopanib Etkinliği

Musa Barış Aykan, Gül Sema Keskin, Ece Örnek, Alper Topal, Çağlar Köseoğlu, Ayşegül Dumludağ, İsmail Ertürk, Nuri Karadurmuş

Department of Medical Oncology, University of Health Sciences, Gülhane School of Medicine, Ankara,Turkey

ABSTRACT

Background: Pazopanib acts as a multitargeted tyrosine kinase inhibitor. It has been shown to be effective in patients with advanced stage Soft Tissue Sarcomas (STSs). We aimed to evaluate survival times and significant side effects by making a retrospective evaluation of real-life data.

Materials and Methods: This study was carried out with a retrospective method. Clinical characteristics of adult patients with advanced STSs treated with the pazopanib were recorded in the hospital's patient registry database. Patients without medical records were excluded from the study. Objective response rate (ORR), Progression-free survival (PFS), overall survival (OS), and treatment-related pneumothorax and hypertension side effects were determined.

Results: Forty adult patients were included (males: 55%). The median age was 44.5 years (range: 20-88). Malignant mesenchymal tumor by histopathology was found in 32.5% of the sample. Eighty-eight percent of the sample had a Stage 3 or higher disease at the time of initial diagnosis. Seventy percent of the patients had lung metastases. Seventy percent of the patients received two or more lines of systemic chemotherapy prior to pazopanib. The ORR to the pazopanib was 45% for whole patients. Median PFS (IQR) was determined as 5.73 (2.67) months (95% Confidence Interval (CI) of 5.19 to 6.19 months). Median OS (IQR) was 8.54 (17.81) months (95% CI of 8.24 to 15.65 months). Pneumothorax was detected during pazopanib in twelve and a half percent of patients. Hypertension was detected during pazopanib in fifteen percent of patients.

Conclusion: Pazopanib led to significant survival in this pretreated population of patients based on real-life data. It also has a manageable side-effect profile.

Keywords: Sarcoma, Vascular endothelial growth factor receptor, Pazopanib

ÖZET

Amaç: Pazopanib, birden çok hedefli bir tirozin kinaz inhibitörü olarak çalışır. İleri evre Yumuşak Doku Sarkomlu (YDS) hastalarda etkinliği gösterilmiştir. Gerçek yaşam verilerinin retrospektif bir değerlendirmesini yaparak sağkalım sürelerini ve önemli yan etkilerini değerlendirmeyi amaçladık.

Materyal ve Metod: Bu çalışma retrospektif yöntemle gerçekleştirilmiştir. Pazopanib ile tedavi edilen ileri ever YDS'li yetişkin hastaların klinik özellikleri hasta kayıt veri tabanından kaydedilmiştir. Tıbbi kaydı olmayan hastalar çalışma dışı bırakılmıştır. Objektif yanıt oranı (ORR), Progresyonsuz sağkalım (PFS), genel sağkalım (OS), tedaviye bağlı pnömotoraks ve hipertansiyon yan etkiler değerlendirilmiştir.

Bulgular: Kırk yetişkin hasta dahil edildi (erkekler: %55). Ortanca yaş 44,5 (aralık: 20-88) olarak saptandı. Histopatolojik olarak malign mezenkimal tümör örneklemin %32,5'inde tespit edildi. Yüzde seksen sekiz hasta ilk tanı anında Evre 3 veya daha yüksek bir hastalığa sahipti. Hastaların yüzde yetmi-

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şinde akciğer metastazı vardı. Hastaların yüzde yetmişi pazopanib öncesinde iki veya daha fazla sıra sistemik kemoterapi almıştır. Pazopanib için ORR tüm hastalar için %45 olarak saptandı. Medyan PFS (IQR) 5,73 (2,67) ay olarak belirlendi (%95 Güven Aralığı (GA) 5,19-6,19 ay). Medyan OS (IQR) 8,54 (17,81) aydı (%95 GA 8,24- 5,65 ay arasında). Pazopanib sırasında hastaların %12'sinde pnömotoraks tespit edildi. Pazopanib sırasında hastaların %15'inde hipertansiyon saptandı.
Sonuç: Pazopanib, gerçek yaşam verilerine dayalı olarak önceden tedavi edilmiş bu hasta popülasyonunda anlamlı sağkalıma yol açmıştır. Ayrıca yönetilebilir bir yan etki profiline sahiptir.

Anahtar Kelimeler: Sarkom, Vasküler endotelyal büyüme faktörü reseptörü, Pazopanib

Introduction

Sarcomas are a rare but heterogeneous group of malignancies of mesenchymal origin. Whole sarcomas constitute less than one percent of all adult cancers [1-3]. Soft tissue sarcomas (STSs) constitute eighty-five percent of the entire sarcoma patient population [3]. STSs most commonly originate from the extremities [4,5].

Primary treatment of STSs consists of surgery and radiotherapy. However, local recurrence is observed in 5-30% of patients and recurrence with clinically detectable distant organ metastasis in approximately 25% of patients [6,7]. There is a poor prognosis for relapsed/refractory STSs. While the median overall survival is less than 12 months with conventional chemotherapy in metastatic sarcomas, in recent years the survival time has increased to longer than 12 months due to developments in the typing of sarcomas and the use of new treatments [8,9].

Angiogenesis and invasion are critical for tumor growth and distant metastasis [10]. Pazopanib is a potent receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, and VEGFR-3 and is approved for the treatment of heavily pretreated STS [11]. Studies demonstrating the efficacy of pazopanib in real life for relapsed/refractory STSs are relatively lacking.

In this study we aimed to demonstrate the efficacy of the pazopanib protocol on survival and disease control endpoints in relapsed/refractory STS.

Methods and Materials

Study Design

This study has a retrospective design. It is a single center study. Study data were collected using the medical records of patients followed for relapsed/refractory STSs at a tertiary care clinic between January 2017 and August 2021. Inclusion criteria were age ≥ 18 years, histologically confirmed advanced STSs, and imaging-proven metastases of this condition. Among the patients with these characteristics, those followed by the oral pazopanib treatment protocol were included in the study. Exclusion criteria were age <18 years and insufficient clinical follow-up data. Oral pazopanib treatment was administered as 1x800 mg. Radiological response evaluation was performed at three-month intervals. Ethical approval was obtained from the local clinical research ethics committee (Desicion number: 2021/97 Date: 02 March 2022). This study was conducted in accordance with the 1964 Declaration of Helsinki and subsequent amendments or comparable ethical standards.

Patients

The age, gender, localization, histology, and stage of the primary malignancy at diagnosis were recorded in the study database. Within the scope of the study, lung, liver, bone, soft tissue, lymph node, and brain metastasis status were evaluated before the pazopanib protocol. The following information was recorded: number of systemic treatment protocols used by the patients before pazopanib, best response with pazopanib treatment, dose

Table 1. Demographic and clinical characteristics of the patients

Features	n: 40
Age, median (range)	44.5 (20-88)
Gender	
Male, n (%)	22 (55)
Primary origin of tumor, n (%)	
Extremities	21 (52.5)
Intraabdominal	17 (42.5)
Head and neck	2 (5)
Histopathology, n (%)	
Malignant mesenchymal tumor	13 (32.5)
Synovial sarcoma	10 (25)
Leiomyosarcoma	9 (22.5)
Rhabdomyosarcoma	5 (12.5)
Fibrosarcoma	3 (7.5)
Stage at Diagnosis, n (%)	
≤ Stage 2	6 (15)
≥ Stage 3	34 (85)
Site of Metastases, n (%)	
Lung	28 (70)
Lymph nodes	25 (62,6)
Liver	13 (32,5)
Bone	17 (42,5)
Soft tissue	23 (57,5)
Brain	2 (5)
Number of systemic lines before pazopanib, n (%)	
< 2 lines	12 (30)
≥ 2 lines	28 (70)

Table 2. Treatment-related characteristics of the patients

Features	n:40
Best Objective Response, n (%)	
Complete Response	- (0)
Partial Response	18 (45)
Stable Disease	10 (25)
Progressive Disease	12 (30)
PFS, median (IQR), months	5,73 (2,67)
OS, median (IQR), months	8,54 (17,81)
Side Effects	
Dose reduction, n (%)	13 (32,5)
Pneumothorax, n (%)	2 (5)
Hypertension, n (%)	6 (15)
Liver enzymes elevation, n(%)	7 (17,5)
LVEF reduction, n(%)	- (0)

PFS: Progression free survival;OS: Overall survival; IQR: Interquartile range

reduction status during pazopanib treatment, and pneumothorax and hypertension adverse events during pazopanib treatment. After scanning the files for the study, eighty-two patients were identified. Forty patients who met the inclusion criteria were included in the study.

Treatment/response evaluation

Objective response rate (ORR) was determined as the sum of the complete response and partial response received. Progression-free survival (PFS) was defined as the time from the onset of pazopanib to the first documented disease progression or death from any cause. Overall survival (OS) was calculated as the time from the onset of pazopanib to the patient's last appearance or date of death.

Statistics

Statistical analyzes were performed using IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Descriptive data were expressed as a percentage of the total. The normality of continuous variables was determined using the Kolmogorov-Smirnov test. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and non-normally distributed median [interquartile range (IQR)]. Kaplan Meier analysis analysis was performed for survival analysis. While evaluating the statistical significance of the results obtained, $p<0.05$ level and 95% confidence interval were taken as basis.

Results

The final sample included 40 patients (males: 55%). The median age was 44.5 years (range: 20-88). The primary tumor site was in the extremities of 52.5% of study participants. Malignant mesenchymal tumor by histo-pathology was found in 32.5% of the sample. The subtype of patients with rhabdomyosar-

coma is embryonal rhabdomyosarcoma in all patients. Eighty-eight percent of the sample had a Stage 3 or higher disease at the time of initial diagnosis. Seventy percent of patients had lung metastases. Seventy percent of patients received two or more lines of systemic chemotherapy prior to pazopanib. The characteristics of the patients are presented in Table 1.

ORR to the pazopanib was forty-five percent. Median PFS (IQR) was determined as 5.73 (2.67) months (95% Confidence Interval (CI) of 5.19 to 6.19 months). Median OS (IQR) was 8.54 (17.81) months (95% CI of 8.24 to 15.65 months). Dose reduction was required in 32.5% of the patients. Pneumothorax and hypertensin were detected at a rate of 12.5% and %15 during pazopanib. The median follow-up (IQR) was 25.64 (31.14) months. Treatment side effects and responses to treatment are presented in Table 2, Figure 1, and Figure 2.

Discussion

Forty patients were evaluated retrospectively in our study. Although pazopanib was approved in the STSs group in those who progressed after initial systemic therapy, 70% of patients in our study sample used this treatment agent after the second line. Despite heavily pretreated patients, the contribution of PFS and OS is acceptable for this line. In this sense, we can say that it is a treatment option with significant antitumor activity. An acceptable level of side-effect profile was observed. Dose reduction was also not needed in most patients.

Sarcomas constitute a rare tumor group encountered. Sarcomas actually consist of a group of diseases that include many subtypes. STSs constitute 75-80% of this group [12,13]. There are also more than 40 malignant histological subtypes of STSs, which constitute one of the most heterogeneous groups of oncological diseases [13,14]. This heterogeneity brings with it difficult treatment, especially in the advanced stage. The treatment process is difficult because of the low success of known systemic chemotherapy protocols. However, clinical and pathological features, which are important in all advanced malignancies, also contribute to determining survival. Among these, performance status, clinical stage, and therefore lymph node metastasis or distant metastasis, and histopathological subtype can be counted [14,15]. Surgery, radiotherapy and systemic treatment options can always be considered during the course of the disease [16]. Systemic therapy in the form of relapsed, refractory, or directly metastatic disease also plays an important role for STSs. While there is no suitable performance or contraindication for almost all tumors in the STSs family, chemotherapy protocols containing ifosfamide and anthracycline can be used initially [15,16]. Although the treatment options are needed in the second and later stages vary according to the subtypes for this heterogeneous tumor group, there is actually a lack of standard systemic treatment with accepted efficacy [17].

Despite new systemic treatments, overall survival is at the level of 11-12 months when evaluated in the second line and after. Taxanes in patients with angiosarcoma and gemcitabine-docetaxel combination in patients with leiomyosarcoma contributed to a slight improvement in overall survival [18,19]. Tyrosine kinase inhibitors such as sunitinib and imatinib have significantly contributed to survival for some STSs, especially gastrointestinal stromal tumors [20,21].

The mean age in the study group was 44.5 years. Yoo KH et al. reported the median age as 54 in a similar number of study samples that had previously received multiple-line therapy [22]. STSs are common in a relatively young age group.

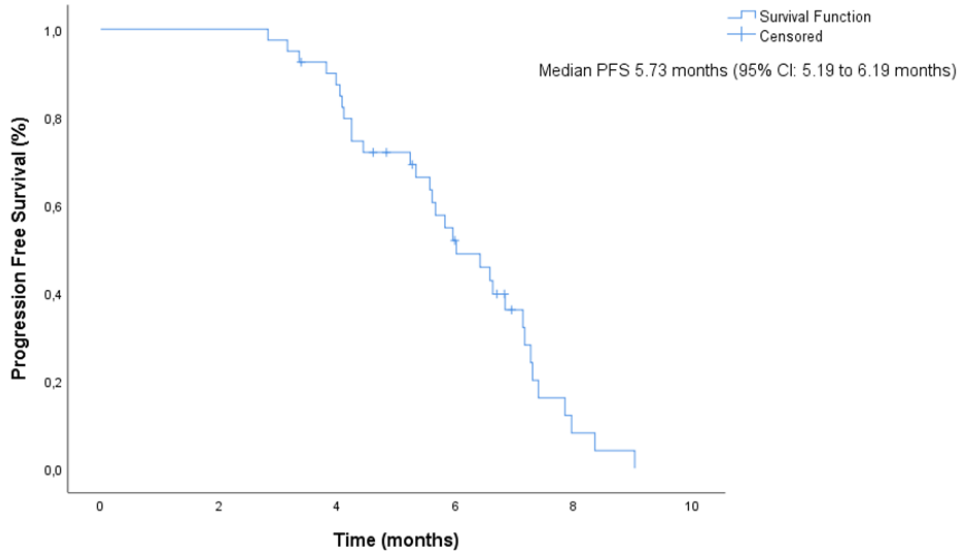

Figure 1: Median progression-free survival curve in patients with metastatic STSs

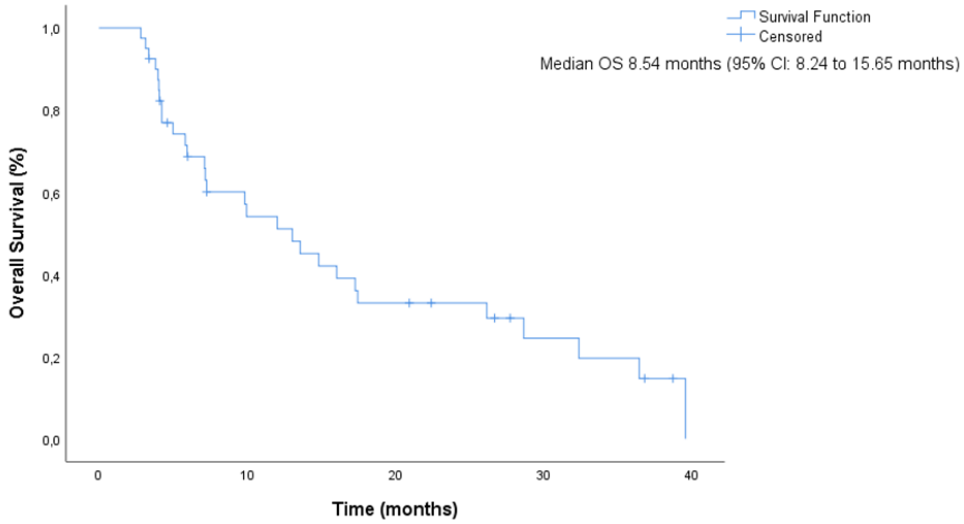

Figure 2: Overall survival curve in patients with metastatic STSs

Lung was the most common site for metastases in our study group. Liver metastases were observed in around 30%. Yoo KH et al. reported lung metastasis as 74% and liver metastasis as 27% [22]. The rates of lung metastases in the SPIRE study were similar to those in our study [23]. In the PALETTE study, which is at the forefront of the pivotal studies for pazopanib, liver metastases are in 30% of patients [24]. The frequent observation of visceral metastases in patients who need second-line and post-treatment therapy is already an indicator of a poor prognosis for this group of patients.

The same cannot be said for pazopanib, although survival times decrease as the

number of systemic treatment steps increases for patients who were previously heavily treated. There are a significant number of patients in our sample with two or more systemic treatments prior to pazopanib. In the study reported by Yoo KH et al., the number of patients who received two or more systemic treatment lines was around 80% [22]. We can state that our study populations are close to each other in this sense. In the PALETTE study, this rate was reported as 56% [24]. The PFS detected in our study is close to that reported by Yoo KH et al. Pazopanib has a significant survival effect in a population heavily exposed to systemic therapy. In contrast, it is difficult to maintain similar statements for OS. Overall survival was reported at around one year in the PALETTE study. In our study, this period is around eight months. The reason for this may be that the patients in our study were exposed to more severe systemic treatment. In this sense, we can deduce the idea that pazopanib should be used in earlier systemic treatment lines.

In our study, the partial response rate was found to be 45%. This rate is higher than the PALETTE study. The reason for this may be that the tumor burden of the patients in the study population is lower than that of PALETTE or their performance is better. In addition, data on the continued use of pazopanib in our study group are limited. This may be the reason why PFS and OS are found to be similar. Since we conducted a retrospective study, it is not possible to evaluate patients in this sense.

The choice of systemic treatments includes their manageable side-effect profiles and the survival advantage. This situation is directly related to patient compliance. It is also a parameter that directly concerns dose reduction. High compliance and the ability to continue without reducing the dose both directly affect success of the treatment. There are many side effects reported with pazopanib. However, we examined the effects on dose reduction, pneumothorax, and hypertension in our study. We found dose reduction rates similar to the PALETTE study, in which pneumothorax was reported at 3% [24]. This rate is around 2% in the SPIRE study [23]. In our sample, this rate was found to be 5%. Hypertension was detected in around 15% of our sample, which is lower than the PALETTE study [24].

In our study, liver enzyme elevation was found at a rate of 17.5%. But because of this, there is no patient whose treatment was stopped. There have been previous reports of pazopanib liver toxicity. This toxicity rate varies between 12-60% [25,26]. Also, we did not find any heart failure-related treatment discontinuation. In the PALETTE study, %11 of patients receiving pazopanib developed heart failure. A significant proportion of these patients had previously used anthracyclines [24].

This paper has several limitations. First, the number of patients was low, limiting the generalizability of the findings to different populations. Second, retrospective design of the study raises the possibility of errors in data quality. Third, since the analysis was cross-sectional, the results cannot be assumed to be causal. Finally, follow-up times and interval cannot be controlled in retrospective analyzes.

In conclusion, pazopanib is a good agent with survival benefit, even in pretreated patients. Demonstrating real-life data consistent with clinical studies is significant in terms of treatment success. Identifying subgroups that will benefit more from pazopanib in the STSs patient group may lead to a better clinical benefit in this sense.

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Corresponding author e-mail: musabarisaykan@gmail.com

Orcid ID:
Musa Barış Aykan 0000-0001-7538-9119
Gül Sema Keskin 0000-0001-6858-6974
Ece Örnek 0000-0002-3579-0706
Alper Topal 0000-0002-9679-9245
Çağlar Köseoğlu 0000-0001-6870-1004
Ayşegül Dumludağ 0000-0002-1171-7782
İsmail Ertürk 0000-0001-6835-0988
Nuri Karadurmuş 0000-0003-3291-8062

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Original Article

An Evaluation of Old Age Cancer Patient Characteristics in Emergency Department Focused on a Retrospective Population-Based Study

Acil Serviste Yaşlı Kanser Hastaları Özelliklerinin Retrospektif Popülasyon Temelli Bir Çalışmada Değerlendirilmesi

Nezih Kavak[1], Gökşen İnanç İmamoğlu[2], Ahmet Seki[3], Nurgül Balcı[4]

[1]University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Emergency Medicine, Ankara, Turkey.
[2]University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of Medical Oncology, Ankara, Turkey.
[3]University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Department of General Surgery Ankara, Turkey.
[4]Ministry of Health, Department of Services, Home Health Services Unit, Speciality of Family Medicine, Ankara, Turkey

ABSTRACT

Introduction: As the population ages, the number of elderly cancer patients is increasing dramatically, and these patients are visiting emergency departments (ED) at an increasing rate. We aim to evaluate the demographic findings, clinical features, mortality, and factors affecting mortality in old age cancer patients who visit ED.

Material and Methods: The patients were divided into three groups according to age groups: 65-74 years old, 75-84 years old, and 85 years and older. A retrospective analysis and evaluation of demographic findings (age, gender), comorbidity, number of ED visits, chief complaints, tumor localization, stage of cancer, metastasis status, treatment status, hospitalization, morbidity, and factors affecting mortality were evaluated across the groups.

Results: 142 (52%) of 273 patients were in the 65-74 age group, 77 (28.2%) were in the 75-84 age group, and 54 (19.8%) were in the 85 and over age group. 60 (33%) patients died in the ED. Patients aged 85 and over had higher mortality ($p<0.001$). The tumor location had no impact on mortality ($p>0.05$). Patients with neurologic and cardiovascular system problems as a chief complaint had higher mortality ($p<0.001$, $p<0.001$, respectively). Patients with metastatic disease had higher mortality than patients with early-stage and locoregional disease ($p<0.01$, $p<0.001$, respectively). Untreated patients had higher mortality ($p<0.001$).

Discussion and Conclusion: Old age cancer patients who visited the ED had different characteristics in the age groups. These patients had high mortality, and factors affecting mortality have been identified.

Keywords: Oncology, mortality, emergency department

ÖZET

Giriş ve Amaç: Nüfus yaşlandıkça, yaşlı kanser hastalarının sayısı çarpıcı biçimde artmakta ve bu hastalar artan bir oranda acil servislere (AS) başvurmaktadır. Bu çalışmada AS'e başvuran yaşlı kanser hastalarında demografik bulguları, klinik özellikleri, mortalite ve mortaliteye etkileyen faktörleri değerlendirmeyi amaçladık.

Yöntem ve Gereçler: Hastalar yaş gruplarına göre 65-74 yaş, 75-84 yaş ve 85 yaş ve üstü olmak üzere üç gruba ayrıldı. Gruplar arasında demografik bulgular (yaş, cinsiyet), lomorbidite, AS'e geliş sayısı, baş şikayetleri, tümör lokalizasyonu, kanser evresi, metastaz durumu, tedavi durumu, hastanaye yatış, mortalite ve mortaliteyi etkileyen faktörler retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya alınan 273 hastanın 142 (%52) 65-74 yaş grubunda, 77 (%28,2) 75-84 yaş grubunda, 54 (%19,8) 85 ve üzeri yaş grubunda idi. AS'te metastatik hastalığı olan 60 (%33) hasta öldü.

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85 ve üzeri yaş grubu hastalarda mortalite, diğer gruplara göre daha yükek idi (p<0.001). Tümör lokalizasyon ile mortalite açısından fark bulunmadı (p>0.05). Baş şikayeti nörolojik ve kardiyovasküler sistem sorunları olan hastalarda mortalite daha yüksekti (sırasıyla p<0.001, p<0.001). Metastatik hastalığı olan hastalarda mortalite erken evre ve lokal hastalığı olanlara göre daha yüksek idi (sırasıyla p<0.01, p<0.001). Tedavi edilmeyen hastalarda mortalite daha yüksek idi (p<0,001).
Tartışma ve Sonuç: AS'e başvuran yaşlı kanser hastalarının yaş gruplarında farklı özelliklere sahip olduğu gözlendi. Bu hastalarda mortalite yüksekti ve mortaliteyi etkileyen faktörler belirlendi.

Anahtar Kelimeler: Onkoloji, mortalite, acil servis

Introduction

Human lifespans have been extended, and the global population has aged as a result of improved living circumstances, advances in medical research, and treatments. This increase in the elderly population, which is defined as the silver (gray) tsunami, is manifesting at an alarming rate in terms of health and also in socio-economic areas [1].

Prolongation of life expectancy leads to increased exposure to environmental carcinogens and an increased accumulation of genetic changes that may lead to tumor formation [2]. The incidence of cancer formation increases with aging [3]. In addition, the 2030, the proportion of aged 65 and older adults is expected to rise to 70% [4].

Cancer patients, as is well known, visit the emergency department (ED) more often than the general population, and the ED plays a crucial role in the management and care of these patients [5,6]. However, given the fast-paced clinical setting of the ED, these patients provide challenging situations for ED staff to manage, and there are not enough studies on the characteristics of these patients [5].

The increasing rate of old age cancer patients visiting the ED has very different characteristics compared to other cancer patients in the population. Various physical and psychological dysfunctions associated with aging is observed with these patients and should be taken into account [7]. Understanding the characteristics of elderly cancer patients in ED has critical importance in managing their symptoms, increasing their quality of life, and reducing morbidity.

We aim to evaluate the demographic findings, clinical features, mortality, and factors affecting mortality in old-age cancer patients who visit ED.

Materials and Methods

This study was approved by the hospital's ethics committee (Decision No:60/24, Date: 25/02/2019).

The medical records of cancer patients aged 65 and over who presented to the ED between January 1, 2014, and January 1, 2020, regardless of whether they were followed-up on in the hospital's oncology department, were evaluated retrospectively from the hospital's electronic system. The exclusion criteria were as follow: (1) the patients with a hematological malignancy diagnosis; (2) lack of hospital records; (3) patients brought to the hospital dead; and (4) the cancer patients admitted with trauma.

Patients were divided into three groups according to age groups: 65-74 years old, 75-84 years old, and 85 years and older. Demographic findings (age, gender), number of ED visits, comorbidity (hypertension, coronary artery disease, congestive heart failure, diabetes mellitus, chronic obstructive pulmonary disease, Dementia/Alzheimer, cerebrovascular disease, other [gastro-intestinal disease, renal disease, rheumatic disease]), number of comorbidities, chief complaint, tumor localization, stage of cancer, receiving treatment, hospitalization,

mortality, and factors affecting mortality were evaluated across age groups.

Statistical Analysis

The SPSS package (Statistical Package for the Social Sciences for Windows, Version 22.0, SPSS Inc., Chicago, IL, U.S.A.) was used for data analysis in the study. In descriptive statistics on continuous data, mean, standard deviation, median, interquartile range (IQR), and discrete data, numbers and percentages were given. Shapiro-Wilk test was used to examine the conformity of continuous data to normal distribution. Kruskal Wallis Variance was used for comparisons of continuous variables between age groups. In the variables found to be different as a result of the Kruskal Wallis Analysis of Variance, the groups that caused the differences were examined with the Kruskal Wallis multiple comparison test. Chi-Square/Fisher's Exact test was used for comparisons of categorical variables between groups. Risk factors affecting mortality were analyzed by multivariate logistic regression analysis. And $p<0.05$ was considered statistically significant.

Results

The mean age of the 273 patients included in the study was 73.61±7.21 years (min 65-max 89), and 165 (60.4%) patients were male. 142 (52.0%) were in the 65-74 age group, 77 (28.2%) were in the 75-84 age group, and 54 (19.8%) were in the 85 and over age group. There was no difference between the age groups regarding gender ($p>0.05$).

The number of patients in the 85 and older age group who visited ED was lower than the patients in other age groups ($p<0.05$, $p<0.05$, respectively). There was no difference between the age groups in terms of 1, 2, and ≥3 ED visits ($p>0.05$) (Table 1).

There was no difference between age groups in terms of comorbidity ($p>0.05$) (Figure 1).

In the 85 and older age group, the number of comorbidities of 3 or more was higher than those in the 65-74 age group, and the number of comorbidities of one was lower ($p<0.05$, $p<0.05$, respectively).

Lung and other cancer types were less and colorectal cancer was more common in the 85 and older age group ($p<0.001$, $p<0.001$, respectively).

While the metastatic disease was more common in n the 85 and older age group compared to other age groups, the early-stage disease was more common in patients aged 65-74 ($p<0.001$, $p<0.001$, respectively).

85 and older age group was less likely to receive treatment compared to other age groups, while patients age groups 65-74 were more likely to receive treatment compared to other age groups ($p<0.001$, $p<0.001$, respectively).

There was no difference between age groups in terms of hospitalization ($p>0.05$).

Sixty (33%) patients with the metastatic disease died in the ED. Mortality was higher in patients 85 and older age group compared to other groups and lower in patients aged 65-74 years age groups ($p<0.001$, $p<0.001$, respectively) (Table 1).

There was no difference in the mortality of male and female patients ($p>0.05$). Mortality was higher in patients with 3 or more visits to ED than those with 1 or 2 visits ($p<0.001$). Mortality was lower in patients with ED duration of 1 day compared to patients with ED duration of both 2-6 days and ≥1 week ($p<0.001$, $p<0.001$, respectively). Mortality was higher in patients with 3 or more comorbidities compared to patients with comorbidity numbers of 1 and 2 ($p<0.001$, $p<0.001$, respectively). Mortality was high in patients with a chief complaint of neurologic and cardiovascular system problems ($p<0.001$, $p<0.001$, respectively). Mortality in

Table 1. Comparison of demographic findings and clinical characteristics according to the age groups

Age group, n (%)	**Total** 273 (100)	**65-74 years** 142 (52)	**75-84 years** 77 (28.2)	**≥85 years** 54 (19.8)	**p value**
Age (Year) Mean± SD	73.61±7.21	67.66±2.36	76.31±1.67	85.42±1.00	
Gender, n (%)					
Male	165 (60.4)	90 (63.4)	44 (57.1)	31 (57.4)	0.585[a]
Female	108 (39.6)	52 (36.6)	33 (42.9)	23 (42.6)	
ED visit, median (IQR)	3 (1-4)	3 (1-4)	3 (2-5)	2 (1-3)	**0.012** [b*]
Number of visit ED, n (%)					
1	70 (25.6)	36 (25.4)	18 (23.4)	16 (29.6)	0.190 [a]
2	39 (14.3)	14 (9.9)	14 (18.2)	11 (20.4)	
≥3	164 (60.1)	92 (64.8)	45 (58.4)	27 (50)	
Number of comorbidities					
1	85 (31.5)	48 (33.8)	26 (33.8)	11 (20.4)	**0.045**[a*]
2	99 (36.3)	55 (38.7)	28 (36.4)	16 (29.6)	
≥3	89 (32.6)	39 (27.5)	23 (29.9)	27 (50)	
Tumour localization					
Brain and nervous system	7 (2.6)	6 (4.2)	1 (1.3)	0 (0)	
Breast	40 (14.6)	16 (11.3)	14 (18.2)	10 (18.5)	**<0.001** [a*]
Lung	71 (26)	48 (33.8)	19 (24.7)	4 (7.4)	
Kolorectal	60 (22)	17 (12)	16 (20.8)	27 (50)	
Other gastrointestinal cancers	27 (9.9)	20 (14.1)	5 (6.5)	2 (3.7)	
Prostate	31 (11.4)	16 (11.3)	10 (13)	5 (9.3)	
Bladder	17 (6.2)	8 (5.6)	6 (7.8)	3 (5.6)	
Other*	20 (7.3)	11 (7.7)	6 (7.8)	3 (5.6)	
Chief complaint					
Pain	27 (9.9)	20 (14.1)	6 (7.8)	1 (1.9)	
Respiratory problems	56 (20.5)	33 (23.2)	18 (23.4)	5 (9.3)	
Fever	25 (9.2)	15 (10.6)	7 (9.1)	3 (5.6)	**0.037**[a*]
Gastrointestinal problems	37 (13.6)	15 (10.6)	14 (18.2)	8 (14.8)	
Neurologic problems	29 (10.6)	13 (9.2)	7 (9.1)	9 (16.7)	
Urogenital problems	25 (9.2)	14 (9.9)	5 (6.5)	6 (11.1)	
Other**	15 (5.5)	10 (7)	3 (3.9)	2 (3.7)	
Impaired general condition	38 (13.9)	14 (9.9)	10 (13)	14 (25.9)	
Cardiovascular system problems	21 (7.6)	8 (5.6)	7 (9.1)	6 (11.1)	
Stage of canser					
Early-stage disease	25 (9.2)	23 (16.2)	2 (2.6)	0	**<0.001** [a*]
Locoregional disease	66 (24.2)	47 (33.1)	17 (22.1)	2 (3.7)	
Metastatic disease	182 (66.6)	72 (50.7)	58 (75.3)	52 (96.3)	
Receiving treatment					
Yes	219 (80.2)	130 (91.5)	63 (81.8)	26 (48.1)	**<0.001** [a*]
No	54 (19.8)	12 (8.5)	14 (18.2)	28 (51.9)	
Hospitalization					
Yes	92 (33.7)	49 (34.5)	23 (29.9)	20 (37)	0.665
No	181 (66.3)	93 (65.5)	54 (70.1)	34 (63)	
Mortality					
Yes	60 (22)	17 (12)	20 (26)	23 (42.6)	**<0.001** [a*]
No	213 (78)	125 (88)	57 (74)	31 (57.4)	

ED: emergency department, other gastrointestinal cancers: liver, gallbladder, pancreas, stomach, intestine, *other: head and neck cancers, other respiratory cancers, renal cancer, other male genital cancers, female reproductive cancers, Other**: psychiatric problems, dermatological problems, a: Chi -Square test, b: Kruskal Wallis test, *p<0.005 regarded significant

Table 2. Demographic data and clinical features of deceased and surviving patients

	Total	Alive	Died	p value
	273 (100)	213 (78)	60 (22)	
Gender, n (%)				
Male	165 (60.4)	135 (81.8)	30 (18.2)	0.061[a]
Female	108 (39.6)	78 (72.2)	30 (27.8)	
Number of visit ED, n (%)				
1	70 (25.6)	66 (94.3)	4 (5.7)	**<0.001 [a]***
2	39 (14.3)	34 (87.2)	5 (12.8)	
≥3	164 (60.1)	113 (68.9)	51 (31.1)	
Number of comorbidity, n (%)				
1	85 (31.5)	77 (90.6)	8 (9.4)	**<0.001 [a]***
2	99 (36.3)	83 (83.8)	16 (16.2)	
≥3	89 (32.6)	53 (59.6)	36 (40.4)	
Tumor localization				
Brain and nervous system	7 (2.6)	6 (85.7)	1 (14.3)	
Breast	40 (14.6)	29 (72.5)	11 (27.5)	0.254[a]
Lung	71 (26)	55 (77.5)	16 (22.5)	
Colorectal	60 (22)	45 (75)	15 (25)	
Other gastrointestinal cancers	27 (9.9)	23 (85.2)	4 (14.8)	
Prostate	31 (11.4)	25 (80.6)	6 (19.4)	
Bladder	17 (6.2)	17 (100)	0	
Other*	20 (7.3)	13 (65)	7 (35)	
C**hief complaint**				
Pain	27 (9.9)	27 (100)	0	
Respiratory problems	56 (20.5)	46 (82.1)	10 (17.9)	
Fever	25 (9.2)	25 (100)	0	**<0.001 [a]***
Gastrointestinal problems	37 (13.6)	28 (75.7)	9 (24.3)	
Neurologic problems	29 (10.6)	10 (34.5)	19 (65.5)	
Urogenital problems	25 (9.2)	23 (92)	2 (8)	
Other**	15 (5.5)	15 (100)	0	
Impaired general condition	38 (13.9)	33 (86.8)	5 (13.2)	
Cardiovascular system problems	21 (7.6)	6 (28.6)	15 (71.4)	
Chief complaint group				
Respiratory problems	56 (20.5)	46 (82.1)	10 (17.9)	
Gastrointestinal problems	37 (13.6)	28 (75.7)	9 (24.3)	**<0.001[a]***
Neurologic problems	29 (10.6)	10 (34.5)	19 (65.5)	
Cardiovascular system	21 (7.7)	6 (28.6)	15 (71.4)	
Other	130 (47.6)	123 (94.6)	7 (5.4)	
Stage of cancer				
Early-stage disease	25 (9.2)	25 (100)	0	**<0.001[a]***
Locoregional disease	66 (24.2)	66 (100)	0	
Metastatic disease	182 (66.6)	122 (67)	60 (33)	
Receiving treatment				
Yes	219 (80.2)	184 (84)	35 (16)	**<0.001[a]***
No	54 (19.8)	29 (53.7)	25 (46.3)	

ED: emergency department, other gastrointestinal cancers: liver, gallbladder, pancreas, stomach, intestine, *other: head and neck cancers, other respiratory cancers, renal cancer, other male genital cancers, female reproductive cancers, Other*: psychiatric problems, dermatological problems, a: Chi-Square test, *p<0.005 regarded significant

Table 3**.** Multivariate logistic regression analysis of factors affecting mortality

Parameter	Regression Coefficient (SE)	OR	95 % CI		p value
Gender (ref male)					
Female	-0.186 (0.436)	1.204	0.513	2.829	0.669
Age group (ref 65-74 age)					
75-84 years	1.384 (0.531)	3.850	1.361	10.896	**0.011***
≥85 years	1.614 (0.687)	5.023	1.308	19.297	**0.019***
Number of ED visits (ref 1 visits)					
2	-0.840 (1.318)	2.314	0.174	30.303	0.524
≥3	0.337 (1.486)	1.400	0.076	25.756	0.821
Number of comorbidity (ref 1 number)					
2	0.271 (0.634)	1.311	0.378	4.545	0.669
≥3	1.404 (0.627)	4.071	1.192	13.908	**0.025***
Chief complaint group (ref Other)					
Cardiovascular system problems	3.898 (0.785)	54.001	11.583	251.762	**<0.001***
Neurologic problems	3.224 (0.703)	25.123	6.329	99.773	**<0.001***
Gastrointestinal problems	1.250 (0.681)	3.858	1.016	14.644	**0.047***
Respiratory problems	1.300 (0.686)	3.761	0.957	14.076	0.058
Receiving treatment (ref Yes)					
No	1.394 (0.496)	4.0032	1.526	10.654	**0.005***

ED: emergency department, *p<0.05 regarded significant, Nagelkerke R Square =0.576

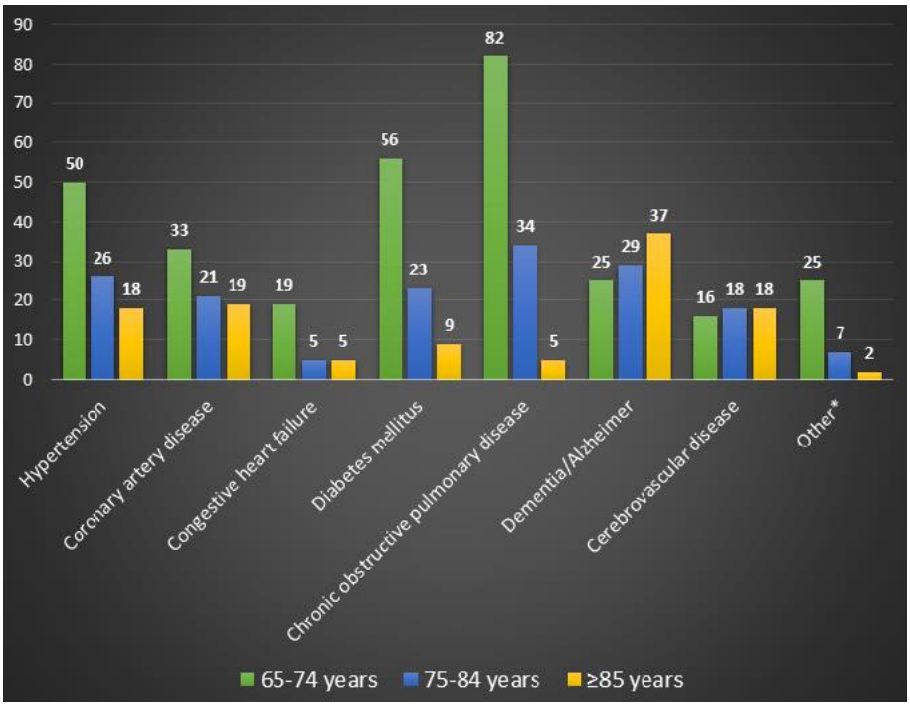

Figure 1. Comorbidities by age groups

Other*: gastrointestinal disease, renal disease, rheumatic disease

patients with neurological and cardiovascular system problems is higher than in patients with respiratory and gastrointestinal problems; mortality in patients with respiratory problems is higher than in patients with other health problems, and mortality of patients with gastrointestinal problems was higher than in patients with other health problems ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, respectively). Mortality was higher in patients with metastatic disease than in patients with early-stage and loco-regional disease ($p<0.01$, $p<0.001$, respectively). Mortality was higher in untreated patients than in treated patients ($p<0.001$) (Table 2).

Independent risk factors found significant in univariate analyses: gender, age group, number of ED visits, number of comorbidity, chief complaint group, and receiving treatment parameters were included in the multivariate logistic regression model. In the stage of cancer variable, only those with metastatic disease were not included in the model because they had died. The factor of patients being in the 75-84 and the 85 and over age group increases the mortality 3,850 times and 5.023 times compared to the 65-75 age group, respectively ($p<0.05$, $p<0.05$, respectively). Having three or more comorbidities increases mortality 4,071 times compared to patients with one comorbidity ($p<0.05$). Mortality increases 54.001, 25.123, and 3.858 times in patients with a chief complaint of cardiovascular disease, neurological disease, and gastrointestinal disease compared to patients with other complaints, respectively ($p<0.001$, $p<0.001$, $p<0.05$, respectively). Mortality increases 4.032 times in untreated patients compared to treated patients ($p<0.01$) (Table 3).

Discussion

As the population ages, the number of elderly cancer patients is increasing dramatically, and these patients are visiting ED at an increasing rate. The old-age cancer patients in the ED are complicated by some factors, including the variety of symptoms observed, fragility, increased comorbidities, polypharmacy, and lack of social support. Determining the characteristics of these patients plays a crucial role in facilitating the management of these patients in ED, increasing their quality of life, and reducing mortality rates. Therefore, this study is important in terms of examining demographic findings, clinical features, mortality, and factors affecting mortality according to age groups of old age cancer patients visiting ED.

Cancer patients visit ED at least once because of many conditions such as cancer progression, cancer-related symptoms, treatment side effects, end-of-life support, and some life-threatening conditions [6,8,9]. In the study of Bayrak et al., 64.6% of cancer patients visited ED more than once [10]. In the study of Sadik et al., 54.5% of cancer patients visited ED once, and 45.5% visited two or more times [11]. In the Barbera et al. study, 36.5% of cancer patients visited the ED once within the last six months, 26.8% visited twice, 15.9% twice, 8.9% four times, 4.9% five times, and 6.9% observed to visit the ED six or more times [12]. In this study, the rate of ED visits of three and more was high among all age groups. Patients with metastatic disease were observed to form the majority of patients visiting ED. The metastatic diseases cause many difficulties and complications as well as increased treatment toxicities in this patient groups. Therefore, it may have caused a major increase in the number of ED visits. In particular, the number of ED visits of these patients, except for emergencies, should be reduced in order to improve the life quality of patients, and reduce the workload of ED personnel and the care costs of patients. The reduction in ED visit numbers can be achieved with appropriate palliative care services management.

Since the prevalence of comorbidity increases with age, the number of old-age cancer patients with comorbidity is gradually

increasing. Some of the conditions that cause comorbidity play a role in the formation of cancer. Comorbidity may obscure symptoms, causing confusion in diagnosis and difficulty in treatment, and increase morbidity and mortality [13]. In addition, new comorbidities such as cardiac toxicity, neuropathy, or renal failure may be observed in cancer patients due to cancer treatment. In one study, it was reported that 53% of cancer patients aged 60-74 years and 63% of patients aged 75 years and older had at least one comorbidity [14]. In the same study, the number of comorbidities of 3 or more was higher in patients aged 85 and over compared to those in the 65-74 age group; this is thought to be due to the natural process of aging [14]. In the study of Bayrak et al. with cancer patients, the most common comorbidities were diabetes mellitus and hypertension [10]. In this study, the most common comorbidity was chronic obstructive pulmonary disease. The reason for the high incidence of this comorbidity is thought to be the majority of lung cancer patients in the study. As it is known, smoking is an important cause of lung cancer, and chronic obstructive pulmonary disease is frequently observed in these individuals [13,14]. In Sadik et al.'s study evaluating cancer patients visiting the ED, the most common cancers were lung cancer (32.5%), followed by the gastro-intestinal system (25.4%); In a similar study, by Tanriverdi et al., lung (30%) cancer was the most common which was followed by colon-rectum (17%) cancer [11,6]. In this study, lung cancer was first, and colorectal cancer was the second most frequently observed cancer in patients visiting ED. In addition, colorectal cancer was statistically higher in patients aged 85 years and older. In literature, the ratio of colorectal cancer increases with age, and approximately 60% of these patients are 70 years or older [15].

In this study, one-fifth of the patients visited the ED because of respiratory problems. The respiratory system is a common site of metastasis [16]. Respiratory problems are difficult for patients to endure and reduce their life quality significantly.

In this study, metastatic disease was statistically higher in patients aged 85 years and older than in other age groups. The elderly are often unaware that they belong to a population at high risk of cancer [17]. In addition, routine cancer screening is not recommended for many reasons, such as the expected short life span, comorbidity, and financial burden on this age group, and therefore the probability of detecting early stage of disease in these patients is lower [18].

Hospitalization of old age cancer patients visiting the ED is very common [8,19]. Lee et al. found in their study that the hospitalization of elderly patients visiting the ED increased with age and that almost half of those over 85 years were hospitalized [20]. Similarly, in this study, the highest hospitalization was in the age group of 85 years and older.

Of cancer patients visiting the ED, 8% in the Tanriverdi et al. study and 16.2% in the Mofid et al. study died [6,9]. In this study, mortality in ED was 22%, which was higher than in these studies. The reason behind this was thought to be due to the fact that the patients in this study group were old of age, and the number of patients with metastatic disease was being high.

There are several limitations in this study. Firstly, the study was retrospective. In the study, chief complaint classification was not done in detail, and the survival of patients was not followed up after being discharged from ED or hospitalization. Furthermore, the lack of oncological treatment and toxicity information received by the patients was another important limitation. Lastly, poly-pharmacy can be an important cause of mortality, and the fact that details of the drugs used by the patients were unknown was another limitation.

Conclusion

The rate of ED visits is gradually increasing due to the increase in the number of old age cancer patients in the aging population. Thus, the role and responsibility of ED in the management of these patients are increasing. Old age cancer patients who visited the ED had different characteristics in the age groups observed. These patients had high mortality, and factors affecting mortality have been identified. In the multivariate analysis, the variables associated with mortality included age group, having 3 or more comorbidities, the chief complaint of cardiovascular disease, neurological disease, and gastrointestinal disease, and receiving treatment.

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Corresponding author e-mail: nezih_kavak@hotmail.com

Orcid ID:
Nezih Kavak 0000-0003-2751-0046
Gökşen İnanç İmamoğlu 0000-0003-0356-0727
Ahmet Seki 0000-0003-3737-5722
Nurgül Balcı 0000-0001-5950-3989

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Original Article

Immune Thrombocytopenia: A Disease With Many Unresolved Questions

İmmün Trombositopeni: Birçok Çözümlenmemiş Sorusu Olan Bir Hastalık

Samet Yaman, Burcu Aslan Candır, Ersin Bozan, Sema Seçilmiş, Semih Başcı, Bahar Uncu Ulu, Tuğçe Nur Yiğenoğlu, Merih Kızıl Çakar, Mehmet Sinan Dal, Fevzi Altuntaş

University of Health Sciences Dr Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Hematology and Stem Cell Transplantation Service

ABSTRACT

Introduction: Immune thrombocytopenia (ITP) is an autoimmune disease and characterized with isolated low platelet count (<100x10^9). There is no single golden standard test for ITP diagnosis. Treatment is not indicated for all ITP patients. Corticosteroids are the first line of treatment. Rituximab, splenectomy, eltrombopag, azathioprine, cyclosporin, cyclophosphamide, dapsone, mycophenolate mofetil, and vinca alkaloid are some of the other therapeutic options. Here, we aimed to present our experience on ITP patients and treatment outcomes.

Materials and methods: The data of the patients were retrieved from retrospective records between 2015-2021.The study included patients over the age of 18 who had a regular follow-up diagnosis of ITP. Patients with primary hematological malignancy and patients with unavailable data or lost follow-up were excluded from the study

Results: A total of 62 patients with a diagnosis of ITP were included in the study. Treatment was indicated in 51 (82.3%) patients. All of the patients with treatment inclusion were given steroids in the first step. In ten patients who didn't respond to steroid treatment, the factors that predicted resistant treatment were explored. Age, mean platelet volume (MPV), C-reactive protein (CRP), ferritin, B12 and folic acid values were taken for analysis, no predictive factor was detected.

Discussion: While steroid treatment is effective in the initial step, recurrences are common. Factors that predict steroid refractoriness seems to require larger studies. Other step treatments should be evaluated on a case-by-case basis at the time of recurrence. Patients should also be encouraged to participate in clinical trials.

Keywords: Immune thrombocytopenia, ITP, splenectomy, steroid refractory

ÖZET

Giriş: İmmün trombositopeni (ITP) izole trombositopeni (<100x10^9) ile karakterize otoimmün bir hastalıktır. ITP teşhisi için altın standart bir test yoktur. Tüm ITP hastaları için tedavi endike değildir. Kortikosteroidler tedavinin ilk basamağıdır. Rituksimab, splenektomi, eltrombopag, azatioprin, siklosporin, siklofosfamid, dapson, mikofenolat mofetil ve vinka alkaloid diğer tedavi seçeneklerinden bazılarıdır. Burada ITP hastaları ve tedavi sonuçları ile ilgili deneyimlerimizi sunmayı amaçladık.

Gereç ve yöntemler: Hastaların verileri 2015-2021 yılları arasında geriye dönük kayıtlardan toplandı. Çalışmaya, düzenli takibine devam eden 18 yaş üstü ITP hastaları dahil edildi. Primer hematolojik malignitesi olan hastalar ve verisi olmayan veya takipten çıkan hastalar çalışma dışı bırakıldı.

Bulgular: Çalışmaya ITP tanılı 62 hasta alındı. 51 (%82,3) hastada tedavi endikeydi. Tedaviye alınan hastaların tamamına ilk basamakta steroid verildi. Steroid tedavisine yanıt vermeyen on hastada tedaviye direnci öngören faktörler araştırıldı. Analiz için yaş, ortalama trombosit hacmi (MPV), C reaktif protein (CRP), ferritin, B12 ve folik asit değerleri alındı, prediktif faktör saptanmadı.

Tartışma: Steroid tedavisi ilk aşamada etkili olmakla birlikte nüksler sık görülmektedir. Steroid refrakterliğini öngören faktörlerin saptanması için daha büyük çalışmalar gerekmektedir. Diğer tedavi seçenekleri, nüks anında vaka bazında değerlendirilmelidir. Hastalar ayrıca klinik araştırmalara katılmaya teşvik edilmelidir.

Anahtar kelimeler: İmmün trombositopeni, ITP, splenektomi, steroid refrakter

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Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease and characterized with isolated low platelet count (<100x10^9). It is also known as idiopathic thrombocytopenic purpura, but this term is less used now, since not all patients have purpura, and the autoimmune mechanism is understood. It appears in both children and adults. Adults are affected at a rate of 1.6 to 3.9 new cases per 100,000 individuals per year. While primary ITP develops due to antiplatelet antibodies, secondary ITP may develop due to another underlying cause, such as infectious or rheumatological diseases. Usually, primary ITP is detected in adults [1,2]. Patients may present with symptoms ranging from asymptomatic to life-threatening bleeding. The risk of serious bleeding is usually low. The risk of venous thromboembolism is approximately doubled compared to the normal healthy population [3].

There is no gold standard test to diagnose ITP. The diagnosis of primary ITP is determined when all other causes of thrombocytopenia have been ruled out. It is determined by the ITP diagnosis timeframe. The terms "new diagnosis" for less than three months, "persistent" for three to twelve months, and "chronic" for more than twelve months are used. Chronic ITP is commonly encountered in the adult population [4].

Treatment is not indicated for all ITP patients. It is usually recommended when the platelet count falls below 20-30 X 10^9 or any ITP associated symptoms such as bleeding. Treatment should be individualized, and the goal of the treatment should be to prevent serious bleeding, maintain the target platelet count, select low-toxicity treatments, and improve quality of life [4,5]. Corticosteroids are the first line treatment. Both standard-dose prednisone and high-dose dexamethasone can provide a long-term response. In individuals who needs a prompt response, high-dose dexamethasone appears to be more efficient. Intravenous immunoglobulin (IVIG) is one of the preferred treatment methods in first-line therapy. It is frequently applied when aim mediate response is desired. Second-line treatment decisions differ depending on the centers' experience and patients' condition. Rituximab, an anti-CD20 monoclonal antibody with a response rate of 28-40%, is an effective choice. Splenectomy is a treatment option that two out of every three patients respond to. Thrombopoietin receptor agonists such as eltrombopag are used as an effective agent that is well tolerated. Azathioprine, cyclosporin, cyclophosphamide, dapsone, mycophenolate mofetil, and vinca alkaloid regimens are some of the other therapeutic options [6-9]. Real world data experience is important for clinicians since mostly the randomized controlled trials are conducted in optimized conditions and usually not reflecting real world data outcomes.

Here, in our study we aimed to present our experience on ITP patients and treatment outcomes.

Patients and Methods

The study was conducted in Ankara Oncology Training and Research Hospital Hematology outpatient clinic. The data of the patients were retrieved from retrospective records between 2015-2021. The local institutional review board approved this study with approval number 2021-09/1392. The study was performed under the ethical principles of the Declaration of Helsinki.

The study included patients over the age of 18 who had a regular follow-up diagnosis of ITP. Patients with primary hematological malignancy and patients with unavailable data

Table-1. Patient demographic and laboratory at diagnosis

Parameters	N, %
Age (median, min-max)	49 (16-75)
Gender (M/F)	22(%35,5)/ 40 (64,5)
Comorbidity (present)	22(%35,5)
Malignancy(present)	5(%8.1)
Laboratory (at diagnosis)	
WBC (x10^{3}cells/uL)	7.25 (2.4-26)
Hgb (g/dL)	13,4 (9.6-18.3)
MCV (fL)	89,3 (61-110)
MPV (fL)	11,8 (7.4-14,6)
Platelets (x10^{3}cells/uL)	11 (1-86)
CRP (mg/L)	4,67 (0.1-31)
B12 (ng/L)	338 (185-2000)
Folate (µg/L)	7.8 (2.85-48)
Ferritin (ng/mL)	45,85 (3.8-262)

Comorbidity: Hypertension, diabetes mellitus, coronary artery disease and chronic renal failure.
WBC: White Blood Cell, MCV: Mean Corpuscular Volume, MPV: Mean Platelet Volume, CRP: C-reactive protein

or lost follow-up were excluded from the study. The study did not exclude patients with solid organ malignancies.

Patients were considered responsive if their platelet count improved by more than 30 x 10^9 after treatment.

At the time of diagnosis, demographic information, comorbidities, and hemogram and biochemistry results were all documented. The patients' therapy and response to treatment, and also their splenectomy histories, were all documented.

The statistical analyses performed with SPSS software (v26, Armonk, NY). The data was summarized by presenting the continuous data as a median (min-max) and the categorical data as a ratio. Logistic regression analysis was used to investigate if any factor influencing steroid refractoriness. Two-sided p value <0.05 was regarded as statically significant.

Results

A total of 62 patients with a diagnosis of ITP were included in the study.22 (35,5%) of the patients were male and 40 (64,5%) of them were female. Demographic data and laboratory findings of the patients are summarized in Table-1.

Treatment was indicated in 51 (82.3%) of the 62 patients followed. All of the patients with treatment inclusion were given steroids in the first step, and the response rate to steroid treatment was 80.3%. Second-line and above treatment options, as well as the proportion of patients who relapsed after response, are summarized in Table-2.

In ten patients who didn't respond to steroid treatment, the factors that predicted resistant treatment were explored. Age, MPV, CRP, ferritin, B12 and folic acid values were taken for analysis. As summarized in Table-3, no predictive factor was detected.

Discussion and Conclusion

In our study, we found that 80,3 % of patients in first line responded to treatment. In patients who did not respond to steroid treatment, no prognostic predictor was found for steroid refractoriness. Splenectomy was performed in 22 patients (35.5%), and the response rate following splenectomy was 86,3%. While 21 (91.3%) of 23 patients who received eltrombopag responded to treatment, patients who received rituximab had a 50% response rate. The response rate was 87.5% when IVIG was used as surgical preparation or rescue therapy.

In the meta-analysis of Siraj Mithoowani et al., standard-dose prednisolone or high-dose dexamethasone treatment was compared. As a result, long-term responses were found to be similar, while less toxicity was observed in the

Table 2. Treatments and outcomes

	N=62, %100	Responders	Relapsed after Response
Observation	11 (%17.7)		
1st line treatment			
Steroid	51 (%82.3)	41(%80.3)	30 (%73,2)
2nd line and other lines			
Eltrombopag	23 (%37.1)	21(%91.3)	11(%52.4)
Splenectomy	22 (%35.5)	19(%86.3)	10 (%52.6)
Rituximab	4(%6.5)	2 (%50)	1(%50)
IVIG	24(%38.7)	21(%87.5)	13(%61.9)
Vincristine	10(%16.1)	6 (%60)	-
Others (CSA, azathioprine)	7 (%11.2)	5 (%71.4)	-

IVIG: Intravenous Immunoglobulin, CSA: Cyclosporine A

Table 3. Predictors of the Steroid Refractoriness

Parameters	OR (95%CI)	P value
Age	0.998 (0.954-1.045)	0.944
MPV	0.963 (0.549-1.689)	0.896
CRP	0.998 (0.852-1.168)	0.978
Ferritin	0.998 (0.983-1.012)	0.736
B12	0,999 (0.997-1.001)	0,403
Folic Acid	0,868 (0,735-1,024)	0,094

MPV: Mean Platelet Volume, CRP: C-reactive protein

Logistic regressionanalysis was used and p value<0.05 was regarded as statistically significant.

group receiving high-dose dexamethasone. On the 14th day, the response rate was higher in the group receiving high-dose dexamethasone, with 79% [6]. In our study, the response rate to steroid treatment was found to be 80.3%, and similar results were obtained with the literature.

In another study, the overall response to steroid treatment was found to be 88.5%. 11.4% of the patients were evaluated as steroid refractory [8]. In our study, the steroid refractory group was found to be 19.6%. We believe our ratio and this ratio is not far, with larger cohort it could be similar. The other reason is that the responses in the group receiving high-dose dexamethasone were higher than the standard-dose prednisolone as we explained above. The use of high-dose dexamethasone in our center has increased in recent years. In previous years, the use of standard dose prednisolone was higher.

Age, serum ferritin level, and positive HbsAg were revealed to be prognostic factors in multivariate analysis by Yu J et al. [10]. In our research, no predicting factor was identified. This could be due to the limited number of steroid-refractory patients we have.

The response rate of IVIG treatment is approximately 80%, but it is generally short [3,11]. The response rate to IVIG treatment was found to be 87.5% in our research, and the available data were determined to be similar to the literature.

In the real-life study of Mishra K et al. with 53 patients, they found the response rate to eltrombopag treatment as 81.1% [9]. In our patient group, this rate was 91.3%. Relapse was detected in more than half of the patients. We do not have high relapse rate after eltrombobag, however our median follow up

was short, this could be explaining the difference.

Response to rituximab treatment has been observed between 40-60% in studies [3]. Two of our four patients who received rituximab responded to treatment. Results similar to the literature were found.

In the study of Al Askar AS et al., the splenectomy rate was found to be 37%. This rate was similar to our study (35.5%). While the recurrence rate after splenectomy was 27.2% in their study, it was 52.6% in our study. Moreover, in the same study, the recurrence rate after rituximab was 15.8%, while in our study this rate was found to be 50%. Splenectomy and rituximab response rates were similar in both studies. The difference in rates can be explained by cohort variation and follow-up time [7]. In another study of Wang T et al., the response after splenectomy was found to be 82.6%, which is similar to our study [13].

Vincristine can be used as an alternative therapy. Response rates of 10-75% have been reported in the literature [11]. In our study, this rate was found to be 60%. Other immunosuppressive drugs can also be used in single therapy and combined therapy.

Our study is valuable in terms of applying a standard strategy because it is a single center study. Our study has limitations as we were unable to mention adverse conditions of the therapies due to missing records. In addition, the small number of patients and the short follow-up period are our other limitations.

In conclusion, while steroid treatment is effective in the initial step, recurrences are common. Factors that predict steroid refractoriness seems to require larger studies. Other step treatments should be evaluated on a case-by-case basis at the time of recurrence. Patients should also be encouraged to participate in clinical trials.

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Corresponding author e-mail: drsametyaman@gmail.com

Orcid ID:
Samet Yaman 0000-0003-4081-1070
Burcu Aslan Candır 0000-0003-3386-8984
Ersin Bozan 0000-0002-3307-3121
Sema Seçilmiş 0000-0003-2957-2339
Semih Başcı 0000-0003-4304-9245
Bahar Uncu Ulu 0000-0002-6230-9519
Tuğçe Nur Yiğenoğlu 0000-0001-9962-8882
Merih Kızıl Çakar 0000-0003-0978-0923
Mehmet Sinan Dal 0000-0002-5994-2735
Fevzi Altuntaş 0000-0001-6872-3780

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Original Article

The Relation Between Tumor and Axillary Lymph Node SUV Values with the Presence of Distant Metastases in Staging F18 FDG PET/CT in Breast Cancer

Meme Kanserinde Evreleme F18 FDG PET/BT İncelemesinde Tümör ve Aksiller Lenf Nodu SUV Değerlerinin Uzak Metastaz ile İlişkisi

Bedriye Büşra Demirel, Hüseyin Emre Tosun, Gülin Uçmak

Ankara Oncology Research and Training Hospital, Department of Nuclear Medicine

ABSTRACT

Introduction: We aimed to investigate the relation between primary tumor and axillary lymph node maximum standardized uptake values (SUVmax) with the presence of distant metastases at initial staging of breast cancer.

Materials and Methods: Fifty-seven women who were referred to our clinic for staging positron emission tomography/computed tomography (PET/CT) with diagnosis of breast cancer were included in the study. Immunohistochemical (IHC) features of the primary tumor [hormone receptor (HR), human epidermal growth factor receptor type-2 (HER2), Ki67 index] were reviewed retrospectively. All patients' HR status was positive and HER2 status was negative. Primary tumor SUVmax (Tmax) and axillary lymph node SUVmax (Nmax) values and primary tumor-to-axillary lymph node (T/N) ratios were calculated in PET/CT. Patients were divided into two groups as metastatic and non-metastatic according to PET/CT findings. The differences between groups in terms of age, Ki67 index and SUV values were statistically analyzed.

Results: The mean age of the patients was 52±14.4 (range 25-79 years). According to PET/CT findings, the patients were divided in two groups, 57% metastatic (n = 33) and 43% non-metastatic (n = 24). While no statistically significant difference was observed between the two groups in terms of age, Ki67 index and Tmax averages, statistically significant differences were found between Nmax values ($p < 0.001$) and T/N ratios ($p = 0.001$). Cut-off value in association with distant metastasis was 7,8 for Nmax value and 8,5 for T/N ratio on ROC curve analysis.

Discussion: Accurate staging is important in terms of treatment plan and prediction of disease prognosis in breast cancer. In our study, it was thought that the difference in Nmax values and T/N ratios, independent of Tmax values, could be a determinant in terms of the overlooked and possible early metastatic disease indicator in the patient group without known distant metastasis.

Keywords: breast cancer, positron emission tomography, metastasis

ÖZET

Giriş: Meme kanseri evrelemesinde primer tümor ve aksiller lenf nodu SUVmax parametrelerinin uzak metastaz varlığı ile ilişkisini araştırmak amaçlanmıştır.

Gereç ve Yöntemler: Çalışmaya kliniğimize meme kanseri tanısı ile evreleme amaçlı positron emisyon tomografi /bilgisayarlı tomografi (PET/BT) incelemesi için refere edilen 57 kadın hasta dahil edildi. Hastaların immünohistokimyasal özellikleri [hormone reseptörü (HR), human epidermal büyüme factor reseptörü tip-2 (HER2), Ki67 indeksi] geriye dönük olarak tarandı. Hastaların tümü HR-pozitif, HER2-negatif idi. PET/BT'de primer tümör SUVmax(Tmax), aksiller lenf nodu SUVmax (Nmax) değerleri ve tümör/aksiller lenf nodu SUVmax (T/N) oranları hesaplandı. Hastalar PET/BT bulgularına göre metastatik ve non-metastatik olarak iki gruba ayrıldı. Gruplar arası yaş, Ki67 indeksi ve SUV değerleri açısından farklılık istatistiksel analizi yapıldı.

Bulgular: Hastaların yaş ortalaması 52 ± 14.4 (aralık 25-79) idi. PET/BT bulgularına göre hastalar %57'si metastatik (n=33), %43'ü non-metastatik (n=24) olmak üzere iki grupta izlendi. İki grup arasında yaş, Ki67 indeksi ve Tmax ortalamaları açısından istatistiksel olarak anlamlı fark izlenmezken ortalama

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Nmax değerleri ve T/N oranları arasında istatistiksel olarak anlamlı fark bulundu (sırasıyla p<0.001, p=0.001). Uzak metastaz varlığı açısından ROC analizde Nmax için kesme değeri 7.8, T/N oranı için 8.5 olarak bulundu.
Tartışma: Meme kanserinde tedavi planı, hastalık prognozu açısından evrelemenin doğru şekilde yapılması önem arzetmektedir. Çalışmamızda Nmax değerinin ve T/N oranının, Tmax değerlerinden bağımsız olarak farklılık göstermesi, uzak metastaz saptanamayan hasta grubunda gözden kaçan ve olası erken metastatik hastalık göstergesi açısından belirleyici olabileceği düşünülmüştür.

Anahtar kelimeler: meme kanseri, pozitron emisyon tomografi, metastaz

Introduction

Breast cancer is the most frequent cancer type in women [1]. In 2020, 2.3 million women were diagnosed with breast cancer and 685 000 of them died globally [2]. Although many strong treatment options such as surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy etc. are achievable, precise staging is a necessity to plan optimal management of the disease.

During the last years, 18F-fluorodeoxy-glucose (FDG) positron emission tomography /computed tomography (PET/CT) has gained an important role in the pretreatment staging of breast cancer. FDG-PET/CT has shown high accuracy in detecting axillary-extra axillary lymph nodes and distant metastases. Also, FDG-PET/CT allows on a single "whole-body" examination to assess for locoregional as well as distant metastases with a positive predictive value exceeding 80% [3-6].

Except nodal and distant metastasis status, it was known that biological characteristics of tumor such as size, grade, histological subtype, hormone receptor status are significance determinant in selecting treatment option and prognosis. Tumor subtypes of breast cancer patients have been reported to show different outcomes, including poor prognosis for the basal-like subtype and a significant difference in the outcome for the HR-positive groups [7,8].

We retrospectively evaluated the utility of tumor and axillary lymph node maximum standardized values (SUVmax) on FDG-PET/CT and clinicopathological characteristics for predicting distant metastasis in patients with breast cancers.

Materials and Methods

Fifty-seven women who were referred to our clinic for PET/CT for staging purposes with diagnosis of breast cancer were included in the study. Patients with prior excisional biopsy of breast were excluded from the study.

This study was approved by the ethics committee of our institution (2022-03/64).

Age and immunohistochemical (IHC) features of the primary tumor such as hormone receptor (HR), human epidermal growth factor receptor type-2 (HER2) status and Ki67 index were recorded from the institution patient information system, retrospectively. All patients included in the study were HR positive and HER2 negative.

PET/CT Imaging Procedure

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

Table 1. Patient and tumor characteristics according to metastatic and non-metastatic groups

	metastatic (n:33) mean±SD	non-metastatic (n:24) mean±SD	*p* value
Age	50,2±15	55,2±13,3	0,2
Ki67 index (%)	31,9±23,7	32,9±23,8	0,6
Tmax	8,4±4,2	7,3±4,9	0,1
Nmax	5,5±3,9	2,5±2,8	<0,001
T/N	2,3±2,2	5,1±4,2	0,001

Tmax: primary tumor SUVmax, Nmax: axillary lymph node SUVmax, T/N: primary tumor-to-lymph node SUVmax ratio

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.

SUVmax was used to quantify FDG uptake. Primary tumor SUVmax (Tmax) and axillary lymph node SUVmax (Nmax) were calculated in PET/CT. Primary tumor-to-lymph node SUVmax (T/N) ratios were measured.

Patients were divided into two groups as metastatic and non-metastatic according to PET/CT findings.

Statistical Analysis

The distributions of variables were tested for normality using Kolmogorov-Smirnov test. Student's t-test and Mann-Whitney U-test were used to compare differences in normally distributed and non-normally distributed variables, respectively. The data were presented as the mean ± standard deviation. The differences between groups in terms of ages were statistically analyzed by using t-test. The differences between Ki67 index, Tmax, Nmax values and T/N ratio according to the presence of distant metastasis were analyzed by Mann–Whitney U test. p values < 0.05 were considered to be statistically significant. Receiver Operating Characteristic (ROC) curve analysis was used to mark the cut-off values of Nmax and T/N in association with the presence of distant metastasis. The statistical analysis was performed using commercial software (SPSS 25.0, IBMSPSS Statistics for Windows, Version 25.0. Armonk NY: IBM Corp.).

Results

The mean age of the patients was 52±14.4 with a range of 25-79 years. All patients of the study were HR-positive and HER2-negative.

PET/CT detected distant metastasis in 33 of 57 patients. According to PET/CT findings, the patients were divided in two groups, 57% metastatic (n = 33) and 43% non-metastatic (n = 24).

Prognostic factors candidates such as age, Ki67 index were evaluated for each group. No statistically significant difference was observed between the two groups in terms of age and Ki67 index (Table 1).

The average primary tumor SUVmax (Tmax) values in metastatic and non-metastatic groupswere 8.4±4.2 (mean±SD) and 7.3±4.9 (mean±SD), respectively. No significance difference was observed in Tmax between two groups (p=0.12). The presence of distant metastasis was analyzed for its association with axillary lymph node SUVmax (Nmax) and primary tumor-to-axillary lymph node ratio (T/N). We observed that Nmax was significantly higher in patients with distant metastasis than in patients without distant metastasis (mean±SD5.5±3.9 vs. 2.5±2.8, respectively, p <0.001).Based on ROC curve analysis, cut-off values in association of distant

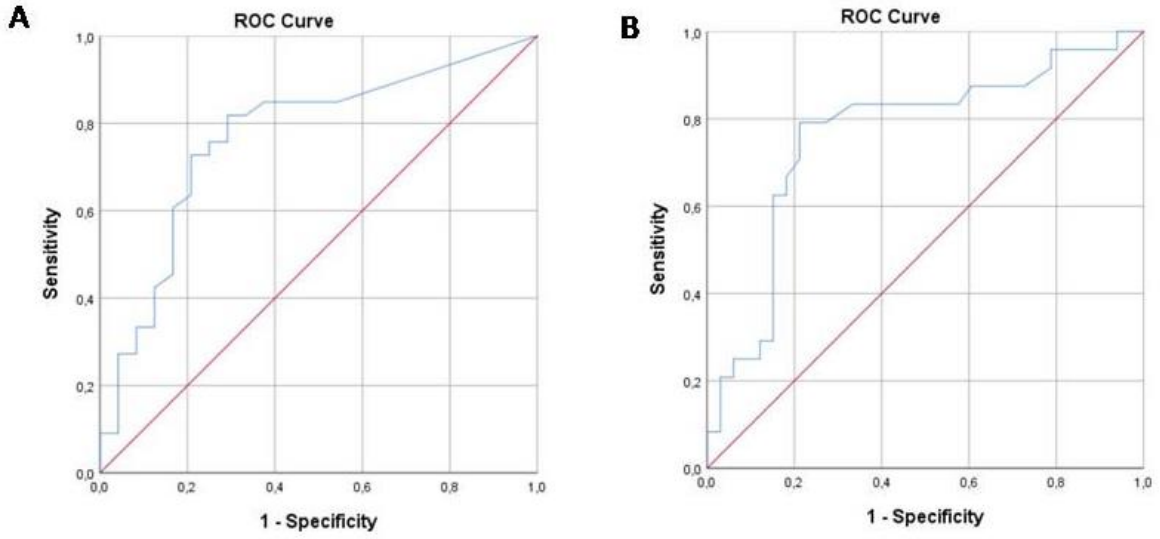

Figure 1. ROC curves demonstrate the cut off values for axillary lymph node SUVmax (A) and primary tumor-to-lymph node SUV ratios (T/N) (B) in association with the presence of distant metastasis. The cut off value for Nmax was 7.8, area under the curve was 77%. The cut off value for T/N ratio was 8.5, area under the curve was 76%.

metastasis were calculated as 7.8 for Nmax (sensitivity: 27%, specificity: 96%, area under the curve (AUC): 0.769) (Figure 1). Also, according to T/N ratios we found significant difference between metastatic and non-metastatic groups (mean±SD 2,3±2,2 and 5,1±4,2, respectively, p=0,001). Cut-off value in association of distant metastasis was calculated as 8.5 for T/N ratio on ROC curve analysis (sensitivity: 20%, specificity: 97%, area under the curve (AUC): 0.764).

Discussion

F-18 FDG PET/CT has an important role in initial staging of breast cancer and it can detect distant metastasis with superior success compared to conventional imaging methods [5,9]. In recent study, FDG PET/CT was compared with conventional imaging modalities for ability of detecting distant metastases, and it was shown that the sensitivity and specificity were 87% and 83% versus 48% and 93% [10]. It was observed that FDG PET/CT determined unexpected metastases and changed the clinical stage in 52% of the patients, especially with locally advanced disease, in another study [11]. Compatible with literature, in our study the detected distant metastasis via FDG PET/CT was 57% of the patients with newly diagnosed breast cancer.

Breast cancer has high structural and molecular heterogeneity between tumors and also within a single tumor. Gene expression profiling enables defining and characterizing of main intrinsic molecular subtypes with different clinical outcomes and responses to treatment. The distinction between subtypes is based on expression of estrogen and progesterone HR and HER2 [7,8]. The highest survival rate is observed among women with HR+/HER2- subtype, while triple negative subtype has the worst survival rate [12]. Despite this ongoing acceptance, it is striking that, in our patient population whom all of HR+/HER2- the distant metastasis rate was 57% at the time of diagnosis.

In routine clinical practice, immune-histochemical evaluation of Ki-67 is frequently utilized to assess proliferative features of tumor cells. It has been used for many years for breast cancer to decide the therapy option. The results of the studies investigating the effect of Ki-67 on survival outcomes were conflicting with each other. Although some of the researchers showed prognostic effects of Ki-67 expression on survival outcomes, the others did not demonstrate any correlation [13-15]. In the current study, no correlation was found between the presence of metastasis and Ki67 index in patients with HR+/HER2- breast cancer at initial staging.

Several studies have shown correlations between the avidity of FDG uptake and some tumor characteristics of breast cancer such as tumor type, grade, HR status, and HER2 status [16-18]. In previous studies, high tumor grade, HR negativity, HER2 positivity and high Ki-67 index, in summary, high mitotic activity was associated with increased SUV values [19]. As a predictor for postoperative clinical outcome, SUVmax on FDG-PET/CT 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 [20]. Nevertheless, Tmax values were not found associated with the presence of distant metastasis in our study.

Clinicopathological parameters such as tumor size and lymph node status have been used as traditional prognostic factors for patients with breast cancer. Today several prognostic models based on clinical prognostic factors are available to estimate survival of breast cancer patients. But the clinical variables for each model are slightly different and the models also showed different prognostic performance [21]. To make an optimal treatment decision for especially early-stage breast cancer, the main importance is to exclude the presence of distant metastasis and also to identify risk of recurrence. Despite the improvement of early diagnosis and a growing progress in treatment strategies, still today metastatic disease remains incurable and the main cause of breast cancer-related mortality.

Also, lymph node involvement has long been recognized as an important prognostic factor in breast cancer. The presence of positive axillary lymph nodes is a predictor of increased risk of local and distant recurrence, directly affecting mortality [22,23]. It has been shown that the overall 5-year survival for breast cancer patients with lymph node metastasis is 40% lower than that of patients who do not have metastasis to the lymph nodes [23]. The number of lymph nodes involved has traditionally been used for post-surgical staging of breast cancer. In addition, the lymph node ratio, defined as the ratio of positive lymph nodes to the total number of lymph nodes removed, has emerged as a prognostic factor in a growing number of studies. A higher lymph node ratio is associated with a poor overall survival and an increased risk of locoregional recurrence in breast cancer [22,24,25].

Several studies have reported the correlation of higher SUVmax of the primary tumor with poorer prognostic behavior in breast cancer [16]. Previously, it was showed that both primary tumor SUVmax and a combination of primary tumor SUVmax and axillary lymph node avidity were significant factors for predicting relapse [26]. However, in another study, it was reported that axillary lymph node SUVmax was the only significant independent factor for predicting relapse and that the optimal cut-off for axillary lymph node SUVmax was 2.8[27]. In our study, we observed that Nmax values and T/N ratios were significantly higher in patients with distant metastasis than without ones at initial staging and cut-off values in association of distant metastasis were measured as 7.8 for

Nmax and 8.5 for T/N. Several studies evaluated whether lymph node-to-primary tumor SUV ratio was a useful factor for prediction of relapse in breast cancer [27-29]. Furthermore, a recent study revealed that lymph node-to-primary tumor SUV ratio is a more accurate value for discriminating axillary lymph node involvement than axillary lymph node SUVmax value [28]. In another study, authors speculated that lymph node and primary tumor SUV ratio could be linearly related, and studied the clinical value of axillary lymph node-primary tumor SUV ratio for predicting disease-free survival in invasive ductal carcinoma with axillary lymph node metastasis [29]. In our study we found that, Nmax values and T/N ratios were significantly higher in HR+/HER2- breast cancer patients with distant metastasis than in patients without distant metastasis at the time of diagnosis. This study revealed that the presence of distant metastasis was associated with Nmax and T/N ratio and both Nmax value and T/N ratio were significant independent factors for predicting prognosis. Even if distant metastasis is not detected in the staging FDG PET/CT with high Nmax and T/N ratio, it should be kept in mind that present distant metastasis may be occult and these patients should be followed more closely. We believe that the results of this study should be supported by studies with follow-up prognosis data. The other limitation of this study is that only patients with HR positive HER2 negative were selected in order to provide homogeneous data because the number of patients with other hormone status (such as HR negative HER2 positive) was insufficient. Further studies with larger number of patients including all hormone and receptor profiles may support our results.

In conclusion, accurate staging is important in terms of treatment plan and prediction of disease prognosis in breast cancer. In our study, it was thought that the difference in Nmax and T/N ratio, independent of Tmax values, could be a determinant in terms of the overlooked and possible early metastatic disease indicator in the patient group without known distant metastasis.

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Corresponding author e-mail: demirelbbusra@hotmail.com

Orcid ID:
Bedriye Büşra Demirel 0000-0002-6494-062X
Hüseyin Emre Tosun 0000-0002-0169-6316
Gülin Uçmak 0000-0002-0268-4747

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Original Article

The Impact of non-COVID-19 Infections to COVID-19 Disease in Hematological and Solid Organ Malignancies

Hematolojik ve Solid Organ Malignitelerinde COVID-19 Dışındaki Enfeksiyonların COVID-19 Hastalığına Etkisi

Atakan Tekinalp[1], Hilal Akay Çizmecioğlu[2], Mevlüt Hakan Göktepe[2], Sinan Demircioğlu[1], Ali Kürşat Tuna[2], Melek Karakurt Eryılmaz[3]

[1]Necmettin Erbakan University Meram Faculty of Medicine, Division of Internal Medicine, Department of Hematology
[2]Necmettin Erbakan University Meram Faculty of Medicine, Division of Internal Medicine
3Necmettin Erbakan University Meram Faculty of Medicine, Division of Internal Medicine, Department of Oncology

ABSTRACT

Introduction: The aim of this study is to evaluate the clinical differences of COVID-19 infection in hematological and solid organ malignancy patients.
Methods: In the study, patients who have followed up in the Necmettin Erbakan University Meram Medical Faculty Clinic of COVID-19 with a diagnosis of malignancy between 01 September 2020 and 01 January 2021 were compared in terms of epidemiological and clinical characteristics.
Results: The study included 134 patients. Hospitalization day, intensive care need, convalescent plasma need, sedimentation and ferritin levels of patients diagnosed with hematological malignancies were significantly higher (p: 0.001, 0.008, 0.001, 0.001, <0.001 respectively), and the neutrophil, lymphocyte, platelet, and neutrophil-lymphocyte ratio was found to be low, according to the findings of the study. The cure rate of COVID infection was significantly lower with additionally infection in hematological malignancies (OR: 3.1, 95%; CI: 1.4-6.9; p: 0.004). In multivariate analysis, it was determined that an presence of non-COVID-19 infection increased the risk of death 2.8 times (95% CI; 1.3-6.5, p: 0.010).
Discussion and Conclusion: Patients with hematological malignancy have experienced a more severe clinical course of COVID-19 and higher mortality than those with solid tumors. The use of a model in the COVID-19 pandemic that summarizes these non-COVID-19 infections, hematological parameters, age, and comorbidities can help in the method of malignant patients with high mortality risk.

Keywords: SARS COV-2, COVID-19 Virus, pandemics, Hematologic Malignancies, cancer.

ÖZET

Giriş ve Amaç: Çalışmanın amacı, hematolojik ve solid organ maligniteli hastalarda COVID-19 enfeksiyonundaki klinik farkların değerlendirilmesidir.
Yöntem ve Gereçler: Çalışmada 01.09.2020-01.01.2021 tarihleri arasında Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi COVID-19 kliniğinde yatarak takip edilen malignite tanılı hastalar epidemiyolojik ve klinik özellikleri açısından karşılaştırıldı
Bulgular: Çalışmaya 134 dahil edildi. Hematolojik maligniteli hastalarda hastanede yatış günü, yoğun bakım ihtiyacı, konvelesan plazma ihtiyacı, sedimentasyon ve ferritin düzeyleri daha yüksek (sırasıyla; p: 0.001, 0.008, 0.001, 0.001, <0.001); nötrofil, lenfosit, trombosit ve nötrofil/lenfosit oranı daha düşük bulundu. COVID-19 enfeksiyonundan iyileşme oranı, ilave enfeksiyonun olduğu hematolojik maligniteli hastalarda, daha düşüktü (OR: 3.1, 95%; CI: 1.4-6.9; p: 0.004). Çok değişkenli analizde, COVID-19 dışında bir enfeksiyon varlığının ölüm riskini 2,8 kat arttırdığı tespit edildi (%95 GA; 1.3-6.5, p: 0.010).

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Tartışma ve Sonuç: COVID-19 enfeksiyonu hematolojik maligniteli hastalarda solid organ maligniteli hastalara göre daha şiddetli seyretmektedir. COVID-19 pandemisinde COVID-19 dışı enfeksiyonlar, hematolojik parametreler, yaş ve ko-morbiditeden oluşan bir modelin kullanılması, yüksek mortalite riski olan malign hastaların yönetiminde yardımcı olabilir.

Anahtar Kelimeler: SARS COV-2, COVİD-19 Virus, Hematoloji Maligniteler, kanser

Introduction

In 2003, the first global health emergency with the sickness termed Severe Acute Respiratory Syndrome was enrolled as the world entered the 21st century (SARS). In addition, pneumonia in the city of Wuhan, Hubei province of China was reported as of 31 December 2019 [1]. The disease was designated coronavirus-2 (COVID-19) because of its similar to SARS CoV, and it was called the cause agent SARS-CoV-2 [2]. On 11 March 2020, the WHO identified COVID-19 as a pandemic. The sickness has infected over 100 countries. At least 186 million people were afflicted as of July 13, 2021, with nearly four million deaths [3].

Due to the presence of COVID-19, an infection with the potential for nosocomial transmission could not be treated in the emergency due to individuals with high fatality [4]. Many respiratory therapies for critical ill patients are considered high risk factors for nosocomial transmission (intubation, manual ventilation, etc) [5]. Cancer patients are particularly susceptible to infections during viral outbreaks because of immunosuppression, one of the most sensitive patient groups. The tumor itself and anticancer therapy lead to immunosuppressive conditions [6]. According to 2015 cancer epidemiology statistics, a China report identified cancer history in 18 (1,13 percent) of the 1,590 COVID-19 cases, which was higher than the overall Chinese population for cancer. Research in China indicated that in all patients, the death rate of COVID 19 patients was 2,3%, however in cancer patients the rate was 5,6% [7].

Patients with solid organ and hematological malignancies may present to emergency services with oncological emergencies, primary disease progression or metastasis, metabolic effects of the malignancy, unfavorable treatment effects, or other diseases. These patients must reduce malignancy-related symptoms, manage treatment-related side effects, and treat oncological emergencies and associated diseases in the emergency department [8-11].

Treatment management of patients diagnosed with malignancy with COVID-19 during the epidemic is difficult. Treatment of COVID-19-positive patients diagnosed with cancer during the outbreak is tough. COVID-19 complications can occur as a result of immunosuppression caused by malignancy and anti-tumor treatment [12,13]. Delaying anti-tumor therapy, on the other hand, may result in tumor progression. Patients who become infected within the first 30 days after completing chemotherapy had a higher mortality rate [14] Furthermore, the fact that the malignancy is not under control contributes to COVID-19's more severe course. Infected patients who are in remission may lose their remission due to SARS-CoV-2 infection [15]. Data on the management of malignant patients with COVID-19 infection were obtained from retrospective studies. The general implementation is to interrupt specific treatment and modify the treatment in the presence of suspected or diagnosed COVID-19 [16]. Based on this context, the aim of the study is to examine the management of COVID-19 infection in hematological and solid organ malignancies patients with tertiary hospital experience.

Materials and Methods

The work plan. This study was designed as a single-center study where epidemological features, malignancy types and laboratory parameters of patients with malignancy who were hospitalized in Necmettin Erbakan University Meram Faculty of Medicine Clinic of COVID-19 between 01.09.2020-01.01.2021 were analyzed. All those patients were included the study.

Ethics committee approval of the study was received from Necmettin Erbakan University Meram Faculty of Medicine Clinical Research Ethics Committee with the number 2021/3034 and by signed form related to Helsinki Declaration.

The epidemiological characteristics (age, gender) and malignancy types of the patients constituting the sample of the study were determined. The patients were analyzed in two groups as hematological malignancy (HM) and solid organ malignancy (SM). The two groups were compared in terms of laboratory values, computed tomography (CT) results, convalescent plasma (CP), intensive care unit (ICU) and mechanical ventilation (MV) needs, hospitalization days and healing status, treatment for malignancy, and presence of additional infection.

Clinical Evaluation. Severe COVID infection was defined as dyspnea, >50% increase in lung infiltration on CT within 24-48 hours, oxygen saturation <93%, PaO2/FiO2 <300, and septic shock [17]. In our center where the study was conducted, CP was applied to these cases.

Statistical Analysis. IBM SPSS Statistics for Windows, Version 22.0 program was used for statistical analysis. Distribution analysis of continuous numerical variables was evaluated with the Kolmogorov-Smirnov Test and, variables were presented by median (minimum-maximum). Mann-Whitney U test was applied for comparison of two groups. Categorical variables were expressed as percent (%) and compared with the Chi-Square test. In Spearman correlation analysis, 0.00-0.24 weak, 0.25-0.49 moderate, 0.50-0.74 strong and 0.75-1.00 very strong correlations were accepted for the coefficient (rho). Multivariate analysis was performed with Logistic regression modeling using the Backward method. Parameters considered to be of clinical importance and resulting in $p<0.25$ in univariate analysis were included in the modeling. One of the correlated parameters was included in the model. $p<0.05$ results were considered statistically significant.

Results

The study included a group 134 patients. Of the patients, 70 (52.2%) were male, 64 (47.8%) were female, and the median age was 66 (24±87). All patients included in the study were diagnosed with COVID-19 according to their clinical and radiological characteristics, and the nasal PCR test was positive in only 17 (12.7%) patients. According to malignancy types, 68 (50.7%) of the patients were diagnosed as solid organ malignancies and 66 (49.3%) of them were diagnosed as hematological malignancies. Diagnostic distribution of patients included in the study by malignancy types is given in Table 1.

The comparison of malignancies in terms of laboratory of the patients is given in Table 2. Sedimentation and ferritin were significantly higher in patients diagnosed with HM; neutrophil, lymphocyte, platelet and neutrophil lymphocyte ratio (NLR) was found to be lower. Additionally, the need for CP was found to be significantly higher in patients diagnosed with HM than in patients diagnosed with SM (HM: 71.2%; SM: 42.6%, p: 0.001). Additionally, patients diagnosed with HM had a significantly longer hospitalization and a higher need for intensive care (HM: 11.5; SM:

Table-1: The Frequency of Malignancies, n(%)

Hematological Malignancies	
Multiple Myeloma	22 (16,4)
Non-Hodgkin Lymphomas	14 (10,4)
Myelodysplastic Syndrome	12 (9,0)
Acute Myeloid Leukemia	10 (7,5)
Chronic Lynphocytic Leukemia	4 (3,0)
Acute Lynphoblastic Leukemia	2 (1,5)
Hodgkin Lymphoma	2 (1,5)
Solid Organ Malignancies	
Colorectal Cancer	14 (10,4)
Breast Cancer	11 (8,2)
Lung Cancer	9 (6,7)
Pancreatic Cancer	8 (6,0)
Gastric Cancer	7 (5,2)
Over Cancer	4 (3,0)
Prostate Cancer	3 (2,2)
Nasopharyngeal Cancer	2 (1,5)
Others*	10 (7,0)

8, p: 0.008). Mortality rate was found to be higher in HM patients, although not significant (HM: 66%; SM: 27.9%, p; 0.458). When all the patients included in the study were analyzed, it was found that 41 (30.6%) patients died.

The number of patients diagnosed with COVID-19 during active chemotherapy (CT) was 111 (82.8%). The need for CP was 60.8% (n:67) in patients in the CT period and 39% (n:9) in the others. The cure rate was 61.2% (n:41) in patients undergoing CT, and 88.9% (n:8) in those who did not. When all patients included in the study were evaluated, the cure rate was 64.5% (n:49) in those who underwent CP.

The distribution of clinical features of all patients included in the study is given in Table 3. According to Table 3, growth in blood, urine or sputum cultures other than COVID-19 was detected in 39 (29.1%) of the patients included in the research. In the presence of additional infection, the cure rate was found to be significantly lower in HM ([HM: 51.3%; SM: 76.9%]; [OR: 3.1-95%; CI: 1.4-6.9], p:0.004). While the need for CP was 71.8% (n:28) in patients with additional infection, the need for CP was 50.5% (n:48) in patients who did not, and it was statistically significant (OR:2.4 9%; CI 1.1-5.5, p: 0.024). When 76 patients who underwent CP were evaluated, the cure rate was 75% (n:36) in patients without growth, while the cure rate was significantly lower at 46.4% (n:13) in patients with growth (OR:3.4-95%; CI:1.3-9.3 p:0.012). Additionally, the frequency of active infection was found to be higher in patients receiving CT, even though it was not statistically significant (32.4% vs. 13%, p:0.062). Multivariate logistic regression analysis in Table 4 showed that the presence of non-COVID-19 infection increased the risk of death 2.8-fold (95% CI; 1.3-6.5, p:0.01).

When the correlation analyzes were analyzed, a moderate correlation (rho: 0.427, p:0.007) was found between female gender and culture positivity, and a strong correlation between the application of CP and the day of hospitalization (rho: 0.62, p<0.001).

Discussion

In the COVID-19 pandemic, patients with malignancy are considered a particularly vulnerable group. To date, nothing is known about the clinical characteristics of COVID-19-infected malignancy patients. COVID-19 infection, on the other hand, is known to worsen in malignant patients [18]. On February 26, 2020, the clinical characteristics of 28 cancer patients from three designated hospitals in Wuhan, China, who had a laboratory-confirmed diagnosis of COVID-19 were described. In 53.6% of the patients, serious events occurred, 21.4% were hospitalized to the intensive care unit, 35.7% suffered life-threatening complications, and 28.6% died [19]. ICU admission, mechanical ventilation, or death were all considered significant events in this study. The percentage of patients with severe infection was 56.7% in our study, with a 30.6% mortality rate. In the general COVID-19 infected population, 4.7% of cases have evolved to a clinical critical state, with almost

Table-2. Comparison of malignancies in terms of laboratory

	Hematological Malignancies (n: 66)	Solid Organ Malignancies (n:68)	p
Age	66 (24-87)	66 (38-85)	0,74
CRP (mg/L)	98,8 (0,9-411)	87,7 (1,7-438)	0,50
Sedimentation (mm/h)	98,5 (5-140)	76 (6-140)	0,001*
Fibrinogen (mg/dL)	481 (182-1032)	445 (147-988)	0,69
D-Dimer (mg/mL)	771,5 (72-46692)	777,5 (61-62560)	0,14
Ferritin (ng/mL)	1539 (77-36472)	865 (13-11691)	<0,001*
Procalcitonin (ng/mL)	0,4 (0,02-67,5)	0,3 (0,03-68)	0,75
Neutrophil (/µL)	1,2 (0,01-21,8)	4,8 (0,05-18,7)	<0,001*
Lymphocyte (/µL)	0,42 (0,01-2,55)	0,65 (0,02-18,7)	0,001*
PLT (/µL)	51,5 (2-494)	190 (12-470)	<0,001
NLR	3,1 (0,01-1227)	5,6 (0,18-54,5)	0,001*

Note: Variables were presented as median (minimum-maximum)
PLT; Platelet, NLR; Neutrophil/Lymphocyte Ratio
*Mann-Whitney U Test

Table-3. Clinical Comparison of Malignancies

	Hematological Malignancies (n: 66)	Solid Organ Malignancies (n:68)	p
Hospitalization day*	11,5 (2-64)	8 (3-23)	0,001[a]
CP Need, n (%)	47 (71,2)	29 (42,6)	0,001[b]
İntensive Care Need, n (%)	31 (47)	17 (25)	0,008[b]
MV Need, n (%)	17 (25,8)	10 (14,7)	0,11
After Treatment, n (%)			0,50
Recovery	44 (33,3)	49 (72,1)	
Dead	22 (66,7)	19 (27,9)	
Degree of CT imaging, n (%)			0,17
Low	16 (24,2)	24 (35,3)	
Mild	21 (31,8)	13 (19,1)	
High	29 (43,9)	31 (45,6)	
Culture, n (%)			0,15
Positive	23 (34,8)	16 (23,5)	
Negative	43 (65,2)	52 (76,5)	
During Chemotherapy, n (%)	53 (80,3)	58 (85,3)	0,44

CP; Convalescent Plasma, MV; Mechanical Ventilator, CT; Computerized Tomography
*Median (minimum-maximum)
[a]Mann-Whitney U test
[b]Pearson's chi-square test

Table 4: Multivariate Analysis of Risk Factors for Death*

Risk Factor	Hazard Ratio (95% CI)	P
Age	1,1 (0,993-1,060)	0,12
Sex (female vs male)	0,7 (0,318-1,551)	0,38
During Chemotherapy (yes vs no)	3,2 (0,857-12,176)	0,84
Non-COVID-19 infection (yes vs no)	**2,8 (1,264-6,422)**	**0,01**

*The possible factors identified by univariate analyses were included into the model. In order to determine independent predictors on death, Logistic regression analysis with backward selection was used and, statistical significantly step was added on the table.

half of critical cases (2.3%) being fatal [20]. In our study, the percentage of patients with severe infection was 56.7%, with a 30.6% mortality rate. The frequency of severe infection in HM patients was 15.5%, the need for intensive care was 18.9%, and the need for MV was found to be significantly higher in a study comparing HM patients with the non-HM population [21]. In similar studies, the duration of mechanical ventilation and ICU stay were found to be lower in patients with mortality [22].

Males were prominent in fatal cases of COVID-19 infection, according to a Wuhan study, and the median age was 65.8 years [23]. Furthermore, patients with lung cancer (>60 years old) from solid organ malignancies are at risk of COVID-19 infection, according to the findings. However, we know that lung cancer is more common in the sixth decade and in males [24]. These two deadly diseases can be seen together in the risk population, given their similar demographic characteristics. In our research, it was found that multiple myeloma (16.4%) was the most common among patients diagnosed with hematological malignancies according to malignancy types, and colorectal carcinoma (10.4%) was the most common among patients diagnosed with solid organ malignancies. This is thought to be due to the patient groups included in the study. Patients with malignancy are especially vulnerable to respiratory infections and severe pneumonia because they are immunosuppressed as a result of their disease and anti-tumor treatment. The presence of non-COVID 19 infections raised the risk of death by 2.8 times in our study, which is linked to the prevalence of serious clinical events in COVID-19 infection. According to Liang and et al., a lower percentage of cancer patients (7 out of 18) have serious events [25]. In a study by Chen et al (2020) with eleven patients (10 with nasal oxygen demand, 8 with severe comorbidity), nasopharyngeal PCRs were still positive in 8 of 10 patients 5-6 days after treatment. It was claimed that 6 of these patients had solid/hematological malignancies as a comorbidity [26]. The main reasons for the difference can be attributed to variation in the definition of serious events and study populations. Liang and et al. defined clinical severe events as an admission of patients to the intensive care unit requiring invasive ventilation or death [25].

Given the rise of COVID-19 disease despite recent advancements, rapid and reliable biomarkers are required for the early diagnosis of patients with high mortality risk, such as those diagnosed with COVID-19 malignancy. To evaluate the severity of a disease, some biomarkers have been proposed [27]. While there was a significant difference in laboratory parameters such as sedimentation and ferritin values in patients

with HM, the neutrophil, lymphocyte, platelet, and neutrophil-lymphocyte ratio (NLR) was found to be low in this study. In severely ill patients with COVID-19 infection, lymphocytopenia is a prominent feature among hematological parameters. The cytoplasmic component of the lymphocyte is damaged and destroyed by the targeted invasion of COVID-19 viral particles [28]. Findings that lymphocytes express ACE-2 receptors on their cell membranes support this hypothesis [29]. Furthermore, pro-inflammatory cytokines including tumor necrosis factor-alpha and (IL-6) can cause a reduction in lymphocyte count [30]. The lymphocyte counts of patients who died with COVID-19 were found to be significantly lower than those of survivors [27]. Lymphocytopenia was found in more than 80% of severely ill patients in one research [31]. In a meta-analysis of 21 studies involving COVID-19 patients, it was determined that patients with critical illness and developing mortality had a decreased lymphocyte count compared to survivors [32]. Lymphocytopenia can be used in the clinical diagnosis of new coronavirus infections or to predict the clinical course.

Sedimentation levels are more stable among inflammatory biomarkers, but CRP levels increase significantly in the early stages of the disease, with a positive correlation between increased CRP levels and disease severity [33,34]. In COVID-19 patients, more severe cases revealed a more dramatic PCT increase than non-severe cases, similar to our findings in studies [35,36]. In a retrospective clinical serial, non-survivors had higher CRP and ferritin levels than survivors [37]. In another study, researchers found increased ferritin levels in patients who died [32]. Additionally, when the Charlson comorbidity index (CCI) is examined, the frequency of solid organ malignancies among the patients who developed mortality is higher than the patients who survived. Accordingly, as the COVID-19 epidemic intensifies, it is considered that it will be beneficial for clinicians to consider low lymphocyte count, ferritin, CRP, and PCT serum levels, considering that the need for early identification biomarkers will increase, especially in patients with high mortality risk such as patients diagnosed with malignancy.

Within 14 days of being diagnosed with COVID-19, patients with a history of malignant tumors were found to undergo anti-tumor treatment and patchy consolidation on computed tomography (CT), independently increasing the risk of serious complications [38]. The frequency of active infection was shown to be greater in patients undergoing active chemotherapy in our study, despite the fact that it was not statistically significant. The cure rate for patients who underwent CP was 64.5% among those who received active chemotherapy in the research. In the study conducted by Shen et al., the detection of an increase in the lymphocyte count and a significant decrease in CRP values in patients who underwent CP, and a regression in the radiological findings of the lung at the end of one week, supports the results of the study [19]. Additionally, the strong correlation between the length of hospital stay and the beneficial effects on the patients who underwent CP is an indicator of this result.

The limitations of our study are that it was retrospective, the stage and risk groups of malignancies were not included, and other infection types were not specified. We believe that our study will contribute to the literature in terms of showing that COVID-19 infection is more severe in patients with hematological malignancies than in patients with solid organ malignancies.

Low lymphocyte count, high CRP, ferritin, and PCT levels, according to the findings, can help clinicians identify patients with malignant diagnosis with a high mortality risk. The use of a model in the COVID-19 pandemic that summarizes the sum of these

non-COVID infections, hematological parameters, age and comorbidities can help in the method of patients with a history of malignant tumors with a high mortality risk.

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Corresponding author e-mail: atakantekinalp@hotmail.com

Orcid ID:
Atakan Tekinalp 0000-0001-7937-4045
Hilal Akay Çizmecioğlu 0000-0002-3312-4638
Mevlüt Hakan Göktepe 0000-0003-1711-5157
Sinan Demircioğlu 0000-0003-1277-5105
Ali Kürşat Tuna 0000-0002-7453-326X
Melek Karakurt Eryılmaz 0000-0003-2597-5931

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Case Report

Fasciola Hepatica Case Considered as Cholangiocarcinoma on Imaging

Görüntülemede Kolanjiokarsinom Olduğu Düşünülen Fasciola Hepatica Olgusu

Ahmet Aydın[1], Sabin Göktaş Aydın[2], Banu Karaalioğlu[3]

[1]Department of Internal Medicine, Istanbul Medipol University Hospital, Istanbul
[2]Department of Medical Oncology, Medipol University Hospital, Istanbul
[3]Department of Radiology, Medipol University Hospital, Istanbul

ABSTRACT

Fascioliasis is a zoonotic infection and causes fever, eosinophilia, nausea, and even a mass interpreted as a malignancy on imaging. The diagnosis of the disease is difficult because of the wide spectrum of clinical features. This trematode infection is mainly observed in developing countries. Here we report a case of hepatic mass, mistakenly reported as cholangiocarcinoma, caused by fasciola hepatica.

Keywords: Fascioliasis, hepatic mass, triclabendazole

ÖZET

Fascioliasis zoonotik bir enfeksiyondur ve ateş, eozinofili, bulantı ve hatta görüntülemede malignite olarak yorumlanan bir kitleye neden olur. Klinik özelliklerinin geniş bir yelpazeye sahip olması nedeni ile hastalığı teşhis etmek zordur. Bu trematod enfeksiyonu daha çok gelişmekte olan ülkelerde görülmektedir. Burada fasciola hepatica'nın neden olduğu yanlışlıkla kolanjiokarsinom olarak bildirilen bir karaciğer kitlesi vakasını sunuyoruz.

Anahtar kelimeler: Fasciolasis, hepatik kitle, triklabendazol

Introduction

Fasciola hepatica is a trematode that infects mammals' livers and causes an infection of the biliary tract [1]. Typical findings are abdominal pain, fever, malaise, weight loss, urticaria, eosinophilia and leukocytosis. Examination of the stool specimens is the diagnostic test [2,3]. However, in some cases, blood tests can be helpful, including parasite antibodies. Radiological imaging supports the diagnosis. In addition, fascioliasis may have a similar radiological appearance to other diseases of the liver and bile ducts such as cholangiocarcinoma etc. [3]. Triclabendazole, used in a single oral dose of 10 mg/kg, is the drug of choice for the treatment [4]. Here we present a case of hepatic mass caused by fasciolosis that was initially thought to be cholangiocarcinoma.

Case

A 46-year-old woman living in Istanbul was admitted to our hospital with the complaint of abdominal pain, fever and itching. She had lost 8 kg in the past 6 months, as well. A complete blood count revealed eosinophilia (2,900/mm3, N: 0–400/mm^3, 36% of leukocytes), which was confirmed by a peripheral blood smear. Serum chemical analysis revealed the following values: albumin, 3.4 g/dl; alkaline phosphatase, 170 U/l (normal range, 53–128); alanine aminotransferase, 43 U/l (normal range, 10–35); aspartate aminotransferase, 54 U/l (normal range, 14–50); and total bilirubin, 1.2

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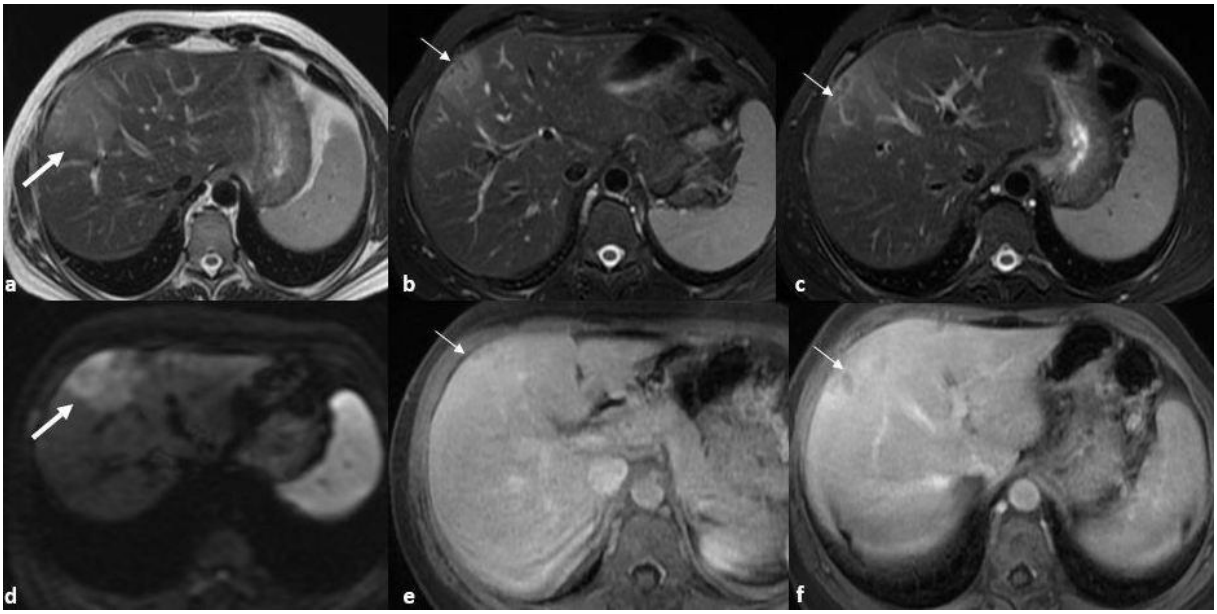

Figure 1. a) Axial T2 FSE image shows a peripherally located hyperintense lesion, favouring a mass. b,c) In axial fat sat T2 FSE image, hypointense tracts were seen in the lesion beneath the capsule extending centrally (thin arrow). d) In DWI, marked diffusion restriction is seen in lesions which is also observed in malignant masses of the liver. e,f) In contrast, enhanced axial fat-sat T1 weighted image, the lesion shows slightly more contrast enhancement.

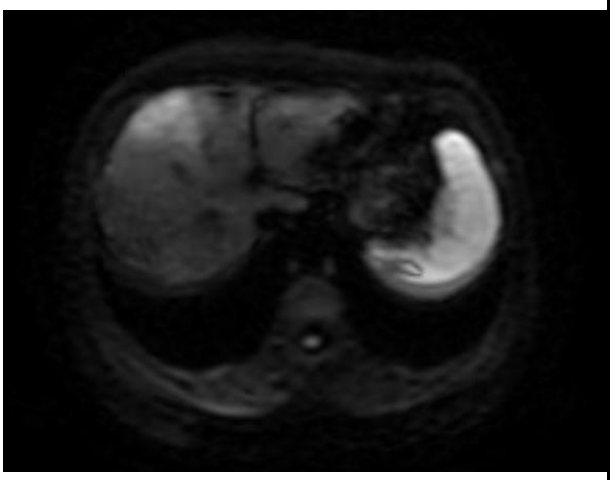

Figure 2. Contrast enhanced T1-weighted image shows the hyperintensity of the mass in right lobe.

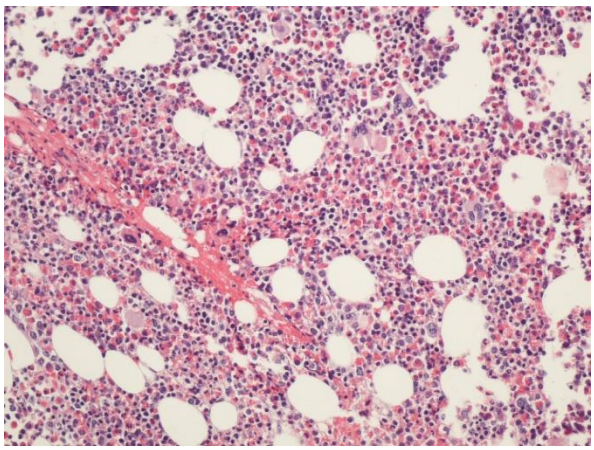

Figure 3. Bone marrow biopsy shows hypercellular bone marrow rich in eosinophilic cells

mg/dl (normal range 0.3–1.2), AFP: 2.3 ng/m) (normal range <6.0 ng/m), erythrocyte sedimentation rates: 55 mm/h (normal range < 30 mm/h). Because of a mass in abdominal ultrasonography, Magnetic resonance imaging (MRI) was revealed, which mass was thought to be a cholangiocarcinoma. (Figure 1,2). In stool specimens, there was not found any parasitic eggs. Hyper-eosinophilic syndrome was excluded by bone marrow biopsy (Figure 3). To establish a definite diagnosis, a hepatic biopsy was performed. Tru-cut liver biopsy in the 5th segment: the material consists of liver parenchyma containing intense and widely eosinophil-rich active inflammation, and granulomatous

lesions consisting entirely of eosinophils were observed. Diagnosis of the parasitic infection was made by serologic test. Serologic test for Fasciola hepatica showed high titer against that (positive titer 1/80). Following the diagnosis, triclabendazole was administered at a dose of 10–12 mg/kg for 1 or 2 days; after which the symptoms disappeared (Figure 3), biochemical values soon returned to normal, hepatic mass disappeared, and the patient was discharged with good condition.

Discussion

Fasciola hepatica is mostly seen in developing countries, and the eggs in stool cannot be detected in the acute stage of the disease unless they become adults. Moreover, parasite eggs cannot be seen in chronic fascioliasis due to an ectopic location of the infection [2].

FAST-ELISA, indirect hemagglutination, complement fixation, indirect immuno-fluorescence (IIF), counter electro-phoresis, and double diffusion can be used as serological tests for the diagnosis of acute fascioliasis. ELISA testing is more rapid and reliable, with a sensitivity rate of 95%. With the treatment, serological titers decline, and antibodies are detectable even for years after infection [5,6].

Radiological evaluation is an important part. Ultrasonography can detect parasite movement in the gall bladder or liver lesion. Contrast-enhanced CT and MRI can demonstrate the parenchymal involvement and subcapsular low attenuation regions. Additionally, the parenchymal lesion shows contrast enhancement relative to liver parenchyma in contrast to the tracts, which is a clue for fascioliasis. [7]. However, fascioliasis may present with multiple nodular lesions, solitary nodular lesions etc., which can cause dilemma or confusion, as in our case.

Triclabendazole is the effective treatment of Fasciola hepatica infections. The drug is administered at a dose of 10 mg/kg for 1 or 2 days and is well-tolerated [4]. We treated our patient with triclabendazole as well.

To conclude, Fasciola hepatica may cause a mass that may mistakenly suggest liver cancer on imaging, as in our case. While evaluating a patient with liver mass and hypereosinophilia, the differential diagnosis should include parasitic infections. It should not be forgotten that the absence of parasite eggs in the stool does not exclude the diagnosis, and it should be kept in mind that the diagnosis can be made with serum tests.

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Corresponding author e-mail: bayrampasadahiliye@gmail.com

Orcid ID:
Ahmet Aydın 0000-0002-8610-768X
Sabin Göktaş Aydın 0000-0002-0077-6971
Banu Karaalioğlu 0000-0003-4864-5652

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Case Report

Chronic Lymphocytic Leukemia-Induced Paraneoplastic Hypercalcemia

Kronik Lenfositik Lösemiye Bağlı Paraneoplastik Hiperkalsemi

Taha Ulutan Kars, Hatice Zeynep Dikici, Atakan Tekinalp, Sinan Demircioğlu

Division of Hematology, Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey

ABSTRACT

Paraneoplastic hypercalcemia is common, especially in advanced stage solid organ malignancies (breast cancer, renal cancer, lung cancer) and multiple myeloma, and is associated with poor prognosis. Paraneoplastic hypercalcemia is rarely observed in chronic lymphocytic leukemia. Due to its low incidence, there is not enough data in the literature about the effect of hypercalcemia on prognosis and its treatment. We reported this rare condition that a 68-year-old male who was followed up with a diagnosis of chronic lymphocytic leukemia and developed symptomatic malignant hypercalcemia. We concluded that ibrutinib was effective in the control of hypercalcemia due to chronic lymphocytic leukemia.

Keywords: leukemia, lymphocytic, chronic, B-cell, hypercalcemia, ibrutinib

ÖZET

Paraneoplastik hiperkalsemi, özellikle ileri evre solid organ malignitelerinde (meme kanseri, böbrek kanseri, akciğer kanseri) ve multipl miyelomda yaygındır ve kötü prognoz ile ilişkilidir. Kronik lenfositik lösemide paraneoplastik hiperkalsemi nadiren görülür. Düşük insidansı nedeniyle literatürde hiperkalseminin prognoza ve tedavisine etkisi hakkında yeterli veri bulunmamaktadır. Kronik lenfositik lösemi tanısı ile takip edilen ve semptomatik malign hiperkalsemi gelişen 68 yaşındaki erkek hastada nadir görülen bu durumu bildirdik. İbrutinibin kronik lenfositik lösemiye bağlı hiperkalsemi kontrolünde etkili olduğu sonucuna vardık.

Anahtar kelimeler: kronik lenfositik lösemi, hiperkalsemi, ibrutinib

Introduction

Malignant hypercalcemia is a common paraneoplastic syndrome that occurs especially due to malignancies. Malignant hypercalcemia is usually symptomatic and indicates a poor prognosis [1]. It is seen less frequently in hematological malignancies compared to solid tumors. Paraneoplastic hypercalcemia is an extremely rare condition in chronic lymphocytic leukemia (CLL) and there is no data in the literature that clearly explains the mechanism of malignant hypercalcemia development in chronic lymphocytic leukemia. In this case report, a patient who was followed up with a diagnosis of chronic lymphocytic leukemia and developed symptomatic malignant hyper-calcemia was discussed.

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Case Report

A 68-year-old male with no concomitant disease and no history of drug use and diagnosed with CLL in May 2016 was treated one year after diagnosis due to disease progression with 6 cycles of fludarabine + cyclophosphamide + rituximab (FCR) chemotherapy. The patient's Rai stage was stage 1, and FISH analysis was normal at the diagnosis. While being followed without treatment for three years in remission, in June 2020, the patient applied with complaints of weakness, fatigue, frequent urination and constipation. Anemia, thrombocytopenia, hypercalcemia, and acute renal failure were detected in the patient. It was found that cervical, axillary and inguinal lymphadenopathies (LAP) reappeared. No other mass was detected in the tomographic evaluation. At admission, the leukocyte count was $10{,}1x10^3/\mu L$, hemoglobin was 10,9 g/dL, platelet count was $61x10^3/\mu L$, creatinine was 2,57 mg/dL, calcium was 17,29 mg/dL, albumin was 42 g/L. Peripheral smear showed 32% neutrophils, 64% lymphocytes, 4% monocytes, smudge cells and thrombocytopenia. The rapidly growing lymph node in the submandibular region was excised. The biopsy result was reported as CLL infiltration, thus Richter transformation and metastasis were excluded. In examinations for hypercalcemia, parathormone (PTH) was 1,8 pg/mL (14-72 pg/mL), 1,25-dihydroxy vitamin D (calcitriol) was 41,7 ng/dL (30-100 ng/dL). Paraneoplastic hypercalcemia due to CLL was considered. After the patient's hydration and diuretic treatment, calcium decreased to 14.03 mg/dL and creatinine to 1.61 mg/dL, and zoledronic acid was administered to the patient on day 4. Flow cytometry was found to be compatible with B-cell CLL. There was 80% mature lymphocyte infiltration in bone marrow aspiration. FISH analysis was normal. On day 6, the patient was re-treated as Rai stage 4 CLL and due to Cumulative Illness Rating Scale (CIRS) >6

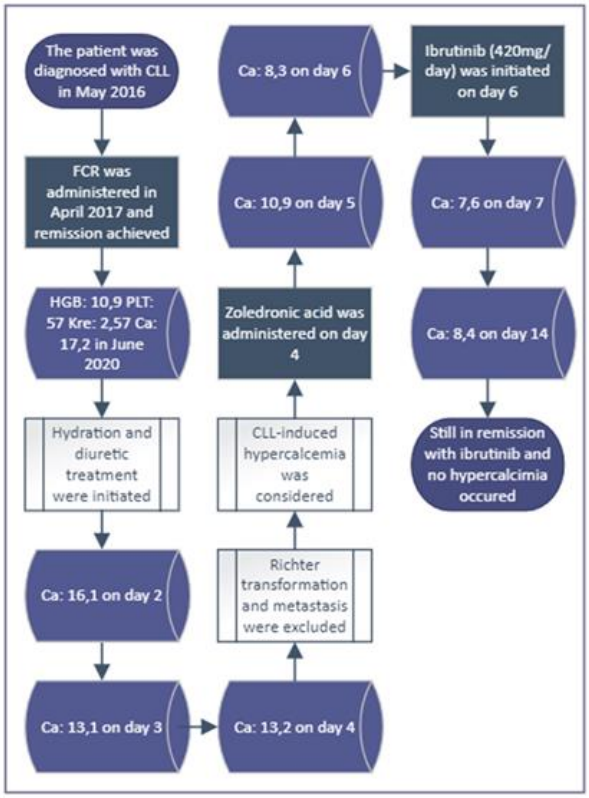

Figure 1 - Flow chart of the patient's clinical course

and recurrence after chemotherapy. During the follow-up, calcium returned to normal limits, anemia and thrombocytopenia improved (Figure 1). He is currently being followed in remission with ibrutinib treatment.

Discussion

Malignant hypercalcemia is a paraneoplastic condition seen in 20-30% of patients followed up with solid or hematological malignancies and is the most common cause of hypercalcemia in hospitalized patients. The malignancies most associated with malignant hypercalcemia are breast cancer, renal cancer, lung cancer and multiple myeloma [2]. Although malignant hypercalcemia is seen in hematological malignancies, especially in multiple myeloma and T-cell lymphomas, this frequency is quite low compared to malignant hypercalcemia due to solid tumors. It is rare in B-cell lymphomas and the majority of these cases are aggressive lymphomas [3]. There

are very rare data in the literature in malignant hypercalcemia due to CLL. In a retrospective study, it was shown that only 7 of 1200 patients with CLL developed malignant hypercalcemia [4].

Major mechanisms in the development of malignant hypercalcemia are parathyroid hormone-associated peptide secretion (PTHrP) from the tumor, osteolytic lesions causing local cytokine secretion, 1,25-dihydroxy vitamin D synthesis from the tumor and ectopic secretion of PTH from tumor cells. Hypercalcemia mediated by PTHrP secretion occurs due to an increase in both bone resorption and renal distal tubular calcium reabsorption [5]. Hypercalcemia via osteolytic metastases occurs due to increased bone reabsorption and increased calcium release from bones [6]. Hypercalcemia mediated 1,25-dihydroxy vitamin D occurs due to an increase in both intestinal calcium absorption and bone resorption [7]. Malignant hypercalcemia can be seen in CLL with one of these mechanisms. Salahudeen et al. treated a case of PTHrP-induced resistant hypercalcemia in a patient with CLL with denosumab [8]. Kampfenkel et al. reported cases with CLL who developed hypercalcemia associated with PTHrP [9]. Fain et al. reported a case of malignant hypercalcemia in a patient with CLL who developed with an increased 1,25-dihydroxy vitamin D level [4]. Malignant hypercalcemia has been reported in the literature in a few cases with prolymphocytic leukemia or immunoblastic lymphoma transformation (Richter Syndrome) while being followed up with a diagnosis of CLL [10].

In our case, low PTH, normal 1,25-dihydroxy vitamin D, absence of Richter transformation findings suggested hypercalcemia associated with PTHrP release in the foreground; however, this diagnosis could not be confirmed because PTHrP levels could not be studied in our center. CLL-induced hypercalcemia in our patient was successfully controlled with ibrutinib. Hypercalcemia did not recur during the period of ibrutinib use, In our case, it was observed that ibrutinib was effective in the control of hypercalcemia due to CLL.

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Corresponding author e-mail: tahaulutankars@gmail.com

Orcid ID:
Taha Ulutan Kars 0000-0003-4013-4647
Hatice Zeynep Dikici 0000-0002-8489-8326
Atakan Tekinalp 0000-0001-7937-4045
Sinan Demircioğlu 0000-0003-1277-5105

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Case Report

JAK2 V617F Mutation and t(8;21) Positive Acute Myeloid Leukemia After Renal Transplantation

Böbrek Nakli Sonrası JAK2 V617F Mutasyonu ve t(8;21) Pozitif Akut Miyeloid Lösemi

Gülden Sincan[1], Murat Altunok[2], Çiğdem Yüce Kahraman[3], Fuat Erdem[1]

[1]Department of Hematology, Medical School, Atatürk University, Erzurum, Turkey
[2]Department of Nephrology, Medical School, Atatürk University, Erzurum, Turkey
[3]Department of Medical Genetics, Medical School, Atatürk University, Erzurum, Turkey

ABSTRACT

There is an increased risk of malignancy after solid organ transplantation. Acute myeloid leukemia is one of these malignancies. The translocation (8;21) is one of the most frequent karyotypic abnormalities in acute myeloid leukemia. The JAK2 V617F mutation is rarely seen in cases of de novo acute myeloid leukemia. There is no case with translocation (8;21) and JAK2 V617F mutation-positive acute myeloid leukemia after kidney transplantation in the literature. We report a 43 years old female patient who had a kidney transplant from her brother 10 years ago applied to our clinic with the complaint of fatigue. The JAK2 V617 mutation and translocation t(8;21) positive acute myeloid leukemia was detected in this patient. The patient received 3+7 remission induction treatments. After chemotherapy, translocation (8,21) and JAK2 V617F mutation were negative. Acute myeloid leukemia cases developing after kidney transplantation should be evaluated in terms of JAK2V617F mutation positivity.

Keywords: JAK2 V617F mutation, translocation (8;21), renal transplantation

ÖZET

Solid organ transplantasyonundan sonra malignite riski artar. Akut miyeloid lösemi bu malignitelerden biridir. Translokasyon (8;21), akut miyeloid lösemide en sık görülen karyotipik anormalliklerden biridir. JAK2 V617F mutasyonu, de novo akut miyeloid lösemi vakalarında nadiren görülür. Literatürde böbrek nakli sonrası translokasyon (8;21) ve JAK2 V617F mutasyon pozitif akut miyeloid lösemi gelişen bir olgu yoktur. 10 yıl önce kardeşinden böbrek nakli olan 43 yaşında halsizlik şikayeti ile kliniğimize başvuran kadın hastayı sunduk. Bu hastada JAK2 V617 mutasyonu ve translokasyon t(8;21) pozitif akut miyeloid lösemi tespit edildi. Hasta 3+7 remisyon indüksiyon tedavisi aldı. Kemoterapi sonrası translokasyon (8,21) ve JAK2 V617F mutasyonu negatifti. Böbrek nakli sonrası gelişen akut miyeloid lösemi olguları JAK2V617F mutasyon pozitifliği açısından değerlendirilmelidir.

Anahtar kelimeler: JAK2 V617F mutasyonu, translokasyon (8;21), böbrek nakli

Introduction

Acute myeloid leukemia (AML) constitutes approximately 80% of acute leukemia seen in the adult age group. Myelodysplastic syndrome, chronic myeloproliferative diseases, Down and Bloom syndrome, radiation exposure, smoking, benzene exposure, and chemotherapeutic agents are risk factors for the development of AML. Approximately 5-10% of de novo AML cases have t(8;21), and this mutation is associated with a more favorable prognosis. The Janus kinase 2 (JAK2) gene has cytoplasmic tyrosine kinase activity and is located on the

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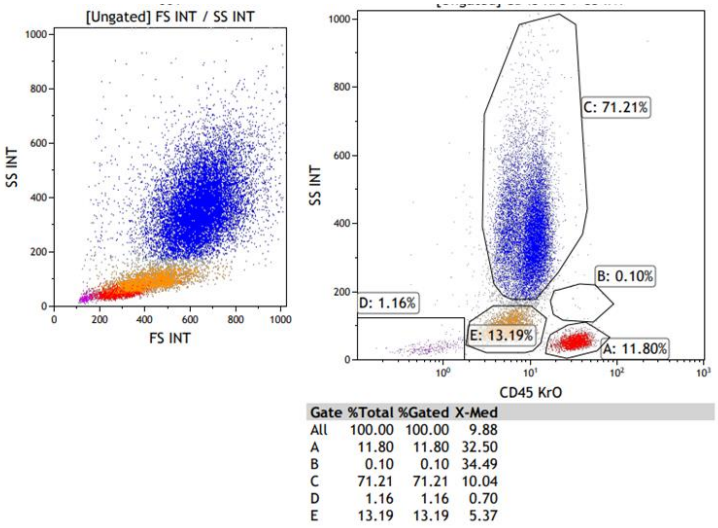

Figure 1. Flow cytometric (CD45) examination of bone marrow aspiration.

short arm of the 9th chromosome. JAK2 V617F mutation may also be positive in cases with AML developing secondary to chronic myeloproliferative disease or de novo AML. Its incidence in de novo AML cases is approximately 1% [1]. The JAK2 V617F mutation is detected in 3.5% of t(8;21) positive AML cases.

Overall survival in patients with chronic renal failure undergoing kidney transplantation is better than in patients undergoing chronic hemodialysis [2]. In particular, immuno-suppressive agents such as Tacrolimus and Mycophenolate Mofetil contribute to the improvement of the prognosis in these patients. It is thought that these agents increase the risk of cancer by disrupting the immune reaction against oncogenetic viruses and increasing cytokine levels [3]. AML accounts for approximately 43% of leukemias that develop after solid organ transplantation [4]. We present our case who developed t(8;21) and JAK2 V617 mutation-positive de novo AML after kidney transplantation, as she is the first case in the literature.

Case Report

A 43-year-old female patient was admitted to our hospital with the complaint of fatigue for 15 days. This complaint did not affect his daily work and increased with effort. The patient had chronic renal failure for 11 years and had a kidney transplant from her brother 10 years ago. She was using Mycophenolate Mofetil tablet (tb) 2x500 mg/day, Tacrolimus tb morning:1.5 mg evening:1 mg and Deltacortil tb 1x2.5mg/day.

During the physical examination of the patient, she was conscious, cooperative, oriented, and arterial blood pressure: 120/70 mmHg, heart rate: 80/minute, and body temperature: 36.5 °C. There were no abnormal findings were found except for the incision scar of the renal transplantation procedure. In the laboratory tests, hemoglobin: 7.1 g/dL, hematocrit: 23.3%, leukocyte: 27240/µL, platelet: 54000 /µL, lactate dehydrogenase (LDH): 439 U/L, kidney and liver function tests were normal. There was no abnormal finding in the complete urinalysis. Since blastic cells were seen in the peripheral smear of the patient, bone marrow aspiration was performed. Blast cell with extensive cytoplasm and prominent nucleolus (13%) was detected in bone marrow aspiration smear (Figure 1). Flow cytometric evaluation of bone marrow aspiration sample revealed cluster differentiation (CD) 13: 71%, CD 33:

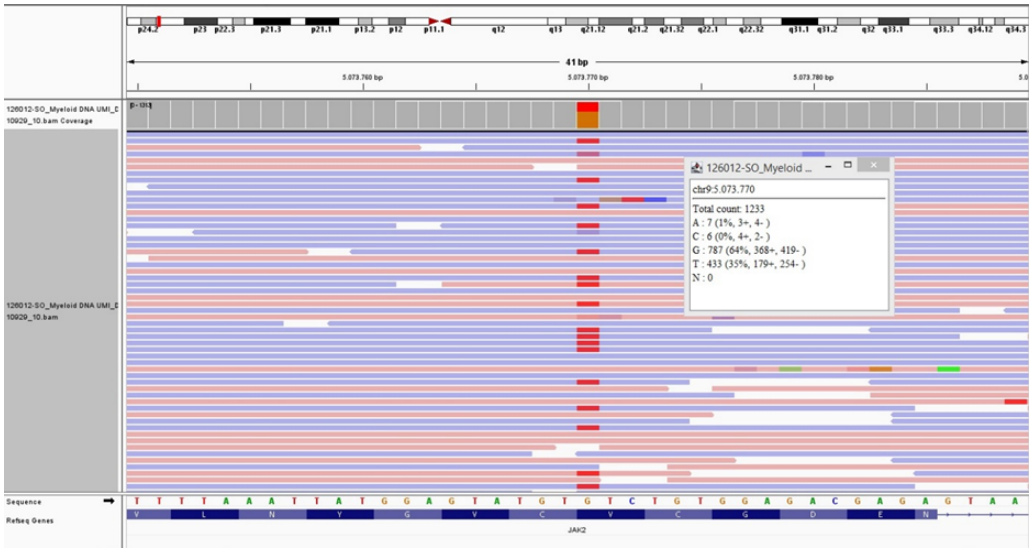

Figure 2. The visualization of JAK2 V617F mutation on IGV software

No.	C	Name	Type	Ct	Ct Comment	Given Conc (Cop	Calc Conc (Copie	% Var
1		our patient	Unknown	23,74			84.167	
3		NTC	NTC					
5		F2	Standard	34,30		100	105	4,8%
7		F4	Standard	23,77		100.000	82.784	17,2%
8		F5	Standard	19,61		1.000.000	1.152.233	15,2%

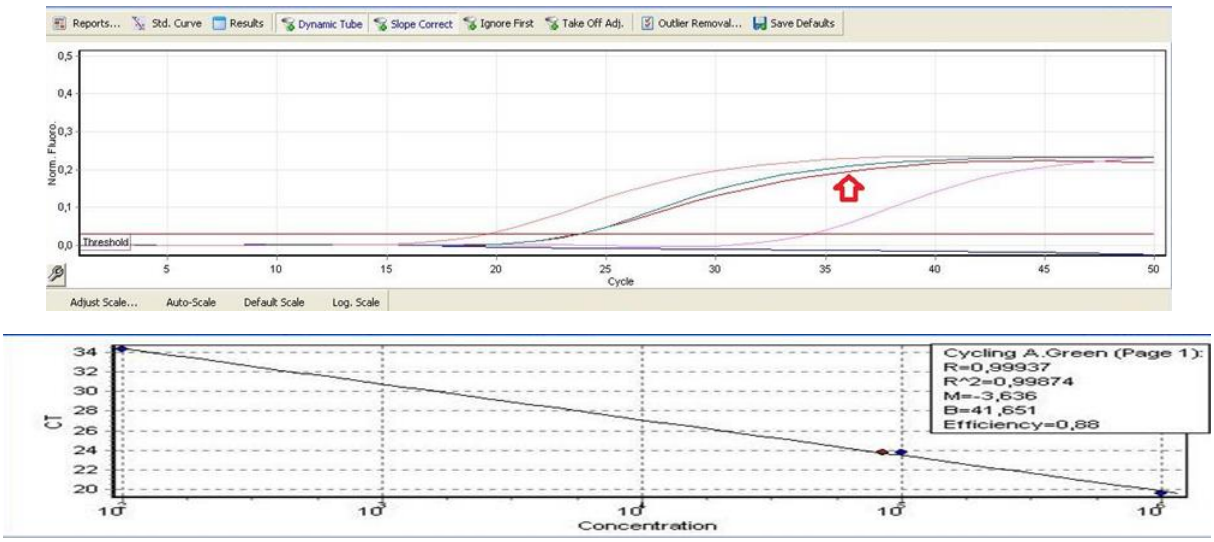

Figure 3. Amplification plots of t(8;21) on qPCR.

28%, myeloperoxidase: 78%, CD 19: 83% positive in the blast gate. The karyotype analysis was normal. JAK2 V617F mutation was detected by the next-generation sequencing method and t(8;21) was positive (5.37%) by the Polymerase Chain Reaction method (Figure 2 and 3, respectively). The blood tacrolimus level was 5.34 ng/ml. Mycophenolate Mofetil and Deltacortil treatment, which the patient was using due to a history of renal transplantation, was discontinued after consultation with the nephrology clinic. Tacrolimus treatment had been arranged according to the blood level of the drug. The patient received 3+7 remission induction treatments (Cytosine Arabinoside 100 mgx2/m^2/day and Doxorubicin 45mg/m^2/day). Tacrolimus treatment was

discontinued when the patient developed neutropenia. The patient's creatinine value was always within the normal range during follow-up. The patient's hemogram parameters and LDH value returned to normal range in the follow-up.

Discussion

Hall et al. reported that the incidence of cancer in solid organ transplant recipients increased between 2000 and 2008 compared to the incidence of cancer between 1987-1999 [5]. The increase in cancer incidence may be related to the prolongation of the life span of transplant patients and the immunosuppressive therapy. Our patient was receiving Tacrolimus, Mycophenolate Mofetil, and Dexamethasone as immunosuppressive therapy. Rashidi et al. reported that 72% of patients who developed AML after solid organ transplantation were male and their median age was 50 years [6]. Our case was female and her age was compatible with the literature.

Rashidi et al reported 51 patients who developed AML after solid organ transplantation[6]. Twenty-three of these patients were kidney transplant recipients, 20 were liver transplant recipients, six were heart transplant recipients, and two were lung transplant recipients. The median time between organ transplant and development of AML was 3.8 years, and more than 70% of cases developed AML within the first 5 years after transplant. The median time between kidney transplant and development of AML was 4.7 years, and more than 70% of these cases developed AML within the first 5 years after kidney transplant. In our case, AML did not develop in the first 5 years after kidney transplantation.

Cardarelli et al. reported a 33-year-old man who developed AML 9 years after kidney transplantation. In this patient, page kidney developed after 3-7 remission induction treatments [7]. Our patient did not develop any renal complications after 3-7 remission induction treatments. Scherrer et al. determined a case with t(9;11) positive AML after kidney transplantation [8]. In our case, t(8;21) was positive.

JAK2 V617 mutation has an important role in the diagnosis of chronic myeloproliferative diseases. But some studies reported that this mutation may be present in de novo AML cases. Steensma et al. analyzed 162 AML patients and found JAK2 V617F mutations in 13 patients [9]. Three of these patients had de novo AML. Döhner et al. examined 61 patients with AML who were positive for t(8;21) and found a JAK2 V617F mutation in 4 (6%) patients [10]. The positivity of JAK2 V617F mutation has negative effects on prognosis in AML cases with t(8,21) and t(16,16) or inv 16 [1]. In our case, only remission induction therapy was given and the hemogram value returned to normal. In conclusion, we present our case who presented with the complaint of fatigue and developed AML after kidney transplantation.

There was no other patient with a diagnosis of de novo AML that included both t(8;21) and JAK2V617F mutations after kidney transplantation in the literature. More comprehensive studies on this subject will provide us with more detailed information about the malignancies developing in solid organ transplant patients in the future.

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Corresponding author e-mail: guldensincan@gmail.com

Orcid ID:
Gülden Sincan 0000-0002-7671-7628
Murat Altunok 0000-0001-6122-6829
Çiğdem Yüce Kahraman 0000-0003-1957-9596
Fuat Erdem 0000-0002-0377-7291

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