Original Article

BRCA and non-BRCA Variants Detected by Next Generation Sequencing in Patients with Hereditary Breast and/or Ovarian Cancer Syndrome

Kalıtsal Meme ve/veya Over Kanseri Sendromlu Olgularda Yeni Nesil Dizileme ile Saptanan BRCA ve non-BRCA Varyantlar

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ABSTRACT

Introduction: Breast cancer is the most frequently diagnosed female cancer according to the 2020 data of the World Health Organization. It is mostly sporadic, 10-15% of which occur on the basis of genetic predisposition. In this study, we aimed to detect mutations in *BRCA* and *non-BRCA* genes in patients admitted with the diagnosis of breast cancer and/or ovarian cancer, and to identify mutations with increased frequency and variants specific to the Turkish population.

Materials and methods: Between January 2019 and August 2021, 120 patients who applied to our clinic with hereditary Breast and/or Ovarian Cancer meeting the genetic test study criteria were included in the study. First, *BRCA1/2* genes next-generation sequencing were performed on these patients, respectively. *BRCA1* and *BRCA2* gene deletion duplication analysis and/or multiple gene panel associated with cancer susceptibility were studied from patients with no mutations.

Results: In this molecular genetic susceptibility study associated with Hereditary Breast and/or Ovarian Cancer, 33.3 % positive variants were found in BRCA and non-BRCA genes. *BRCA1/2* mutations were detected in 20 patients. In addition, *non-BRCA* mutations (*ATM, CHEK2, RAD50, RAD51D, STK11, SDHA, RB1, POLD1, SMAD4, CDH1* and *CDKN22* genes) were detected in 20 patients. We identified a total of 7 new variants in the *BRCA2, ATM, RAD50, RAD51D, STK11* and *POLD1* genes.

Discussion: Clarification of risks specific to non-BRCA genes is necessary for a better understanding of the Hereditary Breast and/or Ovarian Cancer Syndrome (HBOC) genetic susceptibility spectrum. Therefore, multi-gene panel testing is needed after routine *BRCA* genes. In our study, most of the novel mutations were detected in *non-BRCA* genes. In addition, two novel *BRCA* variants have been reported. It also contributed to the identification of mutations specific to the Turkish population.

Keywords: BRCA1/2, non-BRCA, HBOC, Turkish population, Multi-gene panel test

ÖZET

Giriş ve Amaç: Meme kanseri Dünya Sağlık Örgütü'nün 2020 yılı verilerine göre en sık tanı alan kadın kanseridir. Çoğunlukla sporadik olmakla birlikte %10-15 oranında genetik yatkınlık zemininde ortaya çıkar. Meme kanseri ve/veya over kanseri tanısıyla başvuran hastalardaki genetik yatkınlığı araştırdığımız bu çalışmamızda amacımız *BRCA* ve *non-BRCA* genlerinde saptadığımız varyantları sunmak ve Türk popülasyonuna özgü mutasyonları belirmektir.

Yöntem ve Gereçler: Ocak 2019-Agustos 2021 tarihleri arasinda klinigimize kalitsal Meme ve/veya Yumurtalik Kanseri ile basvuran, genetik test calisma kriterlerini karsilayan 120 hasta calismaya dahil edildi. Öncelikle sırasıyla *BRCA1* ve *BRCA2* geni dizi analizi çalışıldı. *BRCA1/2* tüm gen dizi analizi yöntemiyle mutasyon tespit edilmeyen hastalardan *BRCA1* ve *BRCA2* geni delesyon dublikasyon analizi ve/ veya kansere yatkınlıkla ilişkilendirilen çoklu gen paneli çalışıldı.

Bulgular: Herediter Meme ve/veya Over Kanseri ile ilişkili genetik etyolojiyi araştırdığımız bu çalışmada *BRCA* ve *non-BRCA* genlerde %33.3 pozitif varyant saptandı. 20 hastada *BRCA1* ve *BRCA2* genlerinde, 20 hastada ise *non-BRCA* genlerinde (*ATM, CHEK2, RAD50, RAD51D, STK11, MSH6,*

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SDHA, RB1, POLD1, SMAD4, CDH1 ve *CDKN22*) mutasyon tespit edildi. *BRCA2, ATM, RAD50, RAD51D, STK11* ve *POLD1* genlerinde olmak üzere toplam 7 novel varyant tanımlandı.
Tartışma ve Sonuç: Herediter Meme ve/veya Over Kanseri genetik duyarlılık spektrumunun daha iyi anlaşılması için *non-BRCA* genlerine özgü risklerin aydınlatılması gerekmektedir. Bu nedenle rutin *BRCA* genlerinden sonra çoklu gen panel testine ihtiyaç vardır. Çalışmamızdaki, yeni mutasyonların çoğu *non-BRCA* genlerinde tespit edildi. Ek olarak, iki yeni *BRCA* varyantı raporlandı. Ayrıca bu çalışma ile Türk popülasyonuna özgü mutasyonların belirlenmesine de katkı sağlandı.

Anahtar Kelimeler: BRCA1/2, non-BRCA, HBOC, Türk popülasyonuna, Çoklu gen panel test

Introduction

Breast cancer is the most common type of cancer in both genders and all ages, according to the 2020 data of the World Health Organization-International Agency for Research on Cancer (IARC) [1,2]. Ovarian cancer is the most lethal gynecologic cancer in women [3]. Breast cancer is mostly sporadic, and genetic factors play an important role in 10-15% of cases [4].

Hereditary breast and/or ovarian cancer syndrome (HBOC) is characterized by a familial predisposition to cancers such as female and male breast cancer, ovarian cancer and less frequently pancreatic cancer, prostate cancer and melanoma [5]. Mostly, mutations in the *BRCA1* and *BRCA2* genes are associated with HBOC syndrome [6]. These genes are tumor suppressor genes that play critical roles in repair of DNA double strand breaks, homologous recombination and transcription [7,8]. *BRCA1* DNA repair-associated protein (*BRCA1* [MIM no:113705]) gene is located in the 17q21.31 chromosomal region. *BRCA1* gene consists of 24 exons and 23 coding exons, according to the Ensembl ENST00000471181.7 transcript. BRCA2 DNA repair-associated protein (BRCA2 [MIM no:600185]) gene map to 13q13.1. According to the ENST000000380152.8 ensembl transcript, 27 exons consist of 26 coding exons. The 11th exon of the *BRCA2* gene is the most mutated and largest coding part [9].

Mutations in the BRCA1/2 genes are responsible for approximately 25% of HBOC syndrome [10]. More than 50% of HBOC is thought to be caused by mutations in non-*BRCA* genes such *as CHEK2, CDH1, MLH1, MSH2, MSH6, PMS2, PALB2, RAD50, RAD51C, RAD51D, PTEN, STK11 and ATM* [11,12]. Most of these genes are tumor suppressor genes that play a role in DNA damage response by similar mechanisms [13]. It is estimated that the risks of developing breast and ovarian cancer are 87% and 44%, respectively, in individuals carrying *BRCA1/2* gene mutations until the age of 70 [14].

Since breast and ovarian cancers occur on the background of genetic predisposition, genetic analysis plays an important role in the treatment of cancer, screening for other cancer types with increased risk in their lives, and genetic counseling to other family members [15,16]. In conclusion, the genetic susceptibility spectrum needs to be better understood by elucidating the risks specific to *non-BRCA* genes beyond *BRCA1/2*, taking into account regional and ethnic differences. At the same time, the amount of targeted multigene panels has increased in standard clinical practise of HBOC cases with the rapid development of technology, reduced cost and increased accessibility in next generation sequencing (NGS) analyses.

In this study, we aimed to provide new information to the literature of our country by means of targeted multigene panels, where there is not enough data on *non-BRCA* genes yet, by performing molecular genetic analysis in accordance with international guidelines in cases applying for HBOC.

Materials and Methods

Patients

In the present study, 120 female patients who applied to Balıkesir Atatürk City Hospital Medical Genetics Department between

01.01.2019 and 01.08.2021 due to HBOC syndrome were included in the study according to criteria of the National Comprehensive Cancer Network (NCCN) [17]. The criteria used to access the test are: individual who have a pathogenic/probably pathogenic variant in their cancer susceptibility genes in any of their relatives, breast cancer diagnosed ≤45 years, breast and ovarian cancer, multiple primary breast cancers either in one or both breasts, male breast cancer triple negative (estrogen receptor-negative, progesterone receptor-negative, and HER2/neu-negative breast cancer diagnosed <60 years, bilateral breast cancer with the first diagnosed <50 years, personal history of breast cancer and one close blood relative with breast cancer <50 or ovarian cancer or pancreatic cancer. The mean age of the patients was 45 years (32-71 years). This study was conducted in Balikesir University Medical Faculty Health Sciences Ethics Committee dated 24.11.2021 and numbered 2021/260. The study was evaluated as a research file and it was decided that it was scientifically and ethically appropriate.

Genetic Analysis

Sequence analysis of the *BRCA1* and *BRCA2* genes, respectively, was studied from the patients. Then, *BRCA1* and *BRCA2* gene deletion duplication analysis and/or multi-gene panel associated with cancer susceptibility were studied from patients in whom no mutation was detected. The results of familial segregation analysis of patients with mutations were not included in this study.

DNA extraction

Approximately 2 ml of venous blood was collected from all patients in an EDTA tube. DNA was isolated from 200 µl peripheral blood samples from patients using QIAamp DNA Blood Mini Kit (Qiagen Inc.).

BRCA1/2 gene next-generation sequencing

All the coding exons, with flanking intron regions, of the *BRCA1/2* gene were amplified by the polymerase chain reaction and sequenced using next-generation sequencing (NGS). After library enrichment (MiSeq Reagent Kit v2, MS-102-2003) and quality control, the samples were sequenced using the MiSeq platform (Illumina, San Diego, California, United States). Raw reads were quality trimmed with Trimmomatic and were mapped to reference human genome (hg19) with using BWA (Burrows-Wheeler Alignment Tool). Duplicates were removed using SAMTools and realignment across indels and base quality recalibration were performed with GATK. Annotation of detected variants were performed using Illumina BaseSpace Variant Interpreter, InterVar, Franklin, VarSome, ClinVar, OMIM, and Pubmed. Variants with a frequency higher than 0.5% were filtered out. dbNSFP (contains SIFT, PolyPhen-2, LRT, Mutation Taster) was used to predict the pathogenicity about the deleteriousness of variants. Rare variants were classified according to the ACMG/AMP variant interpretation framework.

BRCA1/2 gene Deletion/Duplication Analysis

BRCA1 gene exon deletion/duplication was investigated by multiplex ligation-dependent probe amplification (MLPA) analysis. SALSA® Probemix P002 *BRCA1* MLPA® kit was used to analyze all the coding exons as described by manufacturer's recommendation (MRCHolland, Amsterdam, Netherlands). The reactions were run and analyzed on an ABI Prism 3130xl DNA Sequencer (Applied Biosystems, Foster City, CA, USA) and Coffalyser.Net data analysis software.

BRCA2 gene exon deletion/duplication was investigated by multiplex ligation-dependent probe amplification (MLPA) analysis. SALSA® Probemix P090 *BRCA2* MLPA® kit was used to analyze all the coding exons as described by manufacturer's recommendation (MRCHolland, Amsterdam, Netherlands). The reactions were run and analyzed on an ABI Prism 3130xl DNA Sequencer (Applied Biosystems, Foster City, CA, USA) and Coffalyser.Net data analysis software.

Targeted multigene panel analysis

A custom target enrichment panel was designed to capture 19 genes (*TP53, RAD51D, SMAD4, PTEN, ATM, RB1, PALB2, CDKN2A, RAD50, STK11, RAD51C, MSH2, MSH6, PMS2, CDH1, BLM, CHEK2, MEN1, MUTYH*) related with hereditary cancer. All exons, the 25 base pairs of intronic flanking region and 5′ and 3′ untranslated region of each gene were sequenced. After library enrichment and quality control, the samples were sequenced using the MiSeq platform (Illumina, San Diego, California, USA). Raw reads were trimmed with Trimmomatic and were mapped to reference human genome (hg19) with using the Burrows-Wheeler Aligner (BWA). Duplicates were removed using SAMTools and realignment across indels and base quality recalibration were performed with Genome Analysis Toolkit (GATK). Variants with a frequency higher than 0.5% were filtered out. Annotation of detected variants were performed using, Franklin (https://franklin.genoox.com/ clinical-db/home), VarSome (https://varsome.com/), ClinVar (https:// www. ncbi.nlm. nih.gov/ clinvar/), Online Mendelian Inheritance in Man (OMIM) and Pubmed. Rare variants were classified according to the ACMG/AMP variant interpretation framework [18]. The following public databases were used for the interpretation of the variants: ClinVar, LOVD (https://databases.lovd.nl/shared/genes), the Human Genome Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php), and BRCA Exchange database (https:// brcaexchange. org/). Mutations in all patients were classified according to ACMG criteria into three categories: pathogenic, likely pathogenic, and uncertain significance. Likely benign and benign variants according to ACMG have not been reported.

Results

In our study, BRCA1/2 mutations including 15 pathogenic, one likely pathogenic and four uncertain significant mutations were detected in 20 (16.66%) patients. At the same time, three pathogenic, five likely pathogenic, and 13 uncertain significance mutations in *non-BRCA* genes in 20 (16.66%) patients. *BRCA1* mutations in four (3.33%) patients, *BRCA2* mutations in 11 (9.16%) patients, *ATM* mutations in two (1.66%) patients, and *POLD1* mutation in one (0.83%) patients, a total of 18 (15%) patients pathogenic variant was detected. In addition, one (0.83%) *BRCA2* gene, two (1.66%) *CHEK2* gene, one (0.83%) *ATM* gene, one (0.83%) *RB1* gene and one (0.83%) *CDKN2* gene, a total of six (5%) likely pathogenic variants were detected. Totally, 17 (14.16%) uncertain significance variants were detected, four (3.33%) *BRCA2*, three (2,5%) *ATM*, two (1.66%) *CHEK2*, two (1.66%) *RAD50*, two (1.66%) *SMAD4* and one each in the *RAD51D, STK11, SDHA, CDH1* genes. this study (Table1, Table 2).

Double mutation carriers in different non-*BRCA* genes were found in one case. A 45-year-old patient with breast cancer was found to be a carrier of double mutations, c.670C>T likely pathogenic in the *CHEK2* gene and c.7475T>G mutation of uncertain significance in the ATM gene. In the patient with invasive ductal cancer type, ER 98%, PR 50%, Ki 67 40%, cerb-B2 +3 strong membranous positive staining was found. Diffuse staining was observed with E-cadherin. The patient had relatives with breast cancer and all three daughters suffered from fibroadenomas beginning in the second decade.

Discussion

In this study, routine *BRCA1/2* molecular genetic analyzes and Targeted Multigene Panel analysis for *non-BRCA* genes recommended in international guidelines were performed on hereditary breast and/or ovarian cancer cases. *BRCA1/2* mutation carrier was detected in 20 (16.66%) patients, with 12.5% pathogenic, 0.83% likely pathogenic, and 3.33% uncertain significance. In the study of Bahsi et al., which included the largest number of patients (1419 cases) in the Turkish population, 9.4% pathogenic, 0.3% likely pathogenic, 6.4% uncertain significance BRCA1/2 mutation was detected [5]. The frequency of BRCA1/2 mutations, which varies between different populations and different ethnic groups, is approximately between 5% and

Table 1**:** *BRCA1/2* mutations and their classification according to ACMG

The gene and transcript	Number	dbSNP ID	Mutation	HGVS protein reference	Variant type	ACMG Classification
BRCA1 gene: NM_007300.4	3	rs80357906	c.5329dup	p.Gln1777ProfsTer74	Insertion	Pathogenic
	1	rs80357626	c.2019del	p.Glu673AspfsTer28	Deletion	Pathogenic
BRCA2 gene: NM_000059.4	1	rs397507683	c.3751dup	p.Thr1251AsnfsTer14	Insertion	Pathogenic
	1	rs80359732	c.8940del	p.Glu2981LysfsTer7	Deletion	Pathogenic
	1	rs80359672	c.7673_7674del	p.Glu2558ValfsTer7	Deletion	Pathogenic
	1	rs80359212	c.9382C>T	p.Arg3128Ter	Nonsense	Pathogenic
	1	rs276174813	c.1796_1800del	p.Ser599Ter	Deletion	Pathogenic
	1	rs398122761	c.3302A>G	p.His1101Arg	Missense	Uncertain significance
	1	Novel	c.2117C>T	p.Ala706Val	Missense	Uncertain significance
	1	rs587778119	c.2892A>T	p.Lys964Asn	Missense	Uncertain significance
	1	rs397507639	c.2765dup	p.Lys923GlnfsTer13	Insertion	Pathogenic
	1	Novel	c.682A>C	p.Asn228His	Missense	Likely pathogenic
	1	rs397507639	c.2765dup	p.Lys923GlnfsTer13	Insertion	Pathogenic
	2	rs80359502	c.5270_5286del	p.Tyr1757SerfsTer5	Deletion	Pathogenic
	1	rs876658951	c.8494G>T	p.Glu2832Ter	Nonsense	Pathogenic
	1	rs80359460	c.4631dup	p.Asn1544LysfsTer4	Insertion	Pathogenic
	1	rs786201837	c.2779A>G	p.Met927Val	Missense	Uncertain significance

Table2. Non-*BRCA* mutations and their classification according to ACMG

The gene and transcript	Number	dbSNP ID	Mutation	HGVS protein reference	Variant type	ACMG Classification
ATM gene: NM_000051.4	1	Novel	c.658G>A	p.Ala220Thr	Missense	Uncertain significance
	1	rs1591475608	c.487C>T	p.Gln163Ter	Missense	Pathogenic
	1	rs56399857	c.7475T>G	p.Leu2492Arg	Missense	Uncertain significance
	1	rs567060474	c.6820G>A	p.Ala2274Thr	Missense	Likely pathogenic
	1	rs730881329	c.8762C>T	p.Thr2921Met	Missense	Uncertain significance
	1	rs762083530	c.4852C>T	p.Arg1618Ter	Nonsense	Pathogenic
CHEK2 gene: NM_001005735.2	1	rs137853010	c.670C>T	p.Arg224Cys	Missense	Likely pathogenic
	1	rs587782268	c.1182G>T	p.Glu394Asp	Missense	Uncertain significance
	1	rs531398630	c.1240C>T	p.His414Tyr	Missense	Uncertain significance
	1	rs200050883	c.1441G>T	p.Asp481Tyr	Missense	Likely pathogenic
RAD50 gene: NM_005732.4	1	Novel	c.89C>T	p.Pro30Leu	Missense	Uncertain significance
	1	rs757043253	c.2204T>A	p.Met735Lys	Missense	Uncertain significance
RAD51D gene: NM_002878.4	1	Novel	c.208G>C	p.Asp70His	Missense	Uncertain significance
STK11 gene: NM_000455.5	1	Novel	c.263T>C	p.Ile88Thr	Missense	Uncertain significance
SDHA gene: NM_004168.4	1	rs112307877	c.1945_1946del	p.Leu649GlufsTer4	Deletion	Uncertain significance
RB1 gene: NM_000321.3	1	rs138201027	c.1546T>G	p.Trp516Gly	Missense	Likely pathogenic
POLD1 gene:NM_001256849.1	1	Novel	c.2820+2T>C	-	Splicing	Pathogenic
SMAD4 gene: NM_005359.6	1	rs1568205010	c.512C>T	p.Ser171Leu	Missense	Uncertain significance
	1	rs1599204052	c.1321C>T	p.Arg441Cys	Missense	Uncertain significance
CDH1 gene: NM_004360.5	1	rs1182000968	c.2312A>G	p.Gln771Arg	Missense	Uncertain significance
CDKN2 gene: NM_000077.5	1	rs587782797	c.335G>A	p.Arg112His	Missense	Likely pathogenic

26.1% in Turkish population [5,19-21]. Our study is similar to other publications in terms of BRCA1/2 mutation carriers in Turkish population. The most common c.5329dup (2.5%) mutation was found in the *BRCA1* gene. This result was similar to large studies in the Turkish population [5, 20]. However, there was no *BRCA2* mutation with increasing frequency. At the same time, two novel variants of c.682A>C likely pathogenic and unceratin significance c.2117C>T in the *BRCA2* gene were detected.

Targeted multigene panel analysis is increasingly used to screening for patients with HBOC [22]. We also identified 21 mutations in 20 (17.5%) patients in 12 different *non-BRCA* genes, including *ATM, CHEK2, RAD50, RAD51D, STK11, MSH6, SDHA, RB1, POLD1, SMAD4, CDH1* and *CDKN2*. We reported five novel mutations in different genes, including *ATM, RAD50, RAD51D, STK11* and *POLD1*. In our study, the most common mutation in the *ATM* gene (5%) was found among the *non-BRCA* genes. The prevalence of moderate-penetrance gene *ATM* mutation carriers in breast cancer is 2-4% [23, 24].

We identified 24 (20%) pathogenic or likely-pathogenic variants (PV) in 24 of 120 (20%) participants, including seven insertions, six deletions and seven missense, three nonsense, one splice variants among: *BRCA1, BRCA2, ATM, CHEK2, RB1, POLD1* and *CDKN2* genes. To date, approximately 3000 *BRCA1*, 3500 *BRCA2* pathogenic mutations have been identified in the Clinvar database [25]. It is now very difficult to find novel mutations in *BRCA1/2* genes. While no novel *BRCA1/2* mutations were reported in the report by Bahsi et al., which includes the largest Turkish population (1419 patients), we detected two novel *BRCA2* variants in our study. We found 17 (14.16%) uncertain significance mutations, including 16 missense-type and one deletion-type. The uncertain significance mutations reported here will also contribute to future studies in larger patient groups.

BRCA mutations are responsible for one quarter of HBOC syndrome, yet there is not enough information about the *non-BRCA* genes responsible for the vast majority. Clarification of risks specific to *non-BRCA* genes is necessary for a better understanding of the HBOC genetic susceptibility spectrum. In conclusion, a better understanding of the genetic susceptibility spectrum and clarification of risks specific to *non-BRCA* genes are required. This report supports studies to identify mutations specific to Turkish people.

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Original Article

Can Preoperative Neutrophil-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and APRI Score Reliably Differentiate Uterine Sarcomas from Leiomyomas?

Preoperatif Nötrofil Lenfosit Oranı, Platelet Lenfosit Oranı ve APRİ Skoru Uterin Sarkomları Myomlardan Ayırt Edebilir mi?

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ABSTRACT

Aim: Uterine sarcomas are one of the aggressive gynecologic malignancies. There is still no optimal test for preoperative diagnosis of uterine sarcomas. The aim of this study was to evaluate the role of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and APRI score in predicting preoperative uterine sarcoma.

Materials and Methods: Patients operated on between January 2010 and December 2020 histo-pathologically diagnosed as sarcoma were included in the study group. Patients who were histo-pathologically diagnosed with myoma uteri were included as the control group during the same period. Age, BMI (body mass index), gravida, parity, preoperative mean platelet volume (MPV), platelet distribution width (PDW), red cell distribution width (RDW), NLR, PLR and APRI scores were recorded.

Results: When comparing patients with fibroids and sarcomas, hemoglobin [12.3 g/dl (6.4-15.4) vs. 11.3 g/dl (6-17), p=0.008, respectively], hematocrit [38.5% (22-48.7) vs. 35.9% (21.4-52.1), p=0.002, respectively] and lymphocyte levels [2.2 10^3/ L (0.9-13.8) vs. 1.8 10^3/ L (1-2.6), p=0.001, respectively] were significantly lower and NLR [1.7 (0.2-10.1) vs. 2.3 (1.4-5.9), p=0.001, respectively] and PLR [124 (10.9-352.1) vs. 180.4 (84.9-284.3), p=0.001, respectively] were significantly higher in sarcoma group. The optimal cut-off value for NLR and PLR was calculated to be 2.04 with sensitivity and specificity of 59.4% and 59.5%, respectively, and 150.7 with sensitivity and specificity of 65.6% and 64.7%, respectively.

Conclusion: Preoperative NLR and PLR rates can be useful markers for diagnosing uterine sarcoma. Randomized controlled large series studies are necessary to make a definitive statement.

Keywords: Uterine sarcoma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, APRI score

ÖZET

Giriş ve Amaç: Uterin sarkomlar nadir görülen, agresif seyirli jinekolojik kanserlerden biridir. Preoperatif optimal tanı testi hala bulunmamaktadır. Çalışmamızın amacı preoperatif uterin sarkomu öngörmede nötrofil-lenfosit oranı (NLR), platelet-lenfosit oranı (PLR) ve APRİ skoru değerlen-dirmektir.

Yöntem ve Gereçler: Ocak 2010 ile Aralık 2020 tarihleri arasında histopatolojik sarkom tanısı alan hastalar çalışmaya dahil edildi. Aynı dönemde histopatolojik myom uteri tanısı alan hastalar kontrol grubu olarak alındı. Yaş, vücut kitle indeksi, gravida, parite, preoperatif ortalama platelet hacmi (MPV), platelet dağılım genişliği (PDW), kırmızı hücre dağılım genişliği (RDW), NLR, PLR and APRİ skoru kaydedildi.

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Bulgular: Sarkom ve myom tanılı hastalar karşılaştırıldığında, sarkom hastalarında hemoglobin [sırasıyla 12.3 gr/dl (6.4-15.4) ve 11.3 gr/dl (6-17), p=0.008], hematokrit [sırasıyla %38.5 (22-48.7) ve %35.9 (21.4-52.1), p=0.002] ve lenfosit seviyeleri [sırasıyla 2.2 10^3/ L (0.9-13.8) ve 1.8 10^3/ L (1-2.6), p=0.001,] anlamlı olarak düşük, NLR [sırasıyla 1.7 (0.2-10.1) ve 2.3 (1.4-5.9), p=0.001] ve PLR [sırasıyla 124 (10.9-352.1) ve 180.4 (84.9-284.3), p=0.001] anlamlı olarak yüksek saptandı.
Tartışma ve Sonuç: Preoperatif NLR ve PLR oranları uterin sarkom tanısında kullanılabilecek markırlardır. Bu konuda kesin konuşabilmek adına randomize kontrollü geniş serili çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Uterin sarkom, nötrofil lenfosit oranı, platelet lenfosit oranı, APRİ skoru

Introduction

Uterine sarcomas account for 1% of all gynecologic malignancies and 3-7% of uterine malignancies [1,2]. The most common histological types are leiomyosarcoma and endometrial stromal sarcoma. With the last published classification, carcinosarcoma was excluded from the classification of uterine sarcomas [3]. Patients usually present to the clinic with postmenopausal bleeding or premenopausal abnormal uterine bleeding less commonly, they complain of an abdominal mass and pain [4].

The definitive diagnosis of uterine sarcoma is made by histopathologic examination of the hysterectomy material. Unfortunately, there is still no optimal finding or test for preoperative differentiation of fibroids from sarcomas. Clinically, postmenopausal, rapidly growing uterine masses are suspicious [5], but some studies have shown that fibroids can also grow rapidly [6,7]. Although the sensitivity of preoperative diagnostic imaging is high in studies with small numbers of cases, there are not enough studies on this topic [8].

There are publications showing that parameters such as platelet count, mean platelet volume (MPV), platelet distribution width (PDW), neutrophil count, red cell distribution width (RDW) indicate the diagnosis and severity of some hematological diseases [9-11]. In addition, inflammation and oxidative stress are also thought to play a role in the diagnosis of many gynecologic malignancies [12-14].

In this study, we investigated whether preoperative MPV, PDW, neutrophil-to-lymphocyte ratio (NLR), RDW, platelet-to-lymphocyte ratio (PLR), and AST to Platelet ratio Index (APRI) score have any value in predicting uterine sarcoma.

Materials and Method

Study population

Permission for the study was obtained from the Ethics Committee of our hospital (29.09.2021/ 2021/93). Patients operated on between January 2010 and December 2020 with a provisional diagnosis of myoma uteri (M. uteri) and histopathologically diagnosed as leiomyosarcoma (LMS), endometrial stromal sarcoma (ESS), and adenosarcoma were included in the study group. Patients who underwent surgery with a provisional diagnosis of M. uteri and were pathologically diagnosed with M. uteri were included as the control group during the same period. Patients with other gynecological malignancies and known inflammatory diseases, ovarian cysts, endometriosis, pelvic inflammatory disease or adenomyosis were excluded from the study.

Age, BMI (body mass index), gravida, parity, preoperative whole blood parameters [hemoglobin, hematocrit, lymphocytes, neutrophil granulocytes, monocytes, platelet count, MPV, PDW, RDW], and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were retrospectively obtained from medical records.

Measurement of NLR, PLR, and APRI score:

The NLR was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. PLR was calculated as the absolute platelet count divided by the absolute lymphocyte count. The APRI score was defined as AST /upper limit of normal range/platelet count (10^9/L)×100. The upper limit of normal range for AST was taken as 40 U/L.

Demographic characteristics, hematologic parameters, whether NLR, PLR, and APRI scores differed between fibroid and sarcoma patients, and the role of NLR, PLR, and APRI score in predicting preoperative uterine sarcoma were investigated.

Statistical Analysis

The statistical analysis was performed using the Statistics Package for Social Sciences software (ver. 22.0; SPSS Inc., Armonk, NY: IBM Corp). The distribution of all variables were determined using Shapiro Wilk normality test. Mann-Whitney U test was used for nonparametric variables and expressed as median (min-max). Spearman correlation analyses were used to determine the degree of associations among the variables. Receiver operating Characteritics (ROC) curve analysis was used to determine the optimal cut off values of statistically significant variables to predict the treatment modality. Optimal cut-off value was determined according to Youden's index (sensitivity + specificity -1). The results were evaluated in 95% confidence interval and $p<0.05$ was considered as significant.

Results

A total of 192 patients were enrolled in this study. The final pathology result was fibroids in 158 (81.9%) of all study participants and sarcoma in 34 (18.1%).

The median age of the patients included in the study was 46 (28-71), their gravida was 3 (0-9), parity was 2 (0-7), and BMI was 30 kg/m^2 (17-45 kg/m^2). When comparing patients with fibroids or sarcomas, hemoglobin [12.3 g/dl (6.4-15.4) vs. 11.3 g/dl (6-17), p=0.008, respectively], hematocrit [38.5% (22-48.7) vs. 35.9% (21.4-52.1), p=0.002, respectively] and lymphocyte levels [2.2 10^3/ L (0.9-13.8) vs. 1.8 10^3/ L (1-2.6), p 0.001, respectively] were significantly lower in the sarcoma group.

NLR [1.7% (0.2-10.1) vs. 2.3% (1.4-5.9), p 0.001, respectively] and PLR [124 (10.9-352.1) vs. 180.4 (84.9-284.3), p 0.001, respectively] were found to be significantly higher in sarcoma group. Age, gravida, BMI, neutrophil count, monocyte count, platelet count, MPV, RDW, PDW, ALT, and AST and APRI values were similar in both groups ($p>0.05$). The comparison of the two groups is summarized in Table 1.

In the ROC-analysis, NLR (AUC= 0.696, p=0.001) and PLR (AUC= 0.719, p 0.001) ratios significantly predicted the diagnosis of sarcoma. The optimal cut-off value for NLR and PLR was calculated to be 2.04 with sensitivity and specificity of 59.4% and 59.5%, respectively, and 150.7 with sensitivity and specificity of 65.6% and 64.7%, respectively (Figure 1).

Discussion

This study investigated the role of preoperative inflammatory markers in predicting sarcoma diagnosis in women operated for myoma uteri. In the present study, hemoglobin, hematocrit, and lymphocyte count were low, and NLR and PLR were high in patients with sarcoma as the final pathology outcome. Moreover, pre-operative NLR and PLR ratios predicted sarcoma diagnosis with a sensitivity of 59.4% and specificity of 59.5% and a sensitivity of 65.6% and specificity of 64.7%, respectively.

Sarcomas are a rare but aggressive disease arising from uterine smooth muscle cells. The 5-year survival rate of FIGO stage 3-4 uterine

Table 1. Comparison of groups in terms of demographic and laboratory parameters.

	FIBROID (n=158) Median (min-max)	SARCOMA (n=35) median (min-max)	*p*
Age (year)	45.5 (28-58)	47 (28-71)	NS
Gravity	3 (0-9)	3 (0-9)	NS
Parity	2 (0-6)	3 (0-7)	0.03
BMI (kg/m^2)	30 (17-41)	31.2 (24-45)	NS
Hemoglobin (g/dl)	12.3 (6.4-15.4)	11.3 (6-17)	0.008
Hematocrit (%)	38.5 (22-48.7)	35.9 (21.4-52.1)	0.002
Lymphocyte(10^3/ L)	2.2 (0.9-13.8)	1.8 (1-2.6)	<0.001
Neutrophil(10^3/ µL)	3.9 (2-14.9)	3.7 (2.1-12.7)	NS
Monocyte (10^3/ µL)	0.3 (0.1-3)	0.3 (0.2-1.1)	NS
Platelet (10^3/mm^3)	282 (29-664)	284 (164-493)	NS
MPV (fL)	8.4 (6.3-11.4)	8.5 (6.2-12.6)	NS
RDW(%)	15.3 (12.3-49.8)	14.9 (2-42.9)	NS
PDW(%)	48.4 (13.7-68.8)	49.7 (12.5-70.4)	NS
ALT (U/L)	14 (6-251)	16 (7-106)	NS
AST (U/L)	17 (10-102)	18 (11-139)	NS
NLR	1.7 (0.2-10.1)	2.3 (1.4-5.9)	<0.001
PLR	124 (10.9-352.1)	180.4 (84.9-284.3)	<0.001
APRI score	0.1 (0.02-0.5)	0.1 (0.03-0.4)	NS

NS: Non-significant MPV; Mean Platelet volume, RDW; Red Cell Distribution Width ALT, Alanine aminotransferase, AST; Aspartate aminotransferase NLR; Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, APRI: AST to Platelet ratio Index

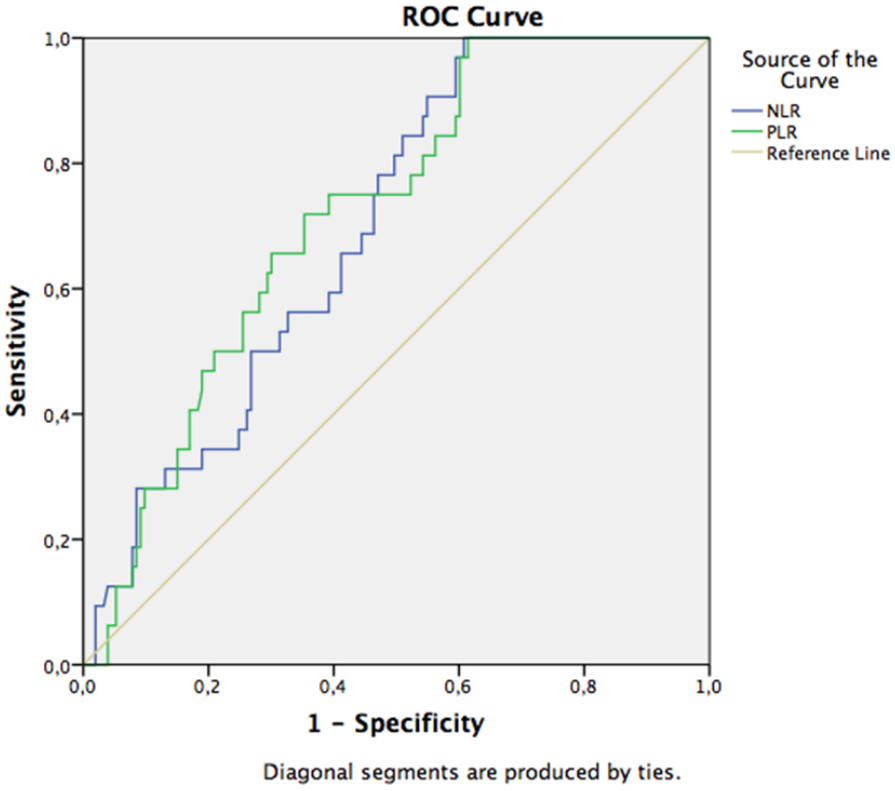

Figure 1. ROC analyses of NLR and PLR

leiomyosarcomas is 25-33% [15]. In recent years, preoperative myoma-sarcoma differentiation has become more critical than ever due to the increase in minimally invasive surgery and the risk of sarcoma spread during laparoscopic myomectomy and morcellation [16].

Sarcomas are often diagnosed incidentally by examination of hysterectomy or myomectomy material [17]. Diffusion-weighted MRI, one of the imaging modalities used in preoperative evaluation, successfully differentiates between sarcoma and fibroma in studies of a small number of patients [18,19]. Goto et al. studied 130 patients with uterine fibroids and ten sarcomas and diagnosed sarcoma with a specificity of 93.8% and a sensitivity of 95.2% using MRI with gadolinium contrast [20]. In addition, they published preliminary results with the combined use of T2-weighted and diffusion-weighted 3-T MRI in eight sarcoma patients with a sensitivity of 100% and a specificity of 100%. Despite the high success rates, this type of MRI in preoperative diagnosis needs to be supported by further studies due to the small number of patients, accessibility, and high cost [21].

Uterine sarcomas are most commonly seen clinically in the postmenopausal period, with a median age of onset of 60 years [22]. Hosh et al. reported that the incidence of sarcoma (6.4/10 vs. 1.5/10, P <0.0001) is approximately 4-fold higher in women older than 50 years compared with younger patients [23]. However, it can also occur at a young age [24]. Chen et al. clinically compared 66 patients with uterine sarcoma and patients with 66 fibroid. They found that the sarcoma patients had postmenopausal, solitary, rapidly growing masses [25]. In our study, the mean age of the patients with myoma and leiomyosarcoma was 45.5 and 47 years, respectively, which is consistent with the literature.

Obesity is known to increase cancer risk for all gynecologic cancers, especially endometrial cancer [26]. Bjorge et al. found that the risk of uterine sarcoma was increased 1.88-fold in patients with BMI ≥30 [27]. In our study, BMI was above 30 in both fibroid and sarcoma patients, which may be due to the gradual increase in obesity in society in recent years, the fact that fibroids are estrogen-dependent tumors, and thus the increased estrogen produced by peripheral adipose tissue.

It has been shown that malignancies may be associated with systemic inflammation [28]. A decrease in lymphocyte count has been noted in cancer patients [29]. It has also been shown that inflammatory markers can be used in the diagnosis of gynecologic malignancies [30,31]. Inflammatory markers have been studied in the preoperative diagnosis of uterine sarcomas. Cho et al. showed that an elevated neutrophil-to-lymphocyte ratio (NLR 2.1), large tumor size (8.0 cm), and low body mass index (BMI≤20) were independent risk factors for uterine sarcoma (p = 0.014, 0.048, and 0.048, respectively) [32]. Kim et al. studied 55 uterine sarcoma patients and found that a cut-off value of NLR ≥2.12 could be used in the diagnosis of preoperative uterine sarcoma with a sensitivity of 75.5% and a specificity of 70.3% [33]. Zhang et al. used a new scoring system in which a cut-off value of NLR ≥ 2.8 (OR 3.032, 95%CI 1.288-7.13) predicted preoperative sarcoma with a sensitivity of 0.800 and a specificity of 0.778 using age, tumor size, NLR, platelets, and LDH [34]. Our study found that preoperative hemoglobin, hematocrit and lymphocyte rates were significantly lower in sarcoma patients than in myoma patients. Sarcoma was detected by NLR ratio with sensitivity of 59.4% and specificity of 59.5% and PLR ratio with sensitivity of 65.6% and specificity of 64.7%; this result proves that these parameters are diagnostic markers for sarcoma unlike other studies. In our study, unlike other studies, the APRI score was also evaluated, and it was found that the preoperative APRI

score was similar in patients with fibroids and sarcomas.

The association of inflammatory markers with survival in sarcoma patients has also been investigated. Five-year progression-free survival was 69.0% and 94.4% in cases with high and low preoperative lymphocyte/ monocyte ratios (cut-off value of 5.86), respectively (p = 0.024) [35]. On the other hand, Jeong et al. found that overall survival and disease-free survival were worse in sarcoma patients with an NLR of 2.60. Moreover, PLR, CA125, and LDH had no effect on survival [36].

Considering the frequency of sarcomas, a large number of patients and the combined evaluation of NLR, PLR and APRI scores are the strengths of the study. The limitations of the study are its retrospective design and the lack of evaluation of serum markers such as CA125 and LDH.

Uterine sarcomas are rare but aggressive malignancies. Preoperative diagnosis cannot be definitively established yet. Preoperative NLR and PLR rates can be useful for diagnosing uterine sarcoma. Randomized controlled large series studies are necessary to make a definitive statement.

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Original Article

Clinicopathological Features and Survival Outcomes of 70 Tongue Squamous Cell Carcinoma Patients

Yetmiş Dil Skuamöz Hücre Karsinomu Hastasının Klinikopatolojik Özellikleri ve Sağ Kalım Sonuçları

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ABSTRACT

Introduction: In this article, it is aimed to present the clinicopathological and demographic characteristics, treatment regimens and survival characteristics of locally advanced tongue squamous cell cancers (TSCC).

Materials and methods: This retrospective study included patients with histologically confirmed locally advanced TSCC followed up at the medical oncology clinic between January 2005 and June 2020. Clinicopathological features and treatment modalities of the patients were recorded from the hospital's patient registry database. The obtained data were compared statistically

Results: A total of 70 patients, 42 male and 28 female, were included in the study. The 5-year OS was found to be 59%. The median disease free survival (DFS) was 4.1 years. OS could not reach the median in the 2/3 anterior tumors of the tongue, while the median OS was 6.9 years in the 1/3 posterior tumors of the tongue (p=0.046). There was no statistically significant difference between age groups in terms of median OS and median DFS. But there was a remarkable point. The median DFS was numerically shorter in patients aged 45 years and younger than in patients over 45 years of age (2 years vs. 4.5 years). Also important here was that both the median OS and the median DFS were numerically worse in women (respectively, median OS: 4.1 years vs. not reached, p=0.075; median DFS: 2.2 years vs. 5.9 years, p=0.349).

Discussion: There are few studies that examine TSCC as a separate title under these headings of oral cavity cancers and oropharyngeal cancers. In this sense, this study will contribute to the literature.

Keywords: oral cavity cancers, oropharengeal cancers, tongue squamous cell cancers

ÖZET

Giriş: Bu yazıda, lokal ileri dil skuamöz hücreli kanserlerin (DSCC) klinikopatolojik ve demografik özellikleri, tedavi rejimleri ve sağkalım özelliklerinin sunulması amaçlanmaktadır.

Gereç ve yöntemler: Bu retrospektif çalışma, Ocak 2005 ile Haziran 2020 arasında medikal onkoloji kliniğinde takip edilen, patolojik olarak doğrulanmış lokal ileri DSCC'li hastaları içermektedir. Hastaların klinikopatolojik özellikleri ve tedavi yöntemleri hastanenin hasta kayıt veritabanından kaydedilmiştir. Elde edilen veriler istatistiksel olarak karşılaştırılmıştır.

Bulgular: Çalışmaya 42 erkek ve 28 kadın olmak üzere toplam 70 hasta dahil edildi. 5 yıllık gene sağ kalım (OS) %59 olarak bulundu. Medyan hastalıksız sağ kalım (DFS) 4.1 yıldı. Dil ön 2/3 tümörlerinde OS medyana ulaşamadı, dilin 1/3 arka tümörlerinde medyan OS 6.9 yıldı (p=0.046). Medyan OS ve medyan DFS açısından yaş grupları arasında istatistiksel anlamlı fark yoktu. Ancak dikkat çekici nokta, medyan DFS 45 yaş ve altındaki hastalarda, 45 yaşın üzerindeki hastalardan (2 yıla karşı 4,5 yıl) sayısal olarak daha kısaydı. Ayrıca hem medyan OS hem de medyan DFS kadınlarda numerik olarak daha

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kısaydı (sırasıyla, medyan OS: 4,1 yıla karşı 'ulaşılamadı', p=0,075; medyan DFS: 2,2 yıla karşı 5,9 yıl, p=0,349).
Tartışma: Oral kavite kanserleri ve orofaringeal kanserler başlıkları altında DSCC'yi ayrı bir başlık olarak inceleyen az sayıda çalışma bulunmaktadır. Bu anlamda bu çalışma literatüre katkı sağlayacaktır.

Anahtar kelimeler: oral kavite kanserleri, orofaringeal kanserler, dil squamoz hücreli kanseri

Introduction

Squamous cell carcinoma of the tongue (TSCC) has increased significantly worldwide over the past decades and it is the second most common cancer of the oral cavity after lip cancer. TSCC was thought to primarily affect middle-aged men and has been associated with tobacco and alcohol use [1]. While men constitute more than 70% of the cases in the elderly, this rate decreases to 50-65% in patients under the age of 45 [2-4]. The incidence of TSCC is increasing, particularly in white women and younger white patients [5]. In the classification of head and neck tumors of the World Health Organization, oropharyngeal and base of the tongue tumors are classified separately from mobile tongue tumors due to their different characteristics [6].

Although the combined use of alcohol and cigarettes is blamed as the cause, the etiological factors are not fully known. It was shown that the incidence of TSCC is on the rise in countries with primary prevention campaigns to quit smoking and alcohol [1, 7, 8]. This suggests that other etiological, genetic and environmental factors are effective in the carcinogenesis of TSCC [9]. In addition, poor oral hygiene and trauma are among the conditions investigated. Epidemiological, studies and laboratory evidence have revealed the relationship between HPV and oro-pharyngeal cancer. However, data from the Surveillance, Epidemiology, and End Results (SEER) database showed that oral tongue tumors were not generally associated with human papillomavirus (HPV) infection and the incidence of HPV-related head and neck carcinomas is decreasing among women [8].

Significant advances have been identified in the locoregional treatment of TSCC due to modern and aggressive surgical resections and advances in adjuvant therapy [10, 11]. Despite all the recent advances in treatment, survival rates have remained stable in the last 5 decades, the 5-year survival rate of SCC cases 33-54% in patients with locally advanced disease [12, 13].

This article aimed to present the clinico-pathological and demographic characteristics, treatment regimens, survival characteristics and also independent prognostic factors of locally advanced TSCC (mobile tongue and base of tongue cancers).

Patients and Methods

This study was approved by Ankara City Hospital Institutional Ethics Committee with decision number E1/1965/2021. The study was carried out in accordance with the Declaration of Helsinki. This retrospective study included patients with histologically confirmed locally advanced TSCC followed up at the medical oncology clinic between January 2005 and June 2021. Clinico-pathological features (smoking, gender, alcohol consumption, comorbidity, Eastern Cooperative Oncology Group Performance Status [ECOG PS], tumor location, pathological features) and treatment modalities of the patients were recorded from the hospital's patient registry database. Patients with oral cavity cancer other than mobile tongue cancer and patients with oropharyngeal cancer other than base of tongue cancer were excluded from the study. The obtained data were compared statistically.

In previous studies on tongue cancer and oral squamous cell cancer in the literature, patients were examined under different age groups. In this study, based on the previous studies in the literature, patients were examined in 3 different groups as ≥45 and >45 years old, <55 and ≥55 years old, <65 and ≥65 years old.

Overall survival (OS) was defined as the time from surgical resection until death due to any reason or last follow-up. Disease-free survival (DFS) was defined as the time from surgical resection to recurrence of the disease or death.

Statistical Analysis

Statistical analyzes were performed using SPSS Statistics version 24.0 (IBM Corp, Armonk NY", link: https: //www.ibm.com/ support/pages/how-cite-ibm-spss-statistics-or earlier-versions-spss). Continuous variables were presented as median (minimum-maximum). Categorical variables were presented as percentages. Normality of quantitative data was analyzed by Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson Chi-square test was used to compare the categorical variables of the two groups, and the independent sample T-test or Mann-Whitney U-test was used to compare the continuous variables of the two groups. Kaplan-Meier (Log rank) method was used for survival analysis. Univariate Cox regression analysis was used to identify independent predictors of OS and DFS. Variables with a p value of <0.05 in univariate analysis were included in multivariate analysis. P value <0.05 was considered statistically significant.

Results

A total of 70 patients, 42 male and 28 female, were included in the study. 48 of the patients were under 65 years of age. The tumor localization was in the anterior 2/3 of the tongue in 19 (27.1%) patients, in the base of the tongue in 46 (65.7%) patients, and on both sides in 5 (7.1%) patients. Nine (12.9%) patients received neoadjuvant treatment (3 patients neoadjuvant chemotherapy [CT], 6 patients induction chemoradiotherapy [CRT]). All patients were operated. 53 patients received adjuvant therapy. Neo-adjuvant CT regimen was DCF (docetaxel 75 mg/m^2, cisplatine 75 mg/m^2, 5-fluorouracil 1000 mg/m^2/gün, 1-4 days). Patients receiving neoadjuvant/adjuvant CRT received RT concurrently with cisplatin 40 mg/m^2 weekly. Surgical pathology reports of 50 patients could be accessed. pTx was detected in 8 (16%) patients, pT1 in 11 (22%) patients, pT2 in 21 (42%) patients, pT3 in 9 (18%) patients, and pT4a in 1 (2%) patients. pNx was detected in 11 (22%) patients, pN0 in 14 (28%) patients, pN1 in 20 (40%) patients, pN2a in 4 (8%) patients, and pN2b in 1 (2%) patients. Grade 1 tumor was detected in 16 (22.9 %) patients, grade 2 tumor in 32 (45.7%) patients, and grade 3 tumor in 2 patients (2.9%). The clinical and pathological features of the patients are summarized in table 1 (Table-1).

The median follow-up period of the patients was 3.1 years. OS did not reach the median in the whole group and the 5-year OS was found to be 59%. The median DFS in the whole group was 4.1 (0.4-7.8) years.

Patients were divided into two age groups as ≤45 years and >45 years; <55 years and ≥55 years; <65 years and ≥65 years. OS did not reach the median in the first age group. 5-year median OS was 54% in patients aged 45 years and younger and 59% in patients over 45 years of age (p=0.872). The median OS was not reached in patients under 55 years of age, whereas it is 7 (2.1-12) years in patients aged 55 years and older (p=0.221). The median OS did not reach the median in patients under 65 years of age, and it was 4.4 years (0.9-8.2) in patients 65 years and older (p=0.140).

The median DFS was 2 (0.8-3.1) years in patients aged 45 years and younger and 4.5 (2.3-6.8) years in patients over 45 years of age (p=0.73). The median DFS was 5.9 (0.3-11.5)

Table 1. Demographic and clinicopathological characteristics of patients

			Median (Minimum;Maximum)	N=70 (%)
Age of diagnosis (years)			56 (22;92)	
Gender	Female			28 (40%)
	Male			42 (60%)
Age	<65 years			48 (68.6%)
	≥65 years			22 (31.4%)
Smoking	Female	Yes		9 (32.1%)
		No		19 (67.9%)
	Male	Yes		34 (80.9%)
		No		8 (19,1%)
Alcohol	No			55 (78.6%)
	Yes			15 (21.4%)
Comorbidity	No			36 (51.4%)
	Yes			34 (48.6%)
ECOG-PS	0			18 (25.7%)
	1			40 (57.1%)
	2			12 (17.2%)
Tumor location	2/3 anterior of the tongue			19 (27.1%)
	1/3 posterior of the tongue			46 (65.7%)
	Both sides			5 (7.1%)
Pathological T	Tx			8 (16%)
	T1			11 (22%)
	T2			21 (42%)
	T3			9 (18%)
	T4a			1 (2%)
Pathological N	Nx			11 (22%)
	N0			14 (28%)
	N1			20 (40%)
	N2a			4 (8%)
	N2b			1 (2%)
Extranodal extension	Negative			20 (40%)
	Positive			5 (10%)
	Unknown			25 (50%)
Perineural invasion	No			11 (22%)
	Yes			18 (36%)
	Unknown			21 (42%)
Lymphovascular invasion	No			17 (34%)
	Yes			10 (20%)
	Unknown			23 (46%)
Grade	Grade1			16 (22.9%)
	Grade2			32 (45.7%)
	Grade3			2 (2.9%)
	Unknown			20 (28.5%)
Neoadjuvant therapy	Yes			9 (12.9%)
	No			61 (87.1%)
Adjuvant therapy	No			17 (24.3 %)
	RT			9 (12.8%)
	CRT			44 (62.9%)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, RT: Radiotherapy, CRT: chemoradiotherapy
Surgical pathology reports of 50 patients could be accessed.

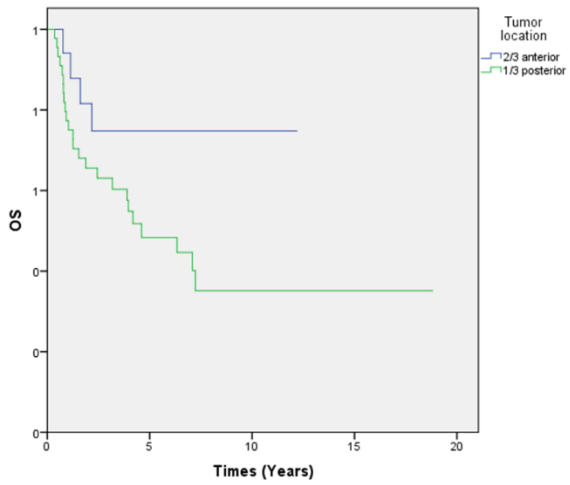

Figure 1. Kaplan-Meier Curve of Overall Survival by Tumor Location

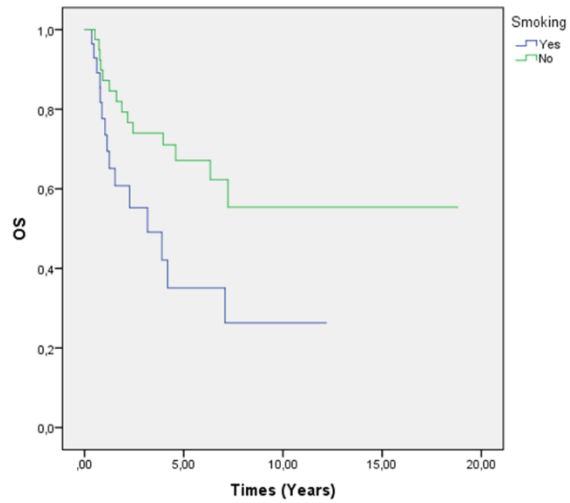

Figure 2. Kaplan-Meier Curve of Overall Survival by Smoking

years in patients <55 years of age, 4 (3.2-4.9) years in patients aged ≥55 years (p=0.450). The median DFS was 4.0 (0.1-7.9) years in patients <65 years of age, 4.5 (1.9-7.2) years in patients aged ≥65 years (p=0.951). There was no statistically significant difference between the groups in terms of median OS and DFS.

The median DFS was 5.9 (3.7-8.1) years in male patients and 2.2 (1.2-3.2) years in females (p=0.349). The median OS was 4.1

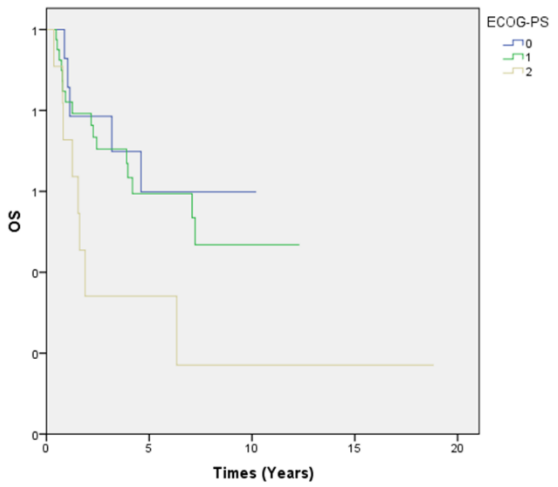

Figure 3. Kaplan-Meier Curve of Overall Survival by ECOG-PS

(1.1-8.2) years in female patients and was not reached in male patients (p=0.075).

When the patients were divided into two groups according to tumor location, median OS could not be reached in the 2/3 anterior tumors of the tongue, while the median OS was 6.9 (2.7-9.8) years in the 1/3 posterior tumors of the tongue (p=0.046) (Figure-1). While the median DFS could not be reached in the anterior 2/3 anterior tumors of the tongue, the median DFS was 3.8 (1.0-6.7) years in the 1/3 posterior tumors of the tongue (p=0.073). While the median OS was 7.2 (6.8-7.6) years in those who did not receive adjuvant therapy, it did not reach the median in those who received adjuvant therapy (RT or CRT) (p=0.877). While the median DFS was 6.5 (0.2-13.2) years in those who did not receive adjuvant therapy, it was 3.9 (1.7-6.1) years in those who received adjuvant therapy (RT or CRT) (p=0.317).

While the median OS was 3.1 (0.5-5.8) years in smokers, the median OS could not be reached in non-smokers (p=0.019) (Figure-2). While the median OS was 1.6 (0.9-2.2) years in the group of patients with ECOG PS of 2, the median OS could not be reached in

Table 2. Univariate and multivariate analysis for overall survival

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male (reference=female)	0.52 (0.24-1.12)	0.098		
Age at diagnosis	1.01 (0.98-1.04)	0.237		
Smoking- No (reference=yes)	0.43 (0.20-0.92)	**0.031***	0.37 (0.17-0.81)	**0.011***
ECOG-PS	1	**0.032***	1	
1 (reference=0)	1.1 (0.41-3.22)		1.13 (0.4-3.15)	**0.025***
2 (reference=0)	3.3 (1.1-10.4)		3.93 (1.26-12.23)	
Neoadjuvant therapy		0.323		
Yes (reference=no)	1.7 (0.59-4.96)			
Adjuvant therapy	1	0.952		
RT (reference=no)	0.85 (0.25-2.92)			
CRT (reference=no)	1.02 (0.41-2.49)			

ECOG PS: Eastern Cooperative Oncology Group Performance Status, RT: Radiotherapy, CRT: chemoradiotherapy

patients with ECOG PS of 0 and 1 (Figure-3) (p=0.054).

Smoking and ECOG PS were found to be prognostically significant factors in univariate and multivariate analysis for OS (Table 2).

Discussion

Most of the studies in the literature examined tongue cancers together with other cancers under the headings of oral cavity cancers or oropharyngeal cancers. Therefore, very few studies have been found examining tongue cancer (mobile tongue and base of tongue) under a separate heading. Therefore, we believe that this study will be a guide for future studies.

Physician's give more aggressive therapies to young patients to achive longer survival. Another important condition is that tongue cancer presenting at a young age is thought to be a poor prognostic factor [14, 15]. Besides, some recent studies [16, 17] that did not find a significant difference in OS between different age groups, there are also studies [7, 18-20] claiming that younger TSCC patients have better survival than older patients. Memorial Sloan-Kettering CancerCenter reported that there was no difference between age groups in terms of OS in patients with TSCC, but a higher rate of locoregional recurrence in younger patients (<40 years) [21]. In addition to these conflicting results reported in the literature, in this study, there was no statistically significant difference between age groups in terms of median OS and median DFS. But there was a remarkable point. The median DFS was numerically shorter in patients aged 45 years and younger than in patients over 45 years of age (2 years vs. 4.5 years). In two different studies comparing patients under 40 years of age and over 40 years of age, OS was similar between age groups, while recurrence rates were higher in the group below 40 years of age [22, 23].

In this study, the median OS was 7 years in patients over 55 years of age, it could not

reach the median in patients 55 years and younger; similarly, while it was 4.4 years in patients over 65 years of age, it could not reach the median in patients 65 years and younger. Although it does not reach statistical significance, these results may be a precursor to a better OS outcome at a younger age, with the prolongation of the follow-up period. But this remains only a hypothesis for now. Many studies have reported that there is no difference in biological behavior, genomic profiles, and frequencies of mutations, tumorigenesis mechanisms, gene-specific mutations and copy number changes between young and elderly patients with TSCC [24-28]. In this study, 52.2% of patients aged 65 and over had comorbidities such as diabetes mellitus, coronary artery disease, hypertension, and chronic obstructive pulmonary disease. Perhaps the reason why the OS rates in elderly patients, albeit numerically, are poor may be due to the existing comorbidities of these patients and their poor tolerance to CT or CRT.

Both the median OS and the median DFS were numerically lower in women than men (respectively, median OS: 4.1 years vs. not reached, median DFS: 2.2 years vs. 5.9 years).The fact that this difference did not reach statistical significance was attributed to the low number of patients. Similarly, in another study examining younger patients with TSCC, women have been shown to have higher recurrence rates than men [29]. Results from the SEER database support an increased incidence of TSCC, particularly in young white women. The increase in the incidence of TSCC with increasing smoking in women may have revealed more clearly that TSCC has a poor prognosis in women.

In this study, in the analysis by tumor location, median OS was found to be significantly higher in tumors located in the anterior 2/3 of the tongue (oral tongue cancer). Although median DFS was numerically better detected in tumors located in the anterior 2/3 of the tongue, statistical significance was not be obtained. According to the results of SEER database, which evaluated 74680 head and neck cancer patients between 1976 and 2015, it was revealed that oral TSCC showed a greater improvement in survival than other oral cavity cancers (37.0% in 1976-1985, 61.7% in 2006–2015). During 2006–2015, the 5-year conditional survival exceeded 90% only for oral TSCC and oropharyngeal SCC. It can be thought that early detection of the disease and the contribution of modern surgical methods to this survival are very important factors.

In this study, overall survival in smokers was shorter than in non-smokers. In a study, no association was found between smoking and DFS/OS in young oral TSCC patients [30]. However, there are also studies with similar results to our study. Previous studies showed that tongue neoplasia (tongue + tongue base) had a high prevalence of advanced disease in smokers, also showed that cancers of the tongue base were more aggressive in smokers [31, 32]. Several large studies reported that current smoking increases overall mortality in patients with head and neck cancer [33, 34]. Cigarette components increase tumor aggressiveness by increasing proliferation, angiogenesis, migration of cancer cells and decrease the response to cytotoxic cancer agents such as chemotherapy/radiotherapy [35, 36]. OS may be shorter in the smokers group due to these effects.

ECOG PS was found to be significant for OS in univariate and multivariate analysis in this study. When ECOG PS was divided into 0, 1, and 2 in the Kaplan-Meier analysis, no statistical difference was found between the groups, but OS was shorter in the group with ECOG PS of 2. This was attributed to the small number of patients in the groups separated according to ECOG PS. There are several studies showing poor ECOG PS were associated with a shorter OS. In a study of patients receiving palliative chemotherapy for

advanced bile duct cancer, poor ECOG PS was associated with shorter OS [37]. Similar results were obtained in patients with advanced melanoma [38].

Treatment strategies such as CRT or surgery following neoadjuvant treatment for TSCC have been shown without significant improvement in survival in many studies. In this study, when the patients were divided into two groups as those who received adjuvant treatment and those who did not, no difference was found between the groups in terms of OS and DFS. Considering that the patients who did not receive adjuvant therapy consisted of patients with T1-2/N0 and without poor risk factors (extranodal extension, positive or close margin, perinoral invasion, vascular invasion, etc.), the fact that patients have poor risk factors, have T3 disease and above, and/or node positivity worsens the prognosis. It suggests that the contribution of adjuvant therapy is limited at this stage. Furthermore, this result demonstrates the importance of an effective surgery ± neck dissection in locally/locally advanced disease.

Limitations

This study had some limitations. The first limitation was that it was a retrospective study. We could not obtain information from the patient files about the surgical method and whether neck dissection was added or not. In this study, nine patients were given neo-adjuvant therapy. However, the neoadjuvant treatment indications of these patients could not be obtained from the patient files. This was another limitation of our study. Although the National Comprehensive Cancer Network stated that HPV positivity or HPV negativity did not make a difference when starting adjuvant treatment for locally advanced oropharyngeal cancer patients, we could not evaluate the effect of HPV on survival.

Conclusion

In conclusion, in TSCC patients, OS was found to be longer in oral cavity TSCC patients than in base of tongue cancers. OS was found to be significantly longer in non-smokers. There was no difference in OS or DFS, especially in patients who received and did not receive adjuvant therapy, may indicate the importance of effective surgery ± neck dissection in patients with locally advanced TSCC. Base of tongue and oral tongue cancers should be considered as a specific title, without being under the headings of oropharyngeal cancers or oral cavity tumors. So, it will be guiding in terms of showing the differences between the two groups.

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Original Article

Comparison the Clinical Features of Newly Diagnosed Multiple Myeloma Patients According to CD23 Expression Status

Yeni Tanı Multipl Miyelom Hastalarının CD23 Ekspresyon Durumuna Göre Klinik Özelliklerinin Karşılaştırılması

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ABSTRACT

Introduction: The aim of the study was to evaluate the relationship between CD23 expression status and clinical features in multiple myeloma patients.
Materials and methods: We retrospectively analyzed the data of 196 patients diagnosed with multiple myeloma in our institution between May 2010 and August 2018.
Results: Compared to the CD23 negative group, in the CD23 positive group, the incidence of anemia was significantly lower, and the incidence of CD20 expression and the rate of R-ISS stage 1 patients was significantly higher. No similar association was found between R-ISS and other cell surface markers
Discussion: In conclusion, clinical presentations of multiple myeloma patients with aberrant CD23 expression show some clinical differences from those without. The fact that MM patients with CD23 expression were clustered in the favorable prognostic group according to R-ISS drew attention to its prognostic value. For MM patients, the addition of CD23 to the routine flow cytometry panel may be considered. In this respect, examination of CD23 expression is required in a larger group of cases to assess its prognostic value in MM.

Keywords: Multiple myeloma, Immunophenotyping, Flow cytometry, Cytogenetics, R-ISS

ÖZET

Giriş: Çalışmanın amacı, multipl miyelom hastalarında CD23 ekspresyon durumu ile hastaların klinik özellikleri arasındaki ilişkiyi değerlendirmektir.
Gereç ve yöntemler: Mayıs 2010 ile Ağustos 2018 tarihleri arasında kurumumuzda multipl miyelom tanısı alan 196 hastanın verilerini retrospektif olarak inceledik.
Bulgular: CD23 negatif gruba kıyasla CD23 pozitif gurupta anlamlı olarak anemi insidansı düşük, CD20 ekspresyon insidansı yüksek ve R-ISS evre 1 hasta oranı fazla gözlendi. R-ISS ile diğer hücre yüzey markırları arasında ise benzer bir ilişki bulunmadı.
Tartışma: Sonuç olarak, aberran CD23 ekspresyonu olan multipl miyelom hastalarının klinik prezentasyonları bazı klinik farklılıklar göstermektedir. CD23 ekspresyonu olan MM hastalarının önemli kısmının R-ISS'ye göre iyi prognostik grupta yer alması CD23'ün prognostik değerine dikkat çekmiştir. MM hastaları için rutin akım sitometri paneline CD23'ün eklenmesi düşünülebilir. Bu açıdan, CD23'ün MM'deki prognostik değerini araştırmak için daha geniş bir vaka grubunda CD23 ekspresyonunun incelenmesi gereklidir.

Anahtar kelimeler: Multipl miyelom, İmmünofenotipleme, Akış sitometrisi, Sitogenetik, R-ISS

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Introduction

Malignant plasma cells (PC) have abnormal antigen expressions that allow an analysis by flow cytometry to separate them from normal/reactive PC, so that can be used for diagnosing, monitoring residual disease and predicting the prognosis[1]. Multiple studies have demonstrated the prognostic value of antigen expression patterns by neoplastic PC[2–4]. Different results have been reported over the past years regarding the phenotype of clonal PC and clinical correlations, in MM. Nevertheless, prognostic value of immuno-phenotyping in MM remains questionable. And also, it is reported that the potential prognostic impact of the immunophenotypic characteristics might be related to the underlying cytogenetic abnormalities[2,5]

CD23 is a transmembrane low-affinity IgE Fc receptor found on the cell surface and has activities associated with cytokine modulation and B-cell growth factor function[6]. CD23 is well described in some hematological malignancies and is particularly helpful in the differentiation of chronic lymphocytic leukemia from mantle cell lymphoma by flow cytometry[7]. Also, CD23 expression has been reported in approximately 10% of multiple myeloma cases at diagnosis. However, there is a limited data in the literature evaluating the role of CD23 in multiple myeloma, and this hypothesis has not been proved whether or not affecting the clinical outcomes in newly diagnosed patients with MM [8–10]. Therefore, we have retrospectively evaluated the immuno-phenotypic profile of the PCs including CD23 expression in a series of 196 patients with newly diagnosed multiple myeloma.

Materials and Methods

Patient Selection and Basic Characteristics: Between May 2010 and August 2018, 196 patients diagnosed with symptomatic multiple myeloma in our institution were included in this cross-sectional study. All data were recorded from patients' chart files and/or electronic medical records. Our retrospective study was conducted in accordance with the Declaration of Helsinki and institutional ethics committee approval was obtained.

The diagnosis of myeloma was established in each patient according to the criteria recently defined by the International Myeloma Working Group[11] and was staged according to the criteria of International Staging System (ISS) and R-ISS[12]. We have recorded the full clinical information including patient age, gender, laboratory parameters such as serum ß2-microglobulin, albumin, calcium, hemoglobin, lactate dehydrogenase, serum creatinine concentrations, and immuno-globulin type of monoclonal protein, image study such as lytic bone lesions and plasmacytoma, surface antigen expression patterns analyzed by Multicolor Flow Cytometry (MFC), and cytogenetic abnormalities before any therapy. Fluorescence in situ hybridization (FISH) analyses were performed in patients for detection of t (4;14), t (14;16), t (11;14), del(13q14), del(17p13) and del(11q22.3). MFC analysis was performed in in the Clinical Flow Cytometry Laboratory of our institution using antibodies against CD38, CD138, CD19, CD20, CD45, CD117, CD56, BCL-2 and CD23. The expression levels of CD19, CD20, CD45, CD117, CD56, BCL-2 and CD23 in CD38 and CD138 positive cells were evaluated using a six-color panel of antibodies. At least 70 000 events were routinely acquired using a FACS Canto II flow cytometer with FACSDIVA software (BD Biosciences). All analyses also included an isotype-matched control tube containing APC-labeled CD38 to establish the positive staining threshold for plasma cells. A surface antigen expression in patients was defined as positive when 20% of the CD138+ population expressed this antigen above the cutoff.

Table 1. Clinical and laboratory characteristics of the 196 patients enrolled in the study at diagnosis

Patients Characteristics	
Median age, y (range)	63 (35-85)
Gender, n (%)	
▪ Male	115 (58.7)
▪ Female	81 (41.3)
Type of M component, n (%)	
▪ IgG	101 (51.6)
▪ IgA	49 (25)
▪ IgM	2 (1)
▪ IgD	1 (0.5)
▪ Biclonal	1 (0.5)
▪ Light chain only	41(20.9)
▪ Non-secretory	1 (0.5)
R-ISS, n (%)	
▪ I	34 (17.3)
▪ II	124 (63.3)
▪ III	38 (19.4)
Hemoglobin, g/dL (range)	9.7 (5.4-15.3)
β2-microglobulin, mcg/mL (range)	5.6 (1.4-120)
Creatinine, mg/dL (range)	1 (0.4-11.2)
Calcium, mg/dL (range)	9.4 (5.5-15.4)
Albumin, g/dL (range)	3.6 (1.3-5.1)
Lactate dehydrogenase, U/L (range)	194 (88-851)
Lytic lesion, n (%)	123 (62.8)
Plasmacytoma, n (%)	34 (17.3)
CD19(+), n (%)	57 (29.1)
CD20(+), n (%)	20 (10.2)
CD117(+), n (%)	57 (29.1)
CD56(+), n (%)	146 (74.5)
CD23(+), n (%)	23 (10.2)
CD45(+), n (%)	32 (16.3)
BCL-2(+), n (%)	60 (30.6)

BCL-2, B-cell lymphoma 2; CD, Cluster of Differentiation; Ig, Immunoglobulin; R-ISS,The Revised International Staging System.

Statistical Analysis

All statistical analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.). Kolmogorov-Smirnov tests were used to test the normality of the data distribution. The data are expressed as median, minimum, maximum, the percentages and numbers. The Pearson chi-square test was used to compare the categorical variables. Mann-Whitney U test was used for comparison of continuous variables between the CD23 positive and CD23 negative groups. A two-sided p value <0.05 was considered to be statistically significant.

Results

Clinical and laboratory characteristics of the 196 patients at diagnosis are shown in Table 1. The patients consisted of 115 men and 81 women ages ranging from 35 to 85 years. According to the R-ISS, 17.3% of patients were stage I; 63.3%, stage II; and 19.4%, stage III. Of 196 PCMs, 23 (10.2%) were found to be CD23 positive by MFC at diagnosis. As shown in Table 2, age, sex, creatinine, albumin, lactate dehydrogenase, beta-2 microglobuline and calcium level, bone lesions, expression of surface antigens were similar for patients with CD23 positive and for those with CD23 negative. Compared with those of CD23 negative patients, in CD23 positive patients, the rate of patients with hemoglobin value <10 g/dl was less (30% vs 55.7%, P=0.029) and CD56 positive patient rate was greater (35% vs. 7.4%, P<0.001). There was no significant relationship between t (11;14) and the CD23 level (p>0.05). There were no statistically significant differences between R-ISS score and the CD45, CD56, CD117, CD19, CD20, BCL-2 levels (all p>0.05); whereas CD23 levels were more expressed in R-ISS 1 score patients compared to the R-ISS 2 and R-ISS 3 patients (p=0.017).

Table 2. Demographical and clinically comparisons of the CD23 (+) and CD23 (-) patients

	CD23 (+) n=20	CD23 (-) n=176	p
Age, (median, min, max)	60.5 (41-83)	64 (35-85)	0.369
Male/Female, n/n	12/8	73/103	0.899
Hb level <10, n (%)	6 (30)	98 (55.7)	0.029*
Beta-2 microglobulin ≥5.5, n (%)	6 (30)	94 (53.4)	0.047*
LDH >240 IU/L, n (%)	3 (15)	48 (27.3)	0.236
Albumin <3.5g/dL, n (%)	7 (35)	69 (39.2)	0.715
Creatinine ≥ 2 mg/dL, n (%)	2 (10)	42 (23.9)	0.159
Calcium ≥ 11 mg/dL, n (%)	2 (10)	21 (11.9)	0.799
Lytic lesions, n (%)	12 (60)	111 (63.1)	0.788
CD19 (+), n (%)	8 (40)	49 (27.8)	0.257
CD20 (+), n (%)	7 (35)	13 (7.4)	<0.001*
CD117 (+), n (%)	7 (35)	50 (28.4)	0.539
CD56 (+), n (%)	14 (70)	132 (75)	0.627
Bcl-2 (+), n (%)	7 (35)	53 (30.1)	0.653
CD45 (+), n (%)	3 (15)	29 (16.5)	0.865

BCL-2, B-cell lymphoma 2; CD, Cluster of Differentiation; Ig, Immunoglobulin; LDH, Laktat dehidrogenaz; R-ISS,The Revised International Staging System. *, p<0.05 regarded as statistically significant.

These results were also found similar using the ISS scores.

There were no statistically significant differences between FISH results [TP53 deletion at 17p13, t (4;14), t (14;16), 11q22 deletion, 13q14, and t (11;14)] and the CD45, CD56, CD117, CD19, CD20, BCL-2 and CD23 levels (all p>0.05).

Discussion

This is the first study evaluating and comparing the clinical outcomes of the newly diagnosed MM patients based on their CD23 expressions. The main finding of this study is: The clinical presentation of multiple myeloma patients with aberrant CD23 expression showed less anemia and more frequent CD20 expression compared to patients without CD23 expression, and there was also a correlation between CD23 expression and R-ISS.

The clinical course of multiple myeloma is various; new cytogenetic mutations may develop and available antigenic markers may be lost in the course of the disease, or the aberrant antigen expressions may be gained. For a disease with such heterogeneity and a dynamic change, predicting prognosis may be difficult. Although an effective prognostic classification is made with current prognostic tools such as ISS and R-ISS, there may be some patients with a different prognosis than expected despite this classification. Therefore, the relationship between immunophenotypic characteristics and prognosis from past to present has been the subject of many studies. An antigen expression at diagnosis may be associated with some clinical features or may provide a cross-sectional prognostic information. Although there are many studies on this subject, CD23 is not well described in

multiple myeloma compared to other hematological malignancies.

Previous studies investigating CD23 expression in MM patients focused on the correlation between CD23 and t (11,14). However, contrary to these studies, there was no correlation between CD23 expression and t (11,14) in our study.

Ruiz-Argüelles et al.[8] identified CD23 as an uncommon antigen and interrelated it with a possible poor prognosis. Although the number of cases was small, Walters et al.[9] reported the rate of CD23 expression in PCM as 10%. CD23 expression did not correlate with laboratory data, but all five CD23 positive cases displayed abnormalities of chromosome 11. Based upon this report, the relationship between t (11;14) positivity and CD23 expression has been investigated by Buonaccorsi et al.[10] They performed a retrospective study on 42 bone marrow biopsies from patients with PCM who had a documented t (11;14) (q13; q32) by conventional cytogenetic analysis or FISH. Of 42 PCMs, 19 (45.2%) were found to be CD23(+) by IHC. They reported that, unlike our results, there was no difference in clinical stage between CD23(+) and CD23(-) patients. This can be explained by the different design of their study in which CD23 related analyzes were performed only in patients with t (11,14) positive. As is known, t (11,14) is defined as standard risk within the cytogenetic risk classification of MM. Therefore, these CD23 related results obtained from (11,14) positive patients cannot be generalized to all MM patients.

Conclusion

The presence of a plasma cell immunophenotype correlating with R-ISS, an accepted tool for prognostic classification of multiple myeloma, may indirectly suggest a prognostic value. As a result, it suggests the idea that CD23 can be integrated into the flow cytometric immunophenotyping panel for multiple myeloma. Due to the correlation observed in our cohort between CD23 and R-ISS, additional examination of a larger set of cases is necessary in order to assess the prognostic relevance of CD23 expression in MM.

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Original Article

Non-Infectious Complications in Patients with Allogeneic Hematopoietic Stem Cell Transplantation- Single Center Experience from Eastern Anatolia

Doğu Anadolu'dan Tek Merkez Deneyimi- Allojenik Hematopoietik Kök Hücre Nakli Yapılan Hastalarda Enfeksiyöz Olmayan Komplikasyonlar

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ABSTRACT

Introduction: The aim of this study was to investigate late non-infectious complications in patients with allogeneic hematopoietic stem cell transplantation (HSCT).

Materials and Methods: The records of 143 patients who underwent allogeneic HSCT between 01.02.2011 and 31.12.2018 in Inonu University Turgut Özal Medical Center Department of Hematology were retrospectively reviewed.

Results: In our study, late non-infectious complications were seen in 68 % of the patients. Graft Versus Host Disease (GVHD) was observed in 43 patients (33%) %. The most common GVHD involvement sites were skin and liver.

It was determined that the number of CD 34 (+) cells had a significant effect on the development of chronic GVHD (p=0,01) and late stage complications (p=0,016). Chronic GVHD and late complication rates were found to be lower in the group given high CD 34 (+) cell count.

When the patients were grouped according to the preparation regimens, statistically significantly more complications were observed at the rate of 78.8% in the patients in the myeloablative regimen group (p=0.005).

It was observed that the rate of recurrence of the primary disease, renal complications and neurological complications was higher in the 90-120th days after transplantation. Ocular and GVHD complications were more likely to develop later. It was observed that endocrine complications were encountered equally in both early and late periods.

Discussion: It was seen that, late complications were common in patients who underwent allogeneic HSCT and these complications were mostly related to GVHD and GVHD treatment.

Keywords: Hematopoietic stem cell transplantation, Late complications, non-infectious complications, GVHD

ÖZET

Giriş: Bu çalışmanın amacı, allojenik hematopoietik kök hücre transplantasyonu (HSCT) olan hastalarda geç enfeksiyon dışı komplikasyonları araştırmaktı.

Gereç ve Yöntemler: İnönü Üniversitesi Turgut Özal Tıp Merkezi Hematoloji Anabilim Dalı'nda 01.02.2011-31.12.2018 tarihleri arasında allojenik HKHT yapılan 143 hastanın kayıtları retrospektif olarak incelendi.

Bulgular: Çalışmamızda hastaların %68'inde geç enfeksiyon dışı komplikasyonlar görüldü. Graft Versus Host Hastalığı (GVHD) 43 hastada (%33) gözlendi. En yaygın GVHD tutulum bölgeleri cilt ve karaciğerdi.

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CD 34 (+) hücre sayısının kronik GVHD gelişimi (p=0,01) ve geç dönem komplikasyonları (p=0,016) üzerinde anlamlı etkisi olduğu belirlendi. Yüksek CD 34 (+) hücre sayısı verilen grupta kronik GVHD ve geç komplikasyon oranları daha düşük bulundu.
Hastalar hazırlık rejimlerine göre gruplandırıldığında miyeloablatif rejim grubundaki hastalarda %78,8 oranında istatistiksel olarak anlamlı derecede daha fazla komplikasyon gözlendi (p=0,005).
Nakil sonrası 90-120. günlerde primer hastalık, böbrek komplikasyonları ve nörolojik komplikasyonların tekrarlama oranlarının daha yüksek olduğu gözlendi. Oküler ve GVHD komplikasyonlarının daha sonra gelişmesi daha olasıydı. Endokrin komplikasyonların hem erken hem de geç dönemlerde eşit oranda görüldüğü gözlendi.
Tartışma: Allojenik HKHT yapılan hastalarda geç komplikasyonların sık görüldüğü ve bu komplikasyonların daha çok GVHD ve GVHD tedavisi ile ilişkili olduğu görüldü.

Anahtar kelimeler: Hematopoetik kök hücre nakli, Geç komplikasyonlar, non-infeksiyöz komplikasyonlar, GVHD

Introduction

Hematopoietic stem cell transplantation (HSCT) is a treatment method that is being used more and more in the curative treatment of many malignant and non-malignant diseases. In allogeneic HSCT, donors are classified as fully matched, haploidentic (semi-matched) and incompatible according to their HLA compatibility with the recipient. Regimens in which the patient's bone marrow is suppressed with high-dose cytotoxic chemoradiotherapy are myeloablative regimens, and regimens in which bone marrow is suppressed with minimal immunosuppression are non-myeloablative regimens [1]. Non-myeloablative regimens are generally applied to people over 55 years of age with comorbidities [2].

Early and late complications of treatment are more common [3]. Early and late complications have a great impact on mortality and morbidity [4]. The main complications that occur in the late period are; chronic Graft Versus Host Disease (GVHD), secondary malignancies, infections, pulmonary complications, cardiac toxicity, endocrine complications. In addition to these, complications of some other organ systems related to treatment may also be seen [5].

GVHD, which is one of the late complications, can also be seen in HLA-matched transplants and affects many organs and systems. Standard prophylaxis regimens given to prevent the development of GVHD and drugs used in its treatment may also lead to various complications in the late period. Late complications were attributed to the primary disease, donor compliance, preparation regimen, steroid use, various drugs used, and many other factors.

The important thing is to anticipate these complications and manage them successfully. Successful treatment of early and late complications will contribute to prolonging survival and improving quality of life. Non-infectious complications in patients wıth allogeneic hematopoietic stem cell transplantation is may be important in these population.

It is aimed to investigate late stage non infectious complications and the factors affecting it.

Materials and Methods

Between 01.02.2011-31.12.2018, 143 patients who had allogeneic HSCT at İnönü University Turgut Özal Medical Center adult stem cell and bone marrow transplant center were fol-

lowed up in our center for at least 3 months were included in the study. Approval was obtained from the Inonu University Malatya Clinical Research Ethics Committee with the date of 02.07.2019 and the approval number

2019/277. The study was conducted in accordance with the Helsinki declaration.

Age, gender, disease subtype, preparation regimen, late complications of our patients were determined through the hospital automation system. Late complications of the patients were considered as complications occurring 100 days after transplantation. Our study was retrospective and no invasive procedure was performed on the patients.

Statistical analyses

Research data was uploaded to the computer environment via "SPSS (Statistical Package for SocialSciences) for Windows 22. Descriptive statistics were presented as mean±standard deviation, median (minimum-maximum), and percentage. Pearson Chi-Square Test and Fisher's Exact Test were used to evaluate categorical variables.

The conformity of the variables to the normal distribution was examined using the Kolmogorov-Smirnov Test. The Mann-Whitney U Test was used as a statistical method for the statistical significance between two independent groups for the variables that were not found to fit the normal distribution. Statistical significance level was accepted as $p<0.05$.

Results

Of the 143 patients included in the study, 60 (42%) were female and 83 (58%) were male. The median age was 41 (18-65) years. In our study, 7 different preparation regimens were used before hematopoietic stem cell transplantation. Peripheral-derived stem cell transplantation was performed in all patients. The demographic and clinical characteristics of 143 patients are given in Table 1.

The distribution of the patients included in the study according to the chemotherapy preparation regimen they received before HSCT is given in Table 2.

When the amount of CD34 (+) cells given to the patients was examined, the minimum amount of CD34 (+) cells was 4.76 x 10^6/kg, the maximum was 15.75 x 10^6/kg, and the median value was 7.45 x 10^6/kg.

When the donors of 143 patients who underwent allogeneic HSCT were examined, 57 were female and 86 were male. The age range was 12-67 years and the median value was 40.

In total, 123 patients underwent relative and 20 patients underwent unrelated transplants, and nine patients underwent haploidentic transplants.

One hundred and twenty five of the patients were transplanted in the first complete remission and 18 in the second complete remission.

When the development of chronic GVHD of the patients was examined, it was seen that chronic GVHD developed in 43 patients (33%). The distribution of GVHD developed in patients who underwent allogeneic HSCT according to the site of involvement is given in Table 3.

There was no effect of patient age, donor age, blood group compatibility, gender, gender match, engraftment time on the development of chronic GVHD. It was determined that the number of CD 34 (+) cells had a significant effect on the development of chronic GVHD (p=0,01) and late stage complications (p=0,016). Chronic GVHD and late complication rates were found to be lower in the group given high CD 34 (+) cell count.

The development rates and times of hepatic complications in the patients were examined. Liver function tests elevation was detected for

Table 1. Demographic and clinical characteristics of our patients

	Patients with complication(n=99)	Patients without complication (n=44)	P value
Age,median (range)	41 (18-65)	38 (18-65)	0,4
Gender (male:female)	58:41	25:19	0,8
Gender Compatibility			0,5
Present, n	52 (%52,5)	21(47,7%)	
Absent, n	47(%47,5)	23(52,2%)	
Diagnosis			
Acute myeloid leukemia, n	57 (57,5%)	26 (59,9%)	
Acute lymphoblastic leukemia, n	25 (25,2%)	7 (15,9%)	
Myelodisplastıc syndrome, n	5 (5,05%)	1 (2,27%)	
Non-hodgın lymphoma, n	4 (4,04%)	1 (2,27%)	
Others, n	8 (8,08%)	9 (20,4%)	
Blood Group Compatibility			0,6
concordant, n	61 (61,6%)	22 (50%)	
major mismatch, n	16 (16,1%)	9 (20,4%)	
minor mismatch, n	11 (11,1%)	7 (15,9%)	
mix mixmatch, n	11(11,1%)	6 (13,6%)	
Donor age, median (range)	40 (12-65)	37 (15-67)	0,899
Relationship			0,1
Matched sibling donor, n	87 (87,8%)	42 (95,4%)	
Matched unrelated donor, n	12 (12,1%)	2 (4,5%)	
Cd34 (+) x 10^6 cell, median(range)	7 (4,7-15,7)	8 (5-13)	0,016
Engraftment time, median (range)	20 (12-35)	18 (11-35)	0,970

Table 2. Distribution of patients according to the preparation regimen

Conditioining chemotherapy regimen	n	%
Busulfan-Cyclophosphamide (Bu-Cy)	89	62.3
Busulfan-Fludarabin-Anti-thymocyte globulin (Bu-Flu-ATG)	26	18.2
Fludarabine–Amsacrin–Cytarabine (Flu-Ams-Siter)	10	6.9
Treosulfan-Flu-ATG	8	5.6
Fludarabine, Anti-thymocyte globulin, Thiotepa (Flu-ATG-Tio)	4	2.8
Busulfan, Cyclophosphamide, Etoposide (Bu-Cy-Eto)	4	2.8
Fludarabine, Anti-thymocyte globulin, Cyclophosphamide (Flu-ATG-Cy)	2	1.4

Table 3. Distribution of GVHD by site of involvement

Site of involvement	n	%
Skin	10	23
Skin and liver	6	16
Gastrointestinal system (GIS)	2	3
GIS and skin	2	3
Gıs and liver	1	2
Kidney	1	2
Lung	1	2

unknown reasons in five patients, due to drug toxicity in 12 patients, iron overload in six patients, associated with GVHD in 19 patients, cholecystitis in one patient, cholestasis in three patients, viral hepatitis in two patients, and pancreatitis in two patients.

Type 2 diabetes mellitus in 11 patients, hypothyroidism in two patients, subclinical hyperthyroidism in two patients, infertility in two patients, early menopause in two patients, euthyroid sick syndrome in one patient, and inappropriate antidiuretic hormone syndrome in one patient were detected.

HSV infection in any region was seen in five of the patients, zona zoster in 16, xerosis in three, paraneoplastic ichthyosis in one and seborrheic dermatitis in one of the patients.

Ocular complications were seen in 18 patients, including conjunctivitis in six patients, dry eye in five patients, blepharitis in two patients, keratitis in one patient, uveitis in one patient, preseptal cellulitis in one patient, subretinal hemorrhage in one patient, and papilledema in one patient.

When the patients were grouped according to the preparation regimens, statistically significantly more complications were observed at the rate of 78.8% in the patients in the myeloablative regimen group (p=0.005).

It was observed that the rate of recurrence of the primary disease, renal complications and neurological complications was higher in the 90-120th days after transplantation. Ocular and GVHD complications were more likely to develop later. It was observed that endocrine complications were encountered equally in both early and late periods.

Discussion

Being able to predict and manage complications that may develop in the early and late period after transplantation has become one of the most important factors affecting the success of transplantation.

Similarly, the prevalence of AML and ALL diagnoses in our study and other studies reviewed confirms that transplantation is mostly performed with leukemia indications and that stem cell transplantation is an effective treatment option in acute leukemia [6,7].

It was determined that the preparatory regimes applied in each center differed, and it was observed that each center applied a preparatory regime in line with its own experience and possibilities [8,9].

In a study involving 121 patients between 2003 and 2009, the mean duration of neutrophil engraftment was found to be 15 (8-41) and when analyzed according to blood group compatibility, it was seen that blood group compatibility had no effect on engraftment duration [10].

In our study, the median value of the mean neutrophil engraftment time was determined as 19 (11-35) days.

In our study, it was observed that blood group compatibility had no effect on the development of any late complications, the development of chronic GVHD, and the engraftment times in line with the literature. In the study published by Nina Worel in 2015, Klump et al.'s study on 240 patients found that ABO mismatch had no effect on the development and severity of chronic GVHD [11,12].

In the studies, it was found that the amount of stem cells given was effective on the success of transplantation and the ideal CD34 (+) amount was determined as $4x10^6$/kg, and the lower limit value was determined as $2x10^6$/kg.

In our study, a statistically significant relationship was found between CD34 (+) cell count and chronic GVHD. It was found that chronic GVHD developed more in the group with low CD34 (+) number. In the study of Przepiorka et al. on 116 patients, CD34 (+) count was $8.3x\ 10^6$. There was no difference in terms of the development of chronic GVHD in patients with and above / kg [13]. In the study of Jose et al., it was observed that the incidence of grade 2-4 chronic GVHD

increased as the number of infused CD34 (+) cells increased [14]. In the literature, there are publications claiming that the number of CD34 (+) cells has an effect on engraftment, as well as publications saying that it has no effect.

In the study of Klump et al. on 240 patients, it was observed that blood group compatibility had no effect on the development of chronic GVHD [12]. In the study, the development of chronic GVHD was observed in the median 6 months [3-17]. In the same study, it was determined that the diagnosis of gender and blood group compatibility, and the preparation regimen had no effect on the development of cGVHD [15]. Since the distribution of disease diagnoses was not proportional in our study, analysis was not performed in terms of the development of GVHD according to the diagnoses. It was determined that more chronic GVHD was seen in the 12-month period, and age, donor age, and gender compatibility had no effect on chronic GVHD, in line with the literature.

It was observed that significantly more complications developed in the group given myeloablative regimen, one of the preparatory regimens. It was observed that there were patients who were given Treosulfan-Flu-ATG and Cyclo-Flu-ATG with the least late complications.

In our literature review, there is no publication on the analysis of patients with and without any late system complications, and our study is original in this regard. The fact that the development of GVHD was mostly observed in patients with any system complication in our study showed us that the development of complications is closely related to GVHD itself and its treatment.

The major limitation of our study was that it was retrospective. The relatively small number of patients was also a limiting factor. Multicenter studies with more patients are needed.

Conclusion

In our study, patients who were followed up for at least three months after HSCT were included in the study. It was determined that the number of CD 34 (+) cells had a significant effect on the development of chronic GVHD and late stage complications. Chronic GVHD and late complication rates were found to be lower in the group given high CD 34 (+) cell count. When the patients were grouped according to the preparation regimens, statistically significantly more complications were observed at the rate of 78.8% in the patients in the myeloablative regimen group.

In order to evaluate the complication analysis more objectively, there is a need for prospective, multicenter studies in which these tests are examined at regular intervals in all patients.

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Original Article

Platelet-to-Lymphocyte Ratio and Neutrophil-to-Lymphocyte Ratio in Patients with Locally Advanced Gastric Cancers

Lokal İleri Mide Kanserli Hastalarda Trombosit Lenfosit Oranı ve Nötrofil Lenfosit Oranı

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ABSTRACT

Aim: This study aimed to determine the relationship between preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) levels with prognosis of locally advanced gastric cancers (GC).

Methods: This was a retrospective single centre study conducted between January 2011 and January 2016 at the Department of General Surgery of Osmangazi University Medical Faculty. A total of 83 patients histologically diagnosed with GC who received curative surgery were included in the study.

Results: Median (first-third quartile) NLR value was 2.62 (1.93-4) and PLR value was 148.1 (117.73-221.43). ROC analysis did not yield optimal cut-off values for NLR and PLR to predict mortality. Lower overall survival rates were reported in GC patients with extracapsular invasion, perineural invasion, lymphovascular invasion, surgical margin positivity, various clinical findings (leakage, infection and recurrence), and lower albumin level (all, $p<0.05$). Cox regression analysis demonstrated that preoperative NLR and PLR were non-significant factors for mortality ($p=0.302$ and 0.147, respectively). Tumour size, perineural invasion, N3 stage, leakage and lower albumin level were independent prognostic determinants for mortality.

Conclusion: Our results indicate that preoperative NLR and PLR were not associated with prognosis and could not be used as prognostic indicators for mortality in patients with GC. Greater tumour size, perineural invasion, N3 stage, leakage and hypoalbuminemia were significantly associated with prognosis. Further prospective studies with longer patient follow-up and larger sample sizes will help to verify our current data on prognostic indicators for GC.

Keywords: Gastric cancer, NLR, PLR, prognosis, overall survival

ÖZET

Amaç: Bu çalışma, ameliyat öncesi nötrofil-lenfosit oranı (NLO) ve trombosit-lenfosit oranı (PLO) düzeylerinin mide kanserinin (MK) prognozu ile ilişkisini belirlemeyi amaçladı.

Gereç ve Yöntem: Bu, Ocak 2011-Ocak 2016 tarihleri arasında Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Genel Cerrahi Kliniğinde yürütülen retrospektif tek merkezli bir çalışmadır. Çalışmaya histolojik olarak GK tanısı konan ve küratif cerrahi uygulanan toplam 83 hasta dahil edildi.

Bulgular: Medyan (1.-3. çeyrek) NLO değeri 2.62 (1.93-4) ve PLO değeri 148.1 (117.73-221.43) idi. NLO ve PLO ile mortaliteyi tahmin etmek için yapılan ROC analizinde uygun bir kesim noktası elde edilmedi. Ekstrakapsüler invazyon, perinöral invazyon, lenfovasküler invazyon, cerrahi sınır pozitifliği, çeşitli klinik bulgular (sızıntı, enfeksiyon ve nüks) ve düşük albümin düzeyi ($p<0.05$) olan MK hastalarında daha düşük genel sağkalım oranları belirlendi. Cox regresyon analizi, preoperatif NLO ve PLO'nun mortalite için anlamlı olmayan faktörler olduğunu gösterdi (sırasıyla $p=0,302$ ve 0,147).

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Tümör boyutu, perinöral invazyon, N3 evresi, sızıntı ve düşük albümin düzeyi mortalite için bağımsız prognostik belirleyiciler olarak bulundu.
Sonuç: Sonuçlarımız, preoperatif NLO ve PLO'nun prognozla ilişkisinin olmadığını ve MK'li hastalarda mortalite için prognostik göstergeler olarak kullanılamayacağını göstermektedir. Daha büyük tümör boyutu, perinöral invazyon, N3 evresi, sızıntı ve hipoalbüminemi prognoz ile anlamlı olarak ilişkiliydi. Hastaların daha uzun süre takip edildiği ve daha büyük örneklem büyüklüklüğüne sahip ileri prospektif çalışmalar, MK için prognostik göstergeler hakkındaki mevcut verilerimizi doğrulamaya yardımcı olacaktır.

Anahtar Kelimeler: Mide kanseri, NLO, PLO, prognoz, genel sağkalım

Introduction

Gastric Cancer (GC) is the third leading cause of cancer-associated mortality, causing about 800,000 deaths worldwide, partially because most patients are diagnosed at an inoperable, advanced stage of disease [1]. Patients usually present with regional or distant metastasis at the time of diagnosis, and their overall 5-year survival still remains below 50%, even with potentially curative surgery [2]. Management approaches to GC are primarily based on clinical prognosis assessment via the tumour node metastasis (TNM) staging system, but patients defined to have the same TNM stage demonstrate heterogeneous clinical course and varying prognosis [3]. In addition, some methods, including magnetic resonance imaging, computed tomography and endoscopic ultrasonography, may be helpful in predicting preoperative tumour stage and prognosis to some extent, but they are expensive and do little to eliminate uncertainty [4]. The ability to identify individualized risk factors and estimate prognosis are essential to implement optimal management and follow-up strategies. Although various factors have been investigated to classify survival in patients with GC, there is still an urgent need for timesaving, reliable and routine prognostic indicators associated with prognosis.

Recently, in vivo and in vitro studies have reported that the tumour microenvironment is associated with both systemic and local inflammatory response and may play a critical role in cancer tumorigenesis and progression through tumour proliferation, invasion, angiogenesis and metastasis [5]. Given the relationship between inflammatory response and overall survival, inflammation-based parameters, including C-reactive protein, IL-6, albumin, Glasgow prognostic score, platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), have been demonstrated to have prognostic value in cancer patients [6]. NLR and PLR are determined simply, by routine laboratory assessment and are widely used to assess the extent of systemic inflammatory response for various types of cancer and have been valuable to predict prognosis in patients with cancer [7]. However, the prognostic significance of preoperative NLR and PLR levels for GC remains complicated and imprecise.

The aim of the study was to determine the associations between preoperative NLR and PLR values and clinicopathological features of locally advanced GC and to investigate their prognostic value in locally advanced GC patients who underwent surgery.

Materials and Methods

This was a retrospective single centre study conducted between January 2011 and January 2016 at the Department of General Surgery of Osmangazi University Medical Faculty. Ethical approval was obtained from the local ethics committee. A total of 83 patients histologically diagnosed with GC who received curative surgery were included in the study. The inclusion criteria for patients involved the following criteria: histo-pathologically proven diagnosis of GC,

complete clinical and follow-up data, and presence of all relevant preoperative biochemical data, including complete blood count (CBC) and albumin levels. Patients with anaemia, hepatic disorder, acute infection, autoimmune or endocrine disorders, haematological diseases, remnant gastric cancer, synchronous or metachronous cancer, those using corticosteroids in the last six months or any medication that could affect biochemical analyses, and those had received neoadjuvant therapy or had undergone emergency gastrectomy for bleeding or perforation were excluded from the study. In total, 20 patients were excluded due to these exclusion criteria. All research procedures were assessed and approved by the Research Ethics Committee of Osmangazi University and were carried out in agreement with the ethical standards specified in the Declaration of Helsinki. Written informed consent from patients was deemed unnecessary due to the retrospective design of our study.

Demographic characteristics, clinical data (histology, size, differentiation and primary location of GC), type of surgical intervention, Lauren classification, clinical TNM stage (in accordance with the pathological classification criteria of American Joint Committee on Cancer Staging/UICC-TNM for GC), the numbers of lymph nodes and metastatic lymph nodes, presence of perineural, lymphovascular or extracapsular invasion, the length of hospitalization, and clinical outcomes, including the presence of leakage or infection, recurrence status and final status were obtained from the hospital records of each patient [8,9]. Patients were evaluated with clinical and radiological examinations every 3 to 6 months. Clinical outcomes, including recurrence and causes of death were examined through reviewing medical records or direct questioning of a family member. The last follow-up examination was carried out in January 2016. Overall survival (OS) was defined as the time from the date of performed surgical procedures to the date of last follow-up or mortality.

Blood samples were obtained preoperatively from the antecubital vein for the measurement of CBC and albumin. Complete blood count, including neutrophil and lymphocyte levels, platelet count and haemoglobin value, was measured with the Mindray BC-6800 auto-analyser (Mindray Electronics Co, Ltd, Shenzhen, China). The NLR was calculated as the neutrophil level divided by the lymphocyte level. The PLR was determined as the platelet count divided by the lymphocyte level. Serum albumin levels were determined via the photometric method on an ADVIA 2400 autoanalyzer (Siemens, Munich, Germany). Analytical procedures of all biochemical markers were carried out within one hour after venepuncture.

Statistical analysis

All analyses were performed on SPSS v21 (IBM, Armonk, NY, USA). For the normality check, the Kolmogorov-Smirnov test with Lilliefors correction was used. Data are given as mean ± standard deviation or median (first quartile-third quartile) for continuous variables according to normality of distribution, while frequency (percentage) was used for categorical variables. NLR and PLR of the alive and mortal cases were analysed with the Mann-Whitney U test. Survival times were calculated with the Kaplan-Meier method. Between-group comparisons of the survival times were performed with the Log rank test. We included age and gender as main characteristics, continuous variables and the factors which were found to be significant ($p<0.05$) in Kaplan Meier Analysis as univariate analysis into multivariate analysis and further checked these factors with Cox regression analysis (forward conditional method). p values of <0.05 were accepted as statistically significant results.

Results

The mean age of patients with GC was 63.82 ± 13.97 years and most of them were male (n = 56, 67.47%). Gastric adenocarcinoma was diagnosed in 56 (67.47%) patients, singlet ring cell adenocarcinoma in 25 (30.12%) patients, and mucinous adenocarcinoma in two patients according to histopathological examinations. Surgical procedures were: total gastrectomy in 59 (71.08%) patients, subtotal gastrectomy in 23 (27.71%) patients, and laparoscopic total gastrectomy in one patient. Tumour locations were: the distal third in 30 (36.14%) patients, the central third in 25 (30.12%) patients, and the proximal third in 24 (28.92%) patients. Linitis plastica was present in four (4.82%) patients. Thirty-four (40.96%) patients presented with extra-capsular invasion, 59 (71.08%) with perineural invasion and 53 (63.86%) with lymphovascular invasion. Adjuvant chemo-therapy was applied to 72 (86.75%) patients, while adjuvant radiotherapy was applied to 52 (62.65%) patients. During the follow-up period, recurrence was found in 33 (39.76%) patients and 64 (77.11%) patients died.

The median lymphocyte count was 1.6 (1.3-2.1) 103/µL, and neutrophil count was 4.8 (3.7-5.5) 103/µL. Mean platelet count was found to be 268.93 ± 90.69 103/µL. Haemo-globin values were 11.89 ± 1.98 g/dL. Laboratory results and clinical characteristics of GC patients are shown in Table 1. Median NLR was 2.60 (IQR: 1.89 - 4.00) in alive cases and was 2.65 (IQR: 1.93 - 4.04) in mortal cases (p=0.573). Median PLR was 138.00 (IQR: 116.80- 183.33) in alive cases and was 150.82 (IQR: 121.36- 221.79) in mortal cases (p=0.380). We performed ROC analysis to obtain optimal cut-off values for preoperative NLR and PLR values that could predict mortality in GC patients. However, analyses did not yield appropriate cut-off values for NLR and PLR to predict mortality (data not shown).

The Kaplan-Meier method was used to evaluate 5-year OS rates and comparison of variables was performed with Log rank test (Table 2). OS rates were 29.1 ± 5.2 % for all patients. Lower OS was reported in GC patients with extracapsular invasion, perineural invasion, lymphovascular invasion, surgical margin positivity and various clinical outcomes (leakage, infection and recurrence). Those with lower albumin levels also had lower OS rate (all, $p<0.05$). Patients with stage 3&4 tumours showed reduced OS rates than those with stage 1&2 ($p<0.001$). Patients presenting with T4 or N3 demonstrated lower OS rate compared to other stages ($p<0.001$). Age (<65) ($p = 0.450$), gender ($p = 0.482$), surgical procedure ($p = 0:165$), differentiation ($p = 0.241$), histology ($p = 0.442$), Lauren classification ($p = 0.064$), location ($p = 0.205$), lymph node dissection ($p = 0.139$), adjuvant chemotherapy ($p = 0.820$), and adjuvant radiotherapy ($p = 0.204$) were not associated with survival.

Cox regression analysis was performed to determine the best prognostic factors associated with mortality. Higher tumour size, the presence of perineural invasion, N3 stage, leakage, and lower albumin level were poor prognostic determinants for mortality (Table 3). Patients presenting with perineural invasion had a 2.481-fold higher risk of mortality than those without (HR: 2.481, 95% CI: 1.271-4.843, p=0.008) (Figure 1). Patients admitted with N3 stage tumour showed a 2.967-fold higher risk of death than other patients (HR: 2.967, 95% CI: 1.674-5.260, $p<0.001$) (Figure 2). Patients with leakage had an 8.546-fold higher risk of mortality than those without (HR: 8.546, 95% CI: 4.108-17.780, $p<0.001$) (Figure 3). Preoperative NLR and PLR were shown to be non-significant factors for mortality (p=0.302 and 0.147, respectively). Other variables included in the model, age (p=0.138), gender (p=0.106),

Table 1. Laboratory results and clinical characteristics of gastric cancer patients

Time between diagnosis and operation, days	16 (9 - 23)
Differentiation	
Poor	49 (59.04%)
Moderate	21 (25.30%)
Well	13 (15.66%)
Lauren classification	
Intestinal	35 (42.17%)
Diffuse	37 (44.58%)
Mixed	11 (13.25%)
Tumor size, mm	50 (30 - 80)
Number of lymph nodes	19 (13 - 33)
Number of metastatic lymph nodes	4 (1 - 13)
Lymph node dissection	
D1	18 (21.69%)
D2	41 (49.40%)
D1+	2 (2.41%)
D2+	22 (26.51%)
Surgical margin positivity	9 (10.84%)
T stage	
T1	12 (14.46%)
T2	4 (4.82%)
T3	34 (40.96%)
T4	33 (39.76%)
N stage	
N0	20 (24.10%)
N1	15 (18.07%)
N2	21 (25.30%)
N3	27 (32.53%)
M stage	
M0	82 (98.80%)
M1	1 (1.20%)
Length of stay in hospital, days	9 (6 - 12)
Leakage	13 (15.66%)
Infection	21 (25.30%)
Albumin, g/dL	3.96 ± 0.57
Neutrophil / Lymphocyte ratio	2.62 (1.93 - 4.00)
Platelet / Lymphocyte ratio	148.10 (117.73 - 221.43)
Follow-up time, months	25 (7 - 53)

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

Table 2. Survival times (months) with Kaplan Meier method and comparisons of groups with Log rank test

	n	Exitus	Median (95.0% CI)	5-years survival rate (%)	p
Overall survival	83	64	25 (17.74 - 32.26)	29.1 ± 5.2	N/A
Extracapsular invasion					
Absent	49	32	51 (20.89 - 81.11)	45.9 ± 7.5	<0.001
Present	34	32	13 (8.72 - 17.28)	5.9 ± 4.0	
Perineural invasion					
Absent	24	13	67 (36.98 - 97.02)	59.1 ± 10.6	<0.001
Present	59	51	14 (8.36 - 19.65)	17.5 ± 5.1	
Lymphovascular invasion					
Absent	30	16	81 (39.32 - 122.68)	56.6 ± 9.6	<0.001
Present	53	48	14 (10.95 - 17.05)	14.3 ± 4.9	
Surgical margin					
Negative	74	55	28 (18.97 - 37.03)	32.7 ± 5.7	<0.001
Positive	9	9	7 (0.00 - 15.77)	0.0 ± 0.0	
T stage					
T1 & T2	16	9	75 (37.01 - 112.99)	59.3 ± 12.9	0.002
T3	34	26	27 (19.97 - 34.03)	33.6 ± 8.4	
T4	33	29	13 (7.37 - 18.63)	10.6 ± 5.6	
N stage					
N0	20	9	84 (69.26 - 98.74)	78.6 ± 9.5	<0.001
N1	15	10	41 (11.67 - 70.33)	36.0 ± 13.3	
N2	21	18	15 (3.04 - 26.96)	11.4 ± 7.4	
N3	27	27	13 (8.00 - 18.00)	3.7 ± 3.6	
TNM stage					
Stage 1	12	5	84 (62.79 - 105.21)	81.8 ± 11.6	<0.001
Stage 2	14	9	61 (20.39 - 101.61)	53.9 ± 14.1	
Stage 3 & 4	57	50	14 (10.83 - 17.17)	12.4 ± 4.6	
Leakage					
Absent	70	51	28 (14.09 - 41.91)	34.7 ± 5.9	<0.001
Present	13	13	2 (0.00 - 4.35)	0.0 ± 0.0	
Infection					
Absent	62	44	34 (17.41 - 50.59)	35.9 ± 6.4	0.001
Present	21	20	11 (2.03 - 19.97)	9.5 ± 6.4	
Recurrence					
Absent	50	32	45 (0.00 - 101.85)	48.6 ± 7.2	0.010
Present	33	32	23 (17.37 - 28.63)	3.0 ± 3.0	
Albumin					
< 3.5	15	14	4 (0.00 - 9.05)	20.0 ± 10.3	0.007
≥ 3.5	68	50	27 (17.10 - 36.90)	30.9 ± 5.9	

CI: Confidence interval. Same letters denote the lack of statistically significant difference between groups.

Table 3. Significant prognostic factors of the mortality, Cox regression analysis

	β Coefficient	Std Error	p	Exp(β)	95.0% CI for Exp(β)	
Tumor size	0.009	0.003	0.008*	1.009	1.002	1.016
Perineural invasion	0.909	0.341	0.008*	2.481	1.271	4.843
N3 stage	1.088	0.292	<0.001*	2.967	1.674	5.260
Leakage	2.145	0.374	<0.001*	8.546	4.108	17.780
Albumin	-0.556	0.234	0.017*	0.574	0.363	0.907

CI: Confidence interval.
*p value <0.05 significant

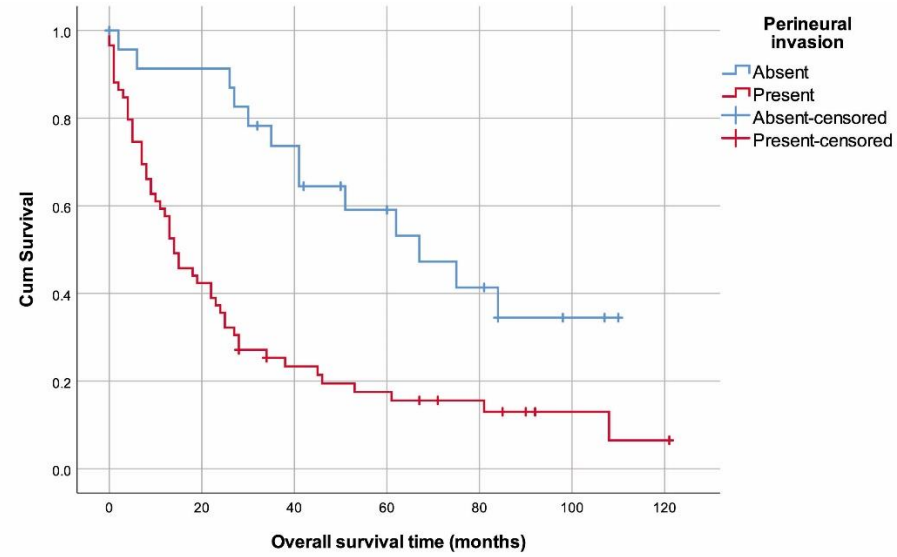

Figure 1. Overall survival plot with regard to perineural invasion

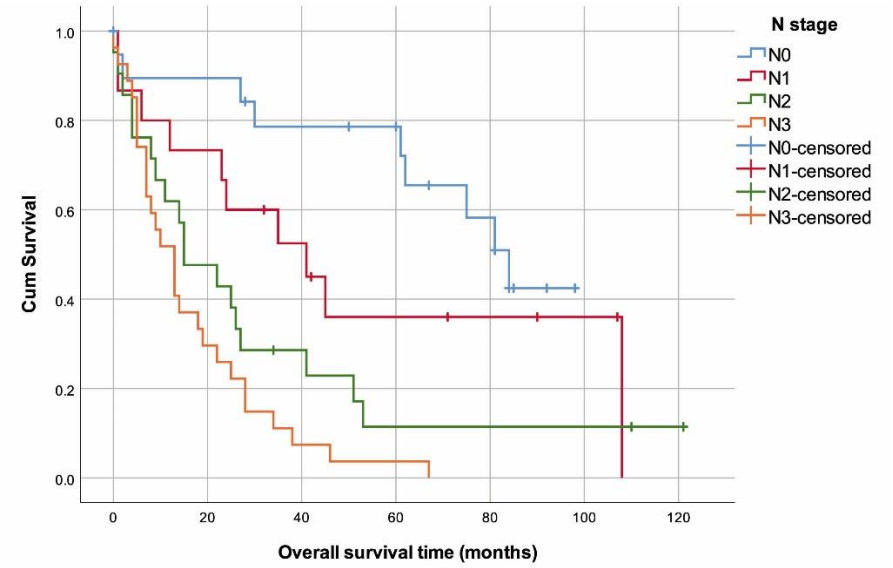

Figure 2. Overall survival plot with regard to N stage

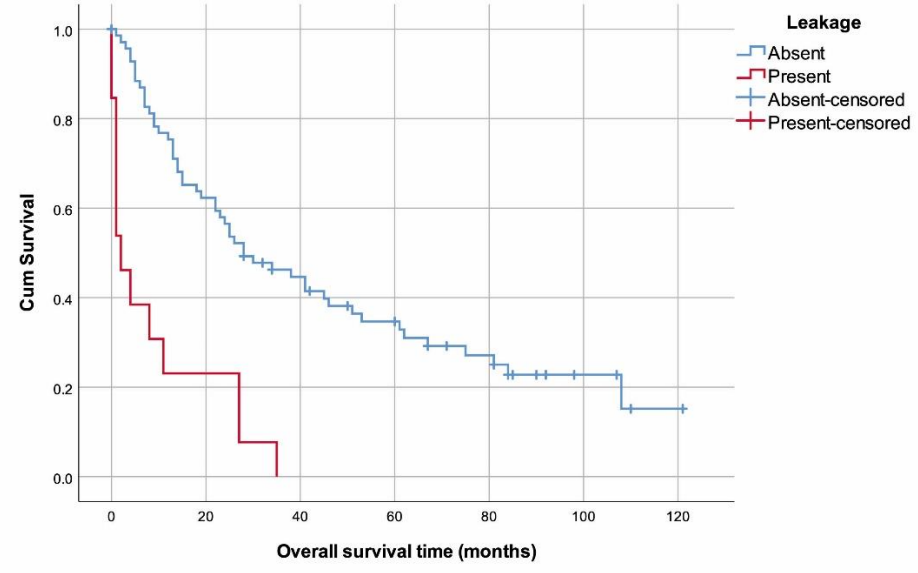

Figure 3. Overall survival plot with regard to leakage

time between diagnosis and surgery (p=0.263), total number of lymph nodes (p=0.659), number of metastatic lymph nodes (p=0.463), extracapsular invasion (p=0.305), lymphovascular invasion (p=0.264), surgical margin positivity (p=0.246), T stage (p=0.130), TNM stage (p=0.448), infection (p=0.456), recurrence (p=0.273), and haemoglobin (p=0.651) were also found to be non-significant.

Discussion

This study aimed to determine possible relationships between preoperative NLR and PLR levels and the clinical characteristics of locally advanced GC, and to assess whether they had predictive significance on disease prognosis. Contrary to previous literature, we did not obtain optimal cut-off values for PLR and NLR to predict mortality, and we demonstrated that preoperative NLR and PLR were non-significant determinants for prognosis in patients with locally advanced GC. We showed that greater tumour size, presence of perineural invasion, N3 stage, leakage, and also lower albumin levels may be poor prognostic predictors for mortality in patients with locally-advanced GC.

Cancer-related inflammation has been described as a substantial cross-talk factor associated with neoplastic growth since it was first suggested by Virchow in the 19th century [10]. In the tumour microenvironment, stromal cells around tumours recruit cytokine-producing inflammatory cells which could facilitate cancer progression in association with proliferation, resistance to apoptosis, induction of angiogenesis, evasion of growth suppressors, development of replicate immortality and activation of invasion and metastasis [2]. Neutrophils may have a critical role in cancer development and progression through pro-angiogenic factors, inflammatory mediators and matrix metalloproteinases [11]. Furthermore, increased neutrophil count in the tumour microenvironment can suppress the antitumor properties of activated T cells and the cytolytic function of immune cells, while also possibly limiting lymphoplasmacytic reactions in tumour cells [12]. Lymphocytes may exhibit a significant role as extrinsic tumour suppressors by attacking and eliminating tumour cells at the outset of tumorigenesis [13]. Patients who have decreased lymphocyte count may have suppressed cell-mediated immune response

against cancer. In addition, platelets may contribute to the inflammatory response by augmenting angiogenesis or releasing growth factors [3]. Thus, cancer-related inflammation may be related with thrombocytosis, leucocytosis, neutrophilia and lympho-cytopenia.

An increase in PLR or NLR may reflect the cancer-related inflammatory status, and these parameters have been broadly examined as potential prognostic factors in many types of solid tumours. Szor et al., in a systematic review and meta-analysis of seven studies comprising 3264 resected GC patients, demonstrated that elevated NLR was associated with lower 5-year OS, older age, male sex, elevated tumour invasion depth, and nodal involvement [14]. Sun et al. showed in a systematic review and meta-analysis of 19 studies comprising 5431 GC patients that increased preoperative NLR was associated with poor OS and progression-free survival [13]. Again, Cao et al. reported in a meta-analysis of 28 studies comprising 15617 patients that increased PLR was related with poor OS in GC, but noted significant publication bias [15]. In contrast, Wang et al. demonstrated in 324 GC patients who had undergone resection for stage 3 cancer that preoperative NLR and PLR were not prognostic and were not associated with disease-free survival and OS [16]. Zamiri et al. reported no significant relationship between NLR and the duration of disease-free survival in 164 patients with non-metastatic and operable GC [17]. Xu et al. revealed in a meta-analysis of 8 studies involving 4513 patients that PLR may not be used as a prognostic indicator for OS in patients with GC [4].

Our study is among the latter group; we did not find optimal NLR or PLR cut-off values that could estimate mortality in patients with locally advanced GC who had undergone resection. We also showed that NLR and PLR had no prognostic association with OS in locally advanced GC patients. This may be related to patients' characteristics; however, the overall controversy in this topic appears to suggest the presence of various biases and confounding factors. For instance, previous studies have demonstrated that sex, race, ethnic heterogeneity and tumour type could influence prognosis and prognostic indicators in GC [18]. Due to the retrospective nature of our study, these factors are also likely to have caused bias in our results. Several conditions, including treatment and concurrent hidden infection(s), could influence the levels of NLR and PLR. Although our study attempted to exclude patients with certain conditions, including acute infection or inflammatory diseases, the retrospective design of this study may not have been able to completely exclude patients with external sources of inflam-matory reactions that were undetectable when blood samples were drawn. In addition, shorter follow-up may have impacted obtained results. Another possible explanation is the relatively small number of GC patients included and unconfirmed cut-off values for preoperative PLR and NLR. Previous studies have shown diverse cut-off values for PLR and NLR in predicting survival [19]. The lack of consensus on cut-off values for PLR and NLR remains a critical issue and shows the need to exercise caution when considering the clinical use of these parameters.

The basis for inconsistent results throughout the literature remains poorly understood and should be another cause of concern. Not with standing the possible sources of error in measurements from centre to centre, the likely presence of publication bias and all's well literature bias could have contributed to a sustained publication of studies reporting value for PLR and NLR in determining prognosis or other disease-related characteristics. This is not unusual, as reports of so-called 'biomarkers' in the literature are almost always positive. For example, an analysis of more than 1900 publications

demonstrated that about 95% of 'cancer biomarker/indicator' studies showed positive results [20]. Publication bias is a well-established phenomenon in medical research, and is caused by refraining from submission of non-significant results or by the generally negative decisions of editors towards such studies. Recording and analysing NLR and PLR data is a simple process that needs only accurate data which can be easily reached through hospital databases. Authors who found no significance in these short assessments are very likely to have decided to avoid publication due to the arduous process of writing their findings as a full article and their established understanding that these results would be unlikely to receive recognition by journals. Indeed, meta-analyses have shown that publication bias may influence the ever-growing body of literature concerning PLR and NLR assessment [21].

Many clinicopathological determinants, such as clinical stage, pathological TNM stage, depth of tumour invasion, tumour size and lymph node metastasis, may affect the prognosis in GC patients. While many researchers continue to investigate various prognostic factors, TNM staging, despite its limitations, is currently accepted to be a crucial prognostic tool. In addition, Yamashita et al. demonstrated that metastatic lymph node ratio was a good prognostic factor in GC patients [22]. Wang et al. revealed in 430 advanced GC patients that tumour invasion, lymph node metastasis, and tumour size were independent prognostic factors [23]. Crumley et al. demonstrated a relationship between low albumin levels and poor survival in patients with GC, dependent on increased levels of C-reactive protein [24]. Hypo-albuminemia may reflect poor nutritional status and increased inflammatory degree, potentially adversely affecting the survival of GC patients. Consistent with the literature, we found that higher tumour size, the presence of perineural invasion, N3 stage, leakage and lower albumin levels were independently associated with mortality and disease prognosis. These factors may be used as prognostic indicators and could be valuable to identify patients at high risk of mortality. Further prospective studies with longer patient follow-up and larger sample sizes will help verify our current data on prognostic indicators for GC.

The study has several limitations. First, the study was conducted as a single-centre, retrospective cohort that included a relatively small sample size, which may have caused bias in results. Second, we were unable to determine those who died from non-GC causes during the follow-up period. This resulted in the failure to identify disease-specific survival rates.

Conclusion

In this study, our results indicate that preoperative NLR and PLR were non-significant factors for prognosis and could not be used as prognostic indicators for mortality in patients with locally advanced GC. Greater tumour size, perineural invasion, N3 stage, presence of leakage, and hypoalbuminemia were independently associated with post-operative mortality and disease prognosis. Future studies could aim to include a greater number of patients with early-stage disease in order to be able to compare parameters with better prognostic resolution and to increase the follow-up time of patients.

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Original Article

Quality of Life Assessment with EORTC QLQ in Patients with Hodgkin Lymphoma: Multicenter Study

Hodgkin Lenfoma Hastalarında EORTC QLQ ile Yaşam Kalitesi Değerlendirmesi: Çok Merkezli Çalışma

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ABSTRACT

Aim: The aim of our study is to obtain data on the quality of life (QoL) in Hodgkin lymphoma (HL) patients in a representative sample of the general population of Turkey with the help of the EORTC QLQ-C30 and QLQ-HL27 questionnaires.

Material and Methods: A total of 68 patients from seven different centers diagnosed with HL between 2018-2020 were included in the study. The questionnaires were answered cross-sectionally by the patient under the control of a physician in the centers participating in the study.

Results: Out of 68 patients, 42.6% (n=29) were female and 57.4% (n=39) were male. The ages of the patients ranged from 18 to 74 years, with a mean of 42.10±16.62 and with a median value of 40 years. There was no significant difference between age subgroups in terms of QLQ-C30 global health status/ QoL, functional or symptom scales and HL27 SB, PC, EI and WF scores ($p>0.05$, for all). It was determined that the constipation scores of females were higher than the scores of males ($p=0.041$). No statistically significant difference was found in terms of HL27 SB, PC, EI and WF sub-dimension scores according to gender ($p>0.05$).

Conclusions: There was only a statistically significant difference in terms of QLQ-C30 constipation sub-dimension scores according to gender. The constipation scores of females were higher than the scores of men. More detailed and large population studies are needed to reveal the effectiveness of QoL assessment in HL patients.

Keywords: Hodgkin lymphoma, EORTC QLQ-C30, QLQ-HL27, quality of life

ÖZET

Amaç: Çalışmamızın amacı, EORTC QLQ-C30 ve QLQ-HL27 anketleri yardımıyla Türkiye genelini temsil eden bir örneklemde Hodgkin lenfoma (HL) hastalarında yaşam kalitesi hakkında veri elde etmekti.

Gereç ve yöntemler: 2018-2020 yılları arasında, HL tanısı almış yedi farklı merkezden toplam 68 hasta çalışmaya dahil edildi. Anketler, araştırmaya katılan merkezlerde hekim kontrolünde hasta tarafından yanıtlandı.

Bulgular: 68 hastanın %42.6'sı (n=29) kadın, %57.4'ü (n=39) erkekti. Hastaların yaşları 18 ile 74 arasında değişmekte olup, ortalama 42.10±16.62 ve ortanca değeri 40 idi. QLQ-C30 global sağlık

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durumu/ yaşam kalitesi, fonksiyonel veya semptom skalaları ve HL27 SB, PC, EI ve WF skorları açısından yaş alt grupları arasında anlamlı fark yoktu (tümü için, p>0.05). Kadınların kabızlık puanlarının erkeklere göre daha yüksek olduğu belirlendi (p=0.041). Cinsiyete göre HL27 SB, PC, EI ve WF alt puanları açısından istatistiksel olarak anlamlı fark bulunmadı (p>0.05).
Sonuç: Cinsiyete göre sadece QLQ-C30 kabızlık alt puanları açısından istatistiksel olarak anlamlı bir fark vardı. Kadınların kabızlık puanları erkeklerin puanlarından daha yüksekti. HL hastalarında QoL değerlendirmesinin etkinliğini ortaya çıkarmak için daha ayrıntılı ve geniş popülasyon çalışmalarına ihtiyaç olduğu görülmektedir.

Anahtar sözcükler: Hodgkin lenfoma, EORTC QLQ-C30, QLQ-HL27, yaşam kalitesi

Introduction

Hodgkin lymphoma (HL) is a rare B-cell malignant neoplasm. Its incidence in the population is 2.3/100.000. The classic HL (CHL) subtype (95%) is the most common, while the nodular lymphocyte-predominant HL (NLPHL) subtype is less common (5%) [1, 2].

Although the incidence of HL is higher between the ages of 20-40, it shows a second peak at the age of 55 and above. There are no clearly defined risk factors for the development of HL, but familial factors, viral exposures, and immunosuppression are thought to be involved [3].

Initial treatment for patients diagnosed with HL is based on the histological features of the disease, the stage of presentation, and the presence of poor prognostic factors. Combined therapy modalities, which include radiotherapy (RT) to the affected area, usually followed by shortened chemotherapy regimens, are applied in early-stage HL patients. In con-trast, patients with advanced HL usually receive long-term, combination chemotherapy regimens, and radiation therapy is used only in selected cases. For patients diagnosed with HL with relapsed or refractory disease, salvage chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation is the standard of care [2]. The current standard treatment of HL disease is the adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) protocol.

Due to the high survival rate in HL patients with successful treatment options, the evaluation of the quality of life (QoL) has gained importance in this patient group [4]. These patients are at risk for long-term physical and psychological side effects after their treatment [5]. Patients cured after HL therapy could have pain, fatigue, sexual, psychosocial, cognitive or emotional problems [5-7]. As an example, persistent fatigue is increased 2.5-3 times in HL patients compared to the normal population, it is seen in up to 40% of patients after treatment and may occur even years after successful treatment [8].

The European Organization for Research and Treatment of Cancer (EORTC) aimed to develop an integrated and modular approach to assessing the quality of life (QoL) of cancer patients. A basic QoL questionnaire called "EORTC QLQ-C30" consisting of 30 questions is used. In addition, EORTC QLQ-HL27 is a special questionnaire consisting of 27 questions and adjusted to evaluate the QoL in HL patients [9]. In our study, both questionnaires were presented to the patients in the Turkish language.

The aim of our study is to obtain data on QoL in HL patients in a representative sample of the general population of Turkey with the help of the EORTC QLQ-C30 and QLQ-HL27 questionnaires. Interpretation of these data will help to improve the patient's QoL by allowing timely appropriate intervention for the symptoms caused by the disease or chemo-

therapy. In our study, we aimed to evaluate the effect of the disease and the primary systemic treatment on QoL in HL patients.

Material and Methods

A total of 68 patients from seven different centers diagnosed with HL between 2018 and 2020 were included in our study. The questionnaires were answered cross-sectionally by the patient under the control of a physician in the centers participating in the study. Written consent was obtained from all patients with HL, using an informed consent form. The QLQ-C30, the core QoL questionnaire of the EORTC, and the QLQ-HL27, the lymphoma module specific for HL patients, were used. Version 3.0 of the EORTC QLQ-C30 has 30 questions and three sections: functional scales, symptom scales, and global health status/ QoL. Functional scales are physical, role, emotional, cognitive and social functioning. The symptom scales are dyspnea, insomnia, appetite loss, nausea and vomiting, constipation, diarrhea, fatigue, pain and financial difficulties [9]. The reliability and validity of the Turkish version of the EORTC QLQ-C30 have been proven [10]. EORTC QLQ-HL27 includes 4 sections and 27 questions on HL and treatment-related disease symptoms, side effects of treatment, body image, and future perspective [9].

Ethical committee approval was received (Approval date and number: Istanbul Medipol University, 2020, 228).

Statistical analysisNCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used while evaluating the study data. The conformity of the quantitative data to the normal distribution was tested with the Shapiro-Wilk test and graphical examinations. The Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution, and the Kruskal-Wallis test was used for comparisons between more than two groups. The Cronbach alpha coefficient was used to determine the internal consistency levels of the scales. Statistical significance was accepted as $p<0.05$.

Results

Out of 68 patients, 42.6% (n=29) were female and 57.4% (n=39) were male. The ages of the patients ranged from 18 to 74 years, with a mean of 42.10±16.62 and with a median value of 40 years. The disease type was nodular sclerosing in 45.6% (n=31), mixed cellular in 36.8% (n=25), lymphocyte rich in 11.8% (n=8), lymphocyte-poor in 1.5% (n=1) and lym-phocyte predominant in 4.4% (n=3) of patients. The general distributions, mean and me-dian values of the scale subscores are shown in Table 1.

There was no significant difference between age subgroups in terms of QLQ-C30 global health status/ QoL, functional or symptom scales ($p>0.05$). Also, no statistically significant difference was found between age subgroups in terms of HL27 SB, PC, EI and WF scores ($p>0.05$) (Table 2).

According to gender breakdown, a statistically significant difference was found in terms of QLQ-C30 constipation scores between males and females ($p=0.041$). It was determined that the constipation scores of females were higher than the scores of males. No statistically significant difference was found in terms of HL27 SB, PC, EI and WF sub-dimension scores according to gender ($p>0.05$) (Table 3).

There was no significant difference between stage subgroups in terms of QLQ-C30 global health status/ QoL, functional or symptom scales ($p>0.05$). Also, no statistically significant difference was found between age

Table 1. General distribution of scale scores

	Mean (SD)	Median	Floor (%)	Ceiling (%)	Item own-scale correlations	Reliability (Cronbach's α)
QLQ-C30						
Global Health Status/QoL	59.6 (24.3)	58.3	0.0 (1.5)	100.0 (8.8)	0.699	0.823
Functional Scales						
Physical Functioning	61.3 (27)	60.0	0.0 (0)	100.0 (11.8)	0.666-0.791	0.877
Role Functioning	67.9 (30.9)	66.7	0.0 (2.9)	100.0 (39.7)	0.766	0.867
Emotional Functioning	60.2 (29.4)	66.7	0.0 (2.9)	100.0 (13.2)	0.676-0.775	0.870
Cognitive Functioning	67.4 (29.1)	66.7	0.0 (1.5)	100.0 (29.4)	0.556	0.714
Social Functioning	61.8 (29.7)	66.7	0.0 (2.9)	100.0 (25)	0.696	0.820
Symptom Scales						
Fatigue	47.1 (30.8)	44.4	0.0 (13.2)	100.0 (5.9)	0.798-0.827	0.902
Nausea and vomiting	25.2 (27.8)	16.7	0.0 (42.6)	100.0 (1.5)	0.545	0.699
Pain	40.9 (32.5)	33.3	0.0 (23.5)	100.0 (7.4)	0.640	0.779
Dyspnea	38.7 (35.3)	33.3	0.0 (36.8)	100.0 (11.8)	-	-
Sleep disturbance	42.2 (36.7)	33.3	0.0 (33.8)	100.0 (16.2)	-	-
Appetite loss	33.3 (38.2)	16.7	0.0 (50)	100.0 (14.7)	-	-
Constipation	27 (33.2)	0.0	0.0 (52.9)	100.0 (7.4)	-	-
Diarrhea	14.7 (24)	0.0	0.0 (67.6)	100.0 (1.5)	-	-
Financial difficulties	49 (33.8)	66.7	0.0 (25)	100.0 (13.2)	-	-
QLQ-HL27						
SB	36.9 (24)	38.9	0.0 (4.4)	100.0 (0)	0.329-0.763	0.808
PC	39 (28.4)	33.3	0.0 (13.2)	100.0 (2.9)	0.534-0.814	0.848
EI	37.5 (26.8)	38.9	0.0 (8.8)	100.0 (0)	0.704-0.806	0.908
WF	43.7 (25.2)	45.5	0.0 (4.4)	100 (0)	0.282-0.784	0.881

Abbreviations: QLQ-C30: The EORTC core quality of life questionnaire, SD: Standard deviation, QoL: Quality of life, QLQ-H27: The EORTC core quality of life questionnaire for Hodgkin lymphoma, SB: Symptom burden, PC: Physical condition, EI: Emotional impacts, WF: Worries/fears

Table 2. Evaluation of scale scores according to age subgroups

Parameters\Age Subgroup	**<65 (n=60)**	**≥ 65 (n=8)**	**p**
	Median (Min, Max)	**Median (Min, Max)**	
QLQ-C30			
Global Health Status/QoL	58.33 (0, 100)	70.83 (33.33, 100)	**0.421**
Functional Scales	60 (6.67, 100)	53.33 (33.33, 100)	**0.731**
Physical Functioning	66.67 (0, 100)	75 (0, 100)	**0.889**
Role Functioning	66.67 (0, 100)	58.33 (16.67, 83.33)	**0.416**
Emotional Functioning	83.33 (0, 100)	50 (33.33, 100)	**0.217**
Cognitive Functioning	66.67 (0, 100)	58.33 (33.33, 100)	**0.770**
Symptom Scales			
Fatigue	44.44 (0, 100)	55.56 (0, 77.78)	**0.977**
Nausea and vomiting	16.67 (0, 100)	25 (0, 83.33)	**0.705**
Pain	33.33 (0, 100)	41.67 (0, 83.33)	**0.915**
Dyspnea	33.33 (0, 100)	66.67 (0, 100)	**0.557**
Sleep disturbance	33.33 (0, 100)	50 (0, 100)	**0.968**
Appetite loss	0 (0, 100)	50 (0, 100)	**0.485**
Constipation	0 (0, 100)	50 (0, 100)	**0.077**
Diarrhea	0 (0, 100)	0 (0, 66.67)	**0.746**
Financial difficulties	66.67 (0, 100)	66.67 (0, 66.67)	**0.557**
QLQ-HL27			
SB	38.89 (0, 88.89)	33.33 (0, 83.33)	**0.939**
PC	33.33 (0, 100)	54.17 (0, 83.33)	**0.667**
EI	38.89 (0, 94.44)	38.89 (5.56, 72.22)	**0.970**
WF	46.97 (0, 96.97)	45.45 (3.03, 78.79)	**0.607**

Mann-Whitney U test was used

Abbreviations: QLQ-C30: The EORTC core quality of life questionnaire, Min: Minimum, Max: Maximum, QoL: Quality of life, QLQ-H27: The EORTC core quality of life questionnaire for Hodgkin lymphoma, SB: Symptom burden, PC: Physical condition, EI: Emotional impacts, WF: Worries/fears

Table 3. Evaluation of scale scores according to gender

Parameters\ Gender	**Female (n=29)**	**Male (n=39)**	**p**
	Median (Min, Max)	**Median (Min, Max)**	
QLQ-C30			
Global Health Status/QoL	58.33 (0, 100)	58.33 (8.33, 100)	**0.413**
Physical Functioning	60 (13.33, 100)	60 (6.67, 100)	**0.672**
Role Functioning	66.67 (33.33, 100)	83.33 (0, 100)	**0.480**
Emotional Functioning	66.67 (0, 100)	66.67 (0, 100)	**0.794**
Cognitive Functioning	66.67 (0, 100)	83.33 (16.67, 100)	**0.262**
Social Functioning	66.67 (0, 100)	66.67 (0, 100)	**0.648**
Symptom Scales			
Fatigue	55.56 (0, 100)	44.44 (0, 100)	**0.321**
Nausea and vomiting	16.67 (0, 100)	16.67 (0, 83.33)	**0.785**
Pain	50 (0, 100)	33.33 (0, 100)	**0.477**
Dyspnea	33.33 (0, 100)	33.33 (0, 100)	**0.500**
Sleep disturbance	66.67 (0, 100)	33.33 (0, 100)	**0.106**
Appetite loss	0 (0, 100)	33.33 (0, 100)	**0.679**
Constipation	33.33 (0, 100)	0 (0, 100)	**0.041***
Diarrhea	0 (0, 66.67)	0 (0, 100)	**0.379**
Financial difficulties	66.67 (0, 100)	66.67 (0, 100)	**0.531**
QLQ-HL27			
SB	44.44 (5.56, 88.89)	38.89 (0, 83.33)	**0.567**
PC	41.67 (0, 100)	33.33 (0, 100)	**0.579**
EI	33.33 (0, 83.33)	38.89 (0, 94.44)	**0.911**
WF	48.48 (0, 87.88)	45.45 (0, 96.97)	**0.687**

Mann-Whitney U test was used

Abbreviations: QLQ-C30: The EORTC core quality of life questionnaire, Min: Minimum, Max: Maximum, QoL: Quality of life, QLQ-H27: The EORTC core quality of life questionnaire for Hodgkin lymphoma, SB: Symptom burden, PC: Physical condition, EI: Emotional impacts, WF: Worries/fears

Table 4. Evaluation of scale scores according to stages

Parameters\ Stages	**Stage 1&2 (n=27)**	**Stage 3&4 (n=41)**	**p**
	Median (Min, Max)	**Median (Min, Max)**	
QLQ-C30			
Global Health Status/QoL	58.33 (0, 100)	58,33 (16.67, 100)	**0.668**
Physical Functioning	60 (6.67, 100)	66.67 (20, 100)	**0.880**
Role Functioning	66.67 (33.33, 100)	66.67 (0, 100)	**0.569**
Emotional Functioning	75 (0, 100)	58,33 (8.33, 100)	**0.457**
Cognitive Functioning	83.33 (0, 100)	66.67 (16.67, 100)	**0.509**
Social Functioning	66.67 (0, 100)	50 (0, 100)	**0.788**
Symptom Scales			
Fatigue	44.44 (0, 100)	44.44 (0, 100)	**0.668**
Nausea and vomiting	0 (0, 66.67)	16.67 (0, 100)	**0.210**
Pain	33.33 (0, 100)	33.33 (0, 100)	**0.559**
Dyspnea	33.33 (0, 100)	33.33 (0, 100)	**0.520**
Sleep disturbance	33.33 (0, 100)	33.33 (0, 100)	**0.710**
Appetite loss	0 (0, 100)	33.33 (0, 100)	**0.108**
Constipation	33.33 (0, 100)	0 (0, 100)	**0.395**
Diarrhea	0 (0, 100)	0 (0, 66.67)	**0.784**
Financial difficulties	66.67 (0, 100)	66.67 (0, 100)	**0.405**
QLQ-HL27			
SB	33.33 (0, 83.33)	38.89 (0, 88.89)	**0.417**
PC	33.33 (0, 100)	50 (0, 100)	**0.439**
EI	33.33 (0, 88.89)	44.44 (0, 94.44)	**0.269**
WF	42.42 (0, 84.85)	48.48 (0, 96.97)	**0.598**

Mann Whitney U Test was used

Abbreviations: QLQ-C30: The EORTC core quality of life questionnaire, Min: Minimum, Max: Maximum, QoL: Quality of life, QLQ-H27: The EORTC core quality of life questionnaire for Hodgkin lymphoma, SB: Symptom burden, PC: Physical condition, EI: Emotional impacts, WF: Worries/fears

Table 5. Evaluation of scale scores according to HL subtypes

Parameters\ Disease Subtype	Nodular sclerosing (n=31)	Mixed cellular (n=25)	Other (n=12)	p
	Median (Min, Max)	Median (Min, Max)	Median (Min, Max)	
QLQ-C30				
Global Health Status/QoL	58.33 (16.67, 100)	58.33 (0, 100)	66.67 (16.67, 100)	**0.684**
Physical Functioning	66.67 (6.67, 100)	60 (13.33, 100)	63.33 (6.67, 100)	**0.871**
Role Functioning	66.67 (0, 100)	66.67 (0, 100)	66.67 (33.33, 100)	**0.997**
Emotional Functioning	66.67 (16.67, 100)	50 (0, 100)	75 (0, 100)	**0.418**
Cognitive Functioning	83.33 (16.67, 100)	66.67 (0, 100)	66.67 (16.67, 100)	**0.540**
Social Functioning	66.67 (33.33, 100)	66.67 (0, 100)	58.33 (16.67, 100)	**0.633**
Symptom Scales				
Fatigue	44.44 (0, 88.89)	55.56 (0, 100)	44.44 (33.33, 100)	**0.148**
Nausea and vomiting	16.67 (0, 83.33)	16.67 (0, 100)	8.33 (0, 66.67)	**0.689**
Pain	33.33 (0, 100)	66.67 (0, 100)	41.67 (0, 100)	**0.528**
Dyspnea	33.33 (0, 100)	33.33 (0, 100)	50 (0, 100)	**0.346**
Sleep disturbance	33.33 (0, 100)	33.33 (0, 100)	33.33 (0, 100)	**0.415**
Appetite loss	0 (0, 100)	33.33 (0, 100)	0 (0, 100)	**0.340**
Constipation	0 (0, 66.67)	0 (0, 100)	16.67 (0, 100)	**0.760**
Diarrhea	0 (0, 66.67)	0 (0, 100)	0 (0, 33.33)	**0.861**
Financial difficulties	66.67 (0, 100)	66.67 (0, 100)	50 (0, 100)	**0.360**
QLQ-HL27				
SB	38.89 (0, 83.33)	44.44 (0, 88.89)	36.11 (11.11, 72.22)	**0.695**
PC	33.33 (0, 91.67)	33.33 (0, 100)	41.67 (8.33, 100)	**0.514**
EI	38.89 (0, 83.33)	33.33 (0, 88.89)	41.67 (5.56, 94.44)	**0.928**
WF	45.45 (0, 87.88)	45.45 (0, 87.88)	46.97 (0, 96.97)	**0.574**

Kruskal-Wallis test was used

Abbreviations: QLQ-C30: The EORTC core quality of life questionnaire, Min: Minimum, Max: Maximum, QoL: Quality of life, QLQ-H27: The EORTC core quality of life questionnaire for Hodgkin lymphoma, SB: Symptom burden, PC: Physical condition, EI: Emotional impacts, WF: Worries/fears

subgroups in terms of HL27 SB, PC, EI and WF scores . (p>0.05) (Table 4).

There was also no significant difference between HL subtypes in terms of QLQ-C30 global health status/ QoL, functional or symptom scales; of HL27 SB, PC, EI and WF scores (p>0.05) (Table 5).

Discussion

Our study is the first from Turkey to evaluate QoL using QLQ-C30 and QLQ-HL27 in a large and multi-center HL patient group. There is limited information on the use of QLQ subtypes in hematological malignancies and no clear evidence for their effectiveness. In a recent study from 2020 [10], health-related QoL (HRQoL) was evaluated using the EORTC QLQ-C30 in a total of 515 hematological malignancies diagnosed with leukemia, lymphoma and multiple myeloma over the age of 18 years. Of the 515 patients included in the study, 46.6% were diagnosed with lymphoma, 34% with leukemia and 19.4% with multiple myeloma; 70.9% of them were with advanced-stage or high risk. Anxiety rate was 15.1% and depression 12.8%. While the mean global health status score was found to be 59.6 in our study, it was found to be 59.2 in this study. In our study, there was no significant difference between age subgroups, stages and disease subtypes in terms of the global health scores/QoL.

In an HL cohort from 2020 [11], patients with advanced HL, 5-year HL-survivors and the general population were compared with each other. Patients reported worse HRQoL scores than survivors across most functional scales and symptom scales. These scores varied as a function of gender but not age. Survivors' HRQoL reports were comparable to the ones of the general population. In addition, even though the QoL scores of HL patients are worse than the general population, they improve over the years.

In another study from Turkey in 2020 [12], in a group of 121 chronic myeloid leukemia patients, who had used a tyrosine kinase inhibitor (TKI) for at least 3 months, the effectiveness of QLQ-C30 and QLQ-CML24 was examined. While the median age of the patients was 53, there was no difference in global health status scores between patients who received different TKIs. In the QLQ-CML24 module, the most common symptom was fatigue with 58.7%; there was no significant difference between the TKI groups in terms of the effect on activities of daily living. In our study in the HL patient group, the median age was 40, and there was no significant difference between the groups we formed in terms of QLQ-C30 and QLQ-HL27 parameters. A statistically significant difference was found only in terms of QLQ-C30 constipation sub-dimension scores according to gender (p=0.041). Another major study [13] included adults aged 18 years and older who had completed treatment for a hema-tological malignancy and were at 1 to 5 years post-treatment. In a total of 131 patients with a mean age of 66, being advanced age was found to be associated with poor QoL. Males reported better physical functioning, fewer pain symptoms, and less insomnia compared to females. While the median age of the study was 66, 77.9% of them were diagnosed with lymphoma (B-cell). In our study, the only difference between males and females was consti-pation. The median age was 40 years due to the younger age group of HL. In another study involving 490 patients from 40 different centers with a diagnosis of multiple myeloma, which is seen as a disease of the older age group [14], the median age was 71 and the mean global health status score was 49.4. In the patient group followed in the no-treatment interval, the global health status scores and functional scores were better and fewer symptoms were observed.

In another MM cohort, a total of 445 patients were evaluated; a high global health status /QoL score has been shown to be associated with good treatment response and fewer side effects; it was also observed that an increase in the score was significantly associated with longer treatment [15]. In our study, the fact that the general health status scores and QLQ-C30 or HL27 parameters did not differ significantly in patients who were with more advanced stages and needed longer treatment should be considered as an important result. According to MM, which is a disease of advanced age; it is important in terms of treatment tolerance in HL where young age is dominant.

There are also limitation points of this study. The most important one is the fact that validity and reliability study of the EORTC QLQ-HL27 was not done in Turkish language. Another important points were the limited patient population and statistical analysis, which became difficult especially when sub-groups were established.

As a result, this study is the first from our country to evaluate the QLQ-C30 and QLQ-HL27 questionnaires, especially in a relatively young patient population com-pared to other hematologic malignancies of literature. There was no significant differ-ence between age, gender and stage subgroups in terms of QLQ-C30 and QLQ-HL27 sub-parameters. There was only a statistically significant difference in terms of QLQ-C30 constipation sub-dimension scores according to gender. The constipation scores of females were higher than the scores of men. More detailed and large population studies are needed to reveal the effectiveness of QoL assessment in HL patients.

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Original Article

The Views of Patients with Hematological Malignancies About Complementary and Alternative Medicine

Hematolojik Maligniteli Hastaların Tamamlayıcı ve Alternatif Tıp Hakkındaki Görüşleri

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ABSTRACT

Introduction: Complementary and alternative medicine (CAM) is often used by cancer patients, but not many studies had been published on the prevalence of CAM use in patients with hematological cancers. This study aims to determine the prevalence of CAM and type of CAM used in this group of patients.

Methods: Patients who were followed up in Ankara Oncology Hospital hematology and stem cell transplant clinic were asked some questions about CAM, art therapy and spiritual support.

Results: A total of 238 patients participated. The prevalence of CAM use was 29,4%. The most common types of CAM used is phytotherapy. There is no significant association of CAM use with age and gender. A higher rate of CAM use was observed in those with a low education level. It was found that those living in the provincial centers also used these treatments at a higher rate.

Discussion and Conclusion: It is noteworthy that the use of CAM is less common in patients with hematologic cancer compared to other studies, patients are confused about CAM and want to get information from their physicians. It was observed that they were also interested in art therapy and spiritual support therapies.

Keywords: Complementary and alternative medicine, hematological malignancies, art therapy, spiritual support

ÖZET

Giriş ve Amaç: Tamamlayıcı ve alternatif tıp (TAT), kanser hastaları tarafından sıklıkla kullanılmaktadır, ancak hematolojik kanserli hastalarda TAT kullanımının yaygınlığı hakkında çok fazla çalışma yayınlanmamıştır. Bu çalışma, bu hasta grubunda kullanılan TAT prevalansını ve kullanılan TAT tipini belirlemeyi amaçlamaktadır

Yöntem ve Gereçler: Ankara Onkoloji Hastanesi hematoloji ve kök hücre nakli kliniğinde takip edilen hastalara TAT, sanat terapisi ve manevi destek ile ilgili bazı sorular soruldu

Bulgular: Toplam 238 hasta katıldı. TAT kullanım yaygınlığı %29,4 idi. Kullanılan en yaygın TAT türleri fitoterapidir. Yaş ve cinsiyet ile TAT kullanımı arasında anlamlı bir ilişki yoktur. Eğitim düzeyi düşük olanlarda daha yüksek TAT kullanım oranı gözlendi. İl merkezlerinde yaşayanların da bu tedavileri daha yüksek oranda kullandıkları belirlendi.

Tartışma ve Sonuç: Hematolojik kanserli hastalarda TAT kullanımının diğer çalışmalara göre daha az olduğu, hastaların TAT konusunda kafalarının karıştığı ve hekimlerinden bilgi almak istedikleri dikkat çekicidir. Sanat terapisi ve manevi destek terapilerine de ilgi duydukları gözlemlendi.

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Anahtar Kelimeler: Tamamlayıcı ve alternatif tıp, hematolojik maligniteler, sanat terapisi, manevi destek

Introduction

For centuries, Complementary and alternative medicine (CAM) has been used in various diseases and in recent years, its popularity especially among cancer patients has been increasing. CAM is defined as "a group of various medical and health interventions, practices, products or disciplines that are not generally considered as a part of traditional medicine"[1]. The use of CAM is common, but its potential positive and negative impacts on patient care is not well understood by patients or healthcare providers. It has been demonstrated that most of the physicians are not discussing the use of CAM with their patients in their daily practice. In a previous study, it has been revealed that 63% to 72% of patients who received concurrent conventional and CAM therapy did not disclose CAM use to their physicians[2]. The high rate of CAM use was shown to be related with female gender, young age and high education level [3,4]. The rate of CAM use seems to be the highest in hematological cancer patients, along with breast, lung and brain cancer patients[5].

Although there are many data on the use of alternative medicine methods in the oncological patient group, the number of studies in patients with hematological malignancies is few. In this respect, it is thought that our study can contribute to the literature. However, there are some limitations of our study due to the heterogeneity of the patient group, and more detailed information can be obtained when working with groups containing more patients.

The use of herbal medicines by patients with cancer may adversely affect traditional anticancer treatments. While more than 35% of cancer patients in the United States report using herbal medicine while chemotherapy treatment continues, this rate exceeds 50% in developing countries[6]. Apitherapy is the science and art of protecting health by using honey, bee pollen, propolis, royal jelly and bee venom obtained from honey bee hives. Acupuncture services are available in many major cancer centers in the United States and are referenced to control nausea and vomiting in patients.

It is known that herbal ingredients can play an important role in cancer treatment by suppressing the antitumor activity pathway or bioactivation of the carcinogen[7]. There are many medicinal plants / products that are beneficial to health and also have antitumor, antimicrobial, antibacterial and antioxidant structures[8]. Turmeric is promoted as an alternative cancer treatment.

Bone marrow transplantation (BMT) is an important treatment option for a various kind of both benign and malignant hematological diseases, furthermore, in the recent years BMT has been used to treat some kinds of metabolic and immunological diseases. Bone marrow transplantation needs a multi-disciplinary approach involving cooperation of a team involving hematologist, enfection specialist, pharmacist, certificated nurses, apheresis technicians and psychologist. Recent articles recommend involving an art therapist in the transplant team. Art therapy can significantly contribute to the physical, psychological and social support of the transplant recipients. In addition, patients in the hematology ward usually receive intensive chemotherapies therefore the length of hospital stay is usually long and art therapy may also be beneficial in this group of patients[9].

Table 1: Socio-demographic data of the patients

Parameters		N(%)
Gender	Male	135(56.7)
	Female	103(43.3)
Age	<40 year	109(45.8)
	40-60 year	76(31.9)
	>60 year	53(22.3)
Educational Level	Primary education	134 (56.3)
	High school	51(21.4)
	University	53(22.3)
Occupation	Civil servant	15(6.3)
	Private sector	32(13.4)
	Worker	34 (14,3)
	Housewives	47(19.7)
	Retired	24(10.1)
	Student	11(4.6)
	Not employed/not disclosed	75 (31,5)
Place of residence	City center	127(53.4)
	District center	62(26.1)
	Village and towns	49(20.5)

Table 2: Types of complementary and alternative medicine used by hematological cancer patients

Types of CAM	N(%)
Phytotherapy	45(18.9)
Leech therapy	8(3.4)
Cupping therapy	8(3.4)
Vacuum therapy	17(7.1)
Hypnosis	3(1.3)
Apitherapy	10(4.2)
Osteopathy	5(2.1)
Reflexology	3(1.3)
Ozone therapy	6(2.5)
Acupuncture	5 (2.1)

Table 3: Details of the herbal agents used in alternative medicine

Types of CAM	N(%)
Black seed	37 (15.5)
Turmeric	25 (10.5)
Reishi mushroom	7 (2.9)
Bee pollen-milk	32 (13.4)
Barley yeast	2 (0.8)
Goat horn	31 (13)
Others	13 (5.5)

National guidelines recommend evaluating and supporting the patients' spiritual concerns in high-quality palliative and supportive cancer care[10]. Although providing spiritual support to cancer patients reduces medical costs, it is not widely used[11].

Material and Methods

Patients who were followed up in Ankara Oncology Hospital hematology and stem cell transplant clinic were asked some questions about alternative and complementary medicine, art therapy and spiritual support.

The analyses were processed with IBM SPSS software v18 (SPSS Inc., Chicago, IL). The descriptive statistics were applied to present data. The categorical data were displayed as percentage and the numerical data were displayed as median (min-max). Chi-square test was used to assess relation between categorical variables. P values ≤ 0.05 were considered statistically significant.

Results

Patients diagnosed with hematological cancer with follow-up in Hematology and Stem Cell Transplant Clinic in Ankara Oncology Hospital were included in the study. The demographic information of 238 patients included in the questionnaire is presented in Table 1.

The patients were asked whether they used CAM methods such as phytotherapy, leech therapy, cupping therapy, vacuum therapy, hypnosis, apitherapy, osteopathy, reflexology, ozone therapy, and acupuncture, and their answers are summarized in Table 2.

While 45 of the patients (18.9%) stated that they used herbal agent for CAM previously, 35 (14.7%) stated that they used more than one herbal agent. The patients were asked whether they used black seed, turmeric, reishi mushroom, bee pollen milk, barley yeast, and goat horn, and their answers are summarized in Table 3.

Table 4. Awareness, Sources of information, Concerns and thoughts about complementary and alternative drugs

Aspects		N(%)
Awareness	Have you ever heard of alternative and complementary medicine?	184 (77,3)
Sources of information	Family and friends	98(41.2)
	Television	73 (30.7)
	Internet	84 (35.3)
	Others	14 (5.9)
Concerns	I don't think it's beneficial	33 (13.9)
	I believe that it would have a detrimental effect on my treatment	37 (15,5)
	Unable to access accurate and reliable information	85 (34,3)
	Others concerns	194 (81,5)
Suggestions	Do you prefer your doctor to provide you information about it?	144 (60,5)
	Do you prefer to receive alternative therapies under the doctor's supervision?	30 (12,6)
Art Therapy	Have you ever joined?	16 (6,7%)
	Would you like to join?	76 (31,9%)
Spiritual Support/Care	Have you ever received?	38 (16%)
	Would you like to receive?	115(48,3%)

Table 5: Alternative Medicine awareness and usage in patients

Parameters		Awareness, N(%)	Usage, N(%)	P value
Gender	Male	100 (74,1)	40 (29,6%)	0,121;0,93
	Female	85 (82,5%)	30 (29,1%)	
Age	<40 year	83 (76,1%)	28 (25,7%)	0,774; 0,452
	40-60 year	59 (77,6%)	26 (34,2%)	
	>60 year	43 (81,1%)	16 (30,2%)	
Educational Level	Primary education	95 (70,9%)	33 (24,6%)	0,01*; 0,134
	High school	42 (82,4%)	20(39,2%)	
	University	48 (90,6%)	17(32,1%)	
Occupation	Civil servant	13 (86,7%)	4(26,7%)	0,745; 0,474
	Private sector	27 (84,4%)	9(28,1%)	
	Worker	24 (70,6%)	9(26,5%)	
	Housewives	36 (76,6%)	12(25,5%)	
	Retired	20 (83,3%)	12(50%)	
	Student	9 (81,8%)	3(27,3%)	
	Not employed/not disclosed	56 (74,7%)	21(28%)	
Place of residence	City center	105 (82,7)	41 (32,3%)	0,044*;0,467
	District center	47(75,8%)	15 (24,2%)	
	Village and towns	27(64,3%)	11 (26,2%)	

The analyses were made by chi-square. *p value<0,05

The questionnaire also included questions about the patients' awareness about CAM, sources of information, and concerns. The answers given by the patients to these questions are summarized in Table 4. The distribution of CAM awareness and use according to the demographic data of the patients was evaluated and the results are summarized in Table 5. A higher rate of CAM use was observed in those with a low educa-

tion level. It was found that those living in the provincial centers also used these treatments at a higher rate.

While 16 (6,7%) of the patients stated that they participated in the art therapy for patients with hematological cancer in the hospital, 76 (31,9%) stated that they wanted to participate. Again, while 38 (16%) of the patients stated that they benefited from the spiritual support service for patients with hematological cancer, 115 (48,3%) stated that they viewed the spiritual support service positively.

Discussion

Studies show that cancer patients use CAM treatments more frequently[12]. It is more common especially in patient groups who have had their illnesses for a long time and traditional medical treatment failed[13]. Complications due to severe chemo-therapeutic drugs are common in patients with malignant hematological diseases. Patients can apply different CAM methods to reduce the discomfort caused by these complications[14].

In contrast to higher rates in the literature with about 30–60% of the oncology patients using CAM[15], we found CAM use only in 29,41% (70/238) of the patient sample. In another study, Perlman et al. reported that CAM use was even higher (75.2%) in patients diagnosed with cancer in the USA[16]. The prevalence of any CAM use in pediatric cancer patients based on 20 articles reported on 2871 children studied, prevalence rates ranged from 12% to 91%, while 14 articles reported prevalence rates between 20% and 60%[17].

The use of CAM in cancer patients may also be related to ethnicity[18]. The prevalence of CAM use in Asian countries appears to be higher than in western countries. For example, the CAM prevalence of use, some studies 61% in Turkey[19], 60% in Palestine[20], 55% in Singapore[21] and 93.4% in China[22]. Although the literature suggests that CAM users are mostly women and younger, in our study it was observed that there was no difference in the use of CAM according to gender and age groups[23]. While CAM users in the same study had higher education levels, our study found higher usage rates in patients with lower education levels[23].

It was seen that phytotherapy was widely used similar to the literature[24]. In a study conducted in Malaysia, the prevalence of CAM use was 70.2%. The most common CAM therapies used were bio-based treatments (90.2%) containing vitamin supplements (68.6%) followed by herbs and folk remedies (58%)[25]. The use of CAM treatments such as acupuncture and homeopathy seems to be more popular in western societies[26]. In this study conducted in Malaysia, the most common reason for using CAM was to improve the immune system (57%), then heal the underlying cancer (24%), reduce treatment-related side effects (14.0%), and prolong survival (10%)[25]. Most of the patients (65%) felt they had enough information about CAM treatments and 94% felt that CAM use did not have any side effects[25]. In our study, the patients were not asked questions about why they used CAM.

The patients stated that similar to other studies in the literature, they obtained the information about CAM with their family members and friends through media products such as television and the internet[27]. Gan et al. in their study, most of the patients (83%) stated that they received information about CAM treatments from their family and friends, and 11% from the media, including the internet. Most of the patients (65%) agreed that CAM was effective. Only 2.3% of the total patients using CAM thought it to be ineffective[25]. In our study, while 13.9% of the patients thought that CAM treatments would not be beneficial, 15.5% had concerns that they would affect their treatment negatively. While 34.3% of the

patients expressed their concerns due to their inability to access reliable information, 60.5% of them stated that they were willing to be informed about CAM by their own doctors.

In a study conducted in Italy, 54 cancer patients were given 4-5 sessions of art therapy for 40 minutes 2 days a week while continuing their chemotherapy treatments, and 51 patients participating in the study defined their experience as beneficial[28]. In our study, 6.7% of the patients stated that they had participated in art therapy before, and 31.9% stated that they wanted to participate in art therapy. In a study conducted at Akdeniz University, 48 cancer patients were given art therapy, and their depression scales and global quality of life were examined, and a statistically significant improvement was found compared to the control group[29].

In a study involving 101 cancer patients undergoing chemotherapy in Brazil, it was observed that spiritual support reinforces that it is an important strategy in dealing with cancer[30]. In a clinical study conducted by Moeini et al. To determine the effects of a supportive spiritual care program on the anxiety of patients with leukemia, there was no significant difference between the two groups before the program, while the average post-program anxiety score was found to be lower in the experimental group than in the control group (P <0.01)[31]. In our study, 16% of the patients stated that they had participated in spiritual support therapy and 46.3% stated that they wanted to participate in spiritual support therapy.

Conclusion:

This study demonstrates the prevalence of use of CAM in patients with hematological cancers and their concerns. The most common type of CAM is phytotherapy. Therefore, it is important that treating physicians take time to question the use of CAM and to monitor any possible interaction. Studies have shown the benefit of art therapy and spiritual support units not only in end-stage patients but also in patients undergoing treatment. Art and spiritual support therapies added to the treatment of patients with hematological malignancies whose chemotherapy continues may provide additional benefits in coping with cancer.

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Original Article

Prognostic Significance of Fibrinogen-to-Albumin Ratio in Small Cell Lung Cancer

Küçük Hücreli Akciğer Kanserinde Fibrinojen-Albümin Oranının Prognostik Önemi

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ABSTRACT

Introduction: It has been found that fibrinogen-to-albumin ratio (FAR) is closely correlated with prognosis in some cancers. But prognostic importance of FAR in small cell lung cancer (SCLC) isn't known completely. We aimed to show the prognostic importance of FAR in SCLC in this study.

Materials and methods: 145 patients followed up with diagnosis of SCLC were included in the study retrospectively. According to the receiver operating characteristic (ROC) curve analysis, the optimal cut-off values were determined for the FAR, and the patients were divided into low (<0.138) and high (≥ 0.138) FAR groups. C-reactive protein (CRP)- albumin ratio (CAR), procalcitonin-CRP ratio (PCR), prognostic nutritional index (PNI) were grouped based on a cut-off point of 0.646, 6.1 and 33.9 respectively. Cox regression analyses were used for evaluating prognostic significances for progression-free survival (PFS) and overall survival (OS) of parameters.

Results: Both PFS (p<0.001, p:0.027, p:0.003, respectively) and OS (p<0.001, p:0.001, p<0.001, respectively) were found shorter in the group with higher FAR, CAR, PCR. Both PFS (p:0.020) and OS (p: 0.001) were found to be longer in the group with higher PNI compared to the group with low PNI. In multivariate analysis, FAR and PNI were found as an independent prognostic factor for both PFS and OS (p:0.039, p:0.021; p:0.034, p:0.016, respectively).

Conclusion: FAR and PNI are independent prognostic parameters predicting survival times in patients with SCLC.

Keywords: C-reactive protein, inflammation mediators, lung neoplasm, procalcitonin

ÖZET

Giriş: Fibrinojen-albümin oranının (FAR) bazı kanserlerde prognoz ile yakından ilişkili olduğu bulunmuştur. Ancak küçük hücreli akciğer kanserinde (KHAK) FAR' ın prognostik önemi tam olarak bilinmemektedir. Bu çalışmada FAR'ın KHAK' deki prognostik önemini göstermeyi amaçladık.

Gereç ve yöntemler: KHAK tanısı ile takip edilen 145 hasta geriye dönük olarak çalışmaya dahil edildi. Alıcı çalışma karakteristiği (ROC) eğrisi analizine göre FAR için optimal cut-off değerleri belirlendi ve hastalar düşük (<0.138) ve yüksek (≥ 0.138) FAR gruplarına ayrıldı. C-reaktif protein (CRP)-albümin oranı (CAR), prokalsitonin-CRP oranı (PCR), prognostik nütrisyonel indeks (PNI) sırasıyla 0.646, 6.1 ve 33.9'luk bir kesme noktasına göre gruplandırıldı. Parametrelerin progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) için prognostik önemlerini değerlendirmek için Cox regresyon analizleri kullanıldı.

Bulgular Hem PFS (sırasıyla p<0,001, p: 0,027, p: 0,003) hem de OS (sırasıyla p<0,001, p: 0,001, p<0,001) FAR, CAR, PCR yüksek olan grupta daha kısa bulundu. Hem PFS (p: 0.020) hem de OS (p: 0.001), PNI'si yüksek olan grupta, PNI'si düşük olan gruba göre daha uzun bulundu. Çok değişkenli analizde FAR ve PNI, hem PFS hem de OS için bağımsız bir prognostik faktör olarak bulundu (sırasıyla p: 0.039, p: 0.021; p: 0.034, p: 0.016).

Tartışma ve Sonuç: FAR ve PNI, KHAK' li hastalarda sağkalım sürelerini öngören bağımsız prognostik parametrelerdir.

Anahtar kelimeler: C-reaktif protein, inflamasyon mediatörleri, akciğer neoplazmı, prokalsitonin

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Introduction

Small cell lung cancer (SCLC) is a histological subtype with the most aggressive clinical course within lung cancers (LC), which frequently appears with metastatic disease at regional lymph nodes or distant organs at the time of diagnosis [1]. Although SCLC is quite sensitive to chemotherapy, patients may respond differently to similar therapies [2]. Therefore, predicting prognosis in SCLC in the clinical setting is important. Although various prognostic factors such as performance score, age, gender and serum lactate dehydrogenase level, have been investigated in order to predict prognosis, no standardized prognostic marker is currently available [3]. Therefore, new prognostic markers are required.

It is known that there is a close relationship between carcinogenesis and systemic inflammation [4]. Proinflammatory mediators tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, interferon-γ (IFN-γ) increase during carcinogenesis [4]. These cytokines, which are elevated during inflammation cause a decrease in albumin level, which is known as a negative acute phase reactant and produced in liver [5]. Fibrinogen is also a protein, synthesized in hepatocytes, and similarly, it is produced as a response to proinflammatory cytokines [6]. Increased proinflammatory cytokines, especially IL-6, cause an increase in C-reactive protein (CRP) simultaneously [7]. Similar to CRP, procal-citonin (PCT) concentration is also recognized as a marker for systemic inflam-mation [8]. Homeostasis is disturbed along with changing levels of inflammatory markers and antioxidant/anti-inflammatory activity and apoptosis decrease [5]. As a result, these elevated cytokines trigger inflammation and contribute in tumor progression and metastasis [9].

CRP/albumin ratio (CAR) is one of the inflammatory markers, found to be prognostic and predictive in many cancers, including esophagus cancer (EC), pancreas cancer (PC) and non-small cell lung cancer (NSCLC) [10-12]. It has been demonstrated that PCT and CRP are prognostic in many cancers, such as colon cancer and NSCLC [13-14]. Prognostic nutritional index (PNI), one of systemic immune-inflammatory indicators, which is calculated by using albumin value, has been found to be associated with prognosis in many solid organ malignancies such as urinary system cancer and LC [15,16]. Raised fibrinogen-to-albumin ratio (FAR) that was started to be used as a new marker recently has been found to be associated with poorer survival and higher recurrence risk in many malignancies, such as hepatocellular cancer (HCC), gastric cancer (GC), NSCLC [17-19]. Despite increasing evidence about effects of inflammation-based scores on prognosis of SCLC patients, there is limited knowledge about the prognostic significance of FAR in SCLC. Therefore in this study, we aimed to exhibit prognostic significance of FAR and other parameters in SCLC.

Materials and Method

In this study, 195 patients, followed-up with pathologically confirmed histological diagnosis of SCLC, were analyzed retrospectively in Medical Oncology Clinic between September 2013 and January 2021. The inclusion criteria of this study were: 1) cytological or histological diagnosis of SCLC, 2) age of at least 18 years, 3) presence of at least one measurable lesion, 4) presence of pretreatment blood test and sufficient laboratory data. The exclusion criteria were: 1) receipt of non-platinum chemotherapy or checkpoint inhibitors as first-line therapy; 2) presence second primary solid organ malignancy, 3) presence of benign or malign

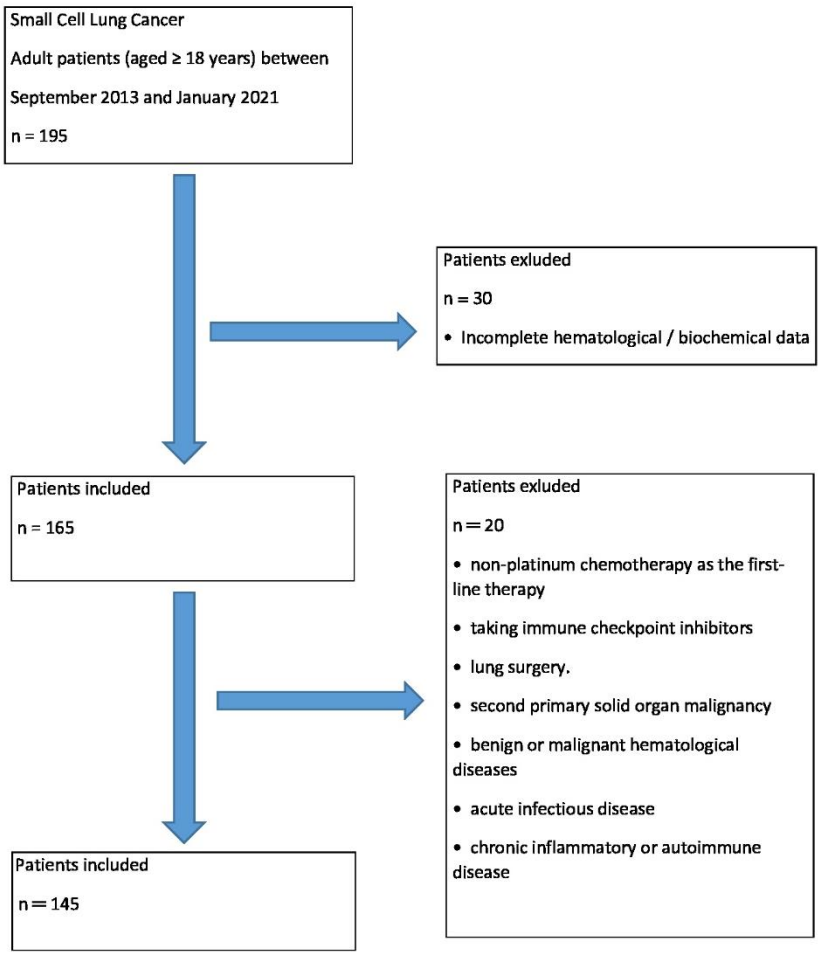

Figure 1. Study inclusion and exclusion criteria.

hematological diseases, acute infectious diseases, chronic inflammatory or auto-immune diseases, 4) history of pulmonary surgery. A total of 50 patients were excluded from study due to these reasons, and 145 patients with SCLC diagnosis were included in the study (Figure 1). Tumor staging was assessed according to the American Joint Committee on Cancer (AJCC) guidelines, 8th edition [20].

Clinical variables, such as, gender, age, Eastern Cooperative Oncology Group (ECOG) performance status and tumor characteristics, were obtained from the patient file records. Laboratory findings, such as, fibrinogen, albumin and CRP at the time of diagnosis were obtained from the hospital data system. CAR was obtained by dividing CRP to albumin. PCR was obtained from ratio of PCT to CRP. PNI values were calculated using the formula of [(10 × albumin (g / L)) + (0.005 × lymphocyte count)]. FAR was obtained by dividing fibrinogen to albumin.

Ethical Approval

All procedures performed in this study were compliant with the ethical standards of the institutional research committee and with 1964 Helsinki Declaration, as amended or comparable ethical standards. Approval was obtained from the local ethics committee of our hospital (2020/235).

Follow-Up

During the treatment period, starting from the date of diagnosis, physical examination and serum chemistry tests of the patients were

performed on a monthly basis and thoracic-abdominal computed tomography (CT) test was performed when necessary. Follow-up visits were provided bimonthly for the first year, quarterly in the 2nd and 3rd years, semi-annually in the 4th and 5th years, and then annually. Thoracic-abdominal CT was performed at each visit, and cerebral magnetic resonance imaging (MRI) or CT was performed every three months in the first year and every six months for two years after the first year.

Study Endpoints

Progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death. OS was defined as the period from the time of diagnosis until death or the last follow-up period for living patients.

Statistics

The receiver operating characteristic (ROC) curve analysis was performed to determine the best cut-off value for variables and the areas under the curve (AUCs) were calculated. CAR, PCR, PNI and FAR were evaluated as dichotomized variables by obtaining the best cut-off value. Shapiro–Wilk test was used to determine if variables were normally distributed. The Chi-square (χ^2) test or Fisher's exact test was used to analyze the relationship between the group of low and high CAR, PCR, PNI and FAR with clinic-pathological parameters. Associations between parameters and survival were analyzed using Kaplan–Meier curves and were compared by the log-rank test. Hazard ratios (HRs), estimated from the Cox analysis, were reported as relative risks with corresponding 95% confidence intervals (CIs). All variables with a p-value <0.05 in the univariate analysis were included in multivariate Cox regression analysis with backward selection. $p < 0.05$ was considered statistically significant in multivariate Cox regression analysis. All analyses were performed using the SPSS statistical software package (SPSS Version, 21, Armonk; NY: IBM Corp).

Results

Determining Optimal Cut-off Values of FAR and Other Parameters

According to ROC curve analysis, best cut-off point for FAR was 0.138, providing 72% sensitivity and 64% specificity. Cut-off values for highest sensitivity and specificity for CAR, PCR and PNI were 0.646, 6.1 and 33.9, respectively. FAR had the highest AUC (0.73) among prognostic factors. AUC values for CAR (0.63), PCR (0.60) and PNI (0.68) were found to be as indicated. The cut-off value determined by the local laboratory was used for serum LDH level (243).

Relationship between FAR with Clinical and Pathological Variables

Median age of 145 patients included in the study was 65±9.5 years. 43 of patients (29.7%) were 60 years and of age and younger and 102 (70.3%) were above 60 years. The clinical and demographic characteristics of the patients are shown in Table 1. Higher FAR was significantly related to; poor ECOG performance status, extensive stage, number of extrapulmonary lesions, higher CAR and higher PCR (p:0.001, p:0.008, p:0.0025, p:0.031, p:0.003 respectively).

Relationship between Survival Results with FAR and Other Parameters

At the end of a median follow up of 15± 15.3 months; while 66 (45.5%) patients showed progression, 40 (27.6%) patients have lost their lives.

According to Kaplan Meier analysis, in the group with FAR≥0.138, both PFS (11.7 months vs. 42.1 months, p<0.001) and OS (16.6 months vs. 64.3 months, p<0.001) were found to be short. Both PFS and OS were found to be shorter in patients with high ECOG

Table 1. Clinical and demographic characteristics of patients

		n (%)
Age groups (years)		
	≤ 60	43 (29.7)
	> 60	102 (70.3)
Gender		
	Male	133(91.7)
	Female	12 (8.3)
ECOG		
	0	49 (33.8)
	1	61 (42.1)
	2	35 (24.1)
Smoking		
	Yes	71 (49)
	No	74 (51)
Comorbidity		
	Yes	92 (63.4)
	No	53 (36.6)
Stage		
	Limited	65 (44.8)
	Extensive	80 (55.2)
PCI		
	Yes	18 (12.4)
	No	127(87.6)
Thoracic RT		
	Yes	29 (20)
	No	116 (80)
Palliative RT		
	Yes	11 (7.6)
	No	134 (92.4)
Extrapulmonary lesion		
	0	65 (44.8)
	1	40 (27.6)
	2	40 (27.6)
LDH		
	< 243	41 (28.3)
	≥ 243	104 (71.7)
PNI		
	< 33.9	60 (41.4)
	≥ 33.9	85 (58.6)
CAR		
	< 0.646	79 (54.5)
	≥ 0.646	66 (45.5)
FAR		
	< 0.138	72 (49.7)
	≥ 0.138	73 (50.3)
PCR		
	< 6.1	107 (73.8)
	≥ 6.1	38 (26.2)

ECOG Eastern Cooperative Oncology Group performance status, TNM tumor, node, metastasis, PCI prophylactic cranial irradiation, Thoracic RT: Thoracic Radiotherapy, Palliative RT: Palliative Radiotherapy, LDH: lactate dehydrogenase, CAR C-reactive protein/ albumin ratio, PCR procalcitonin/ C-reactive protein ratio, PNI prognostic nutritional index, FAR fibrinojen-to-albumin ratio,

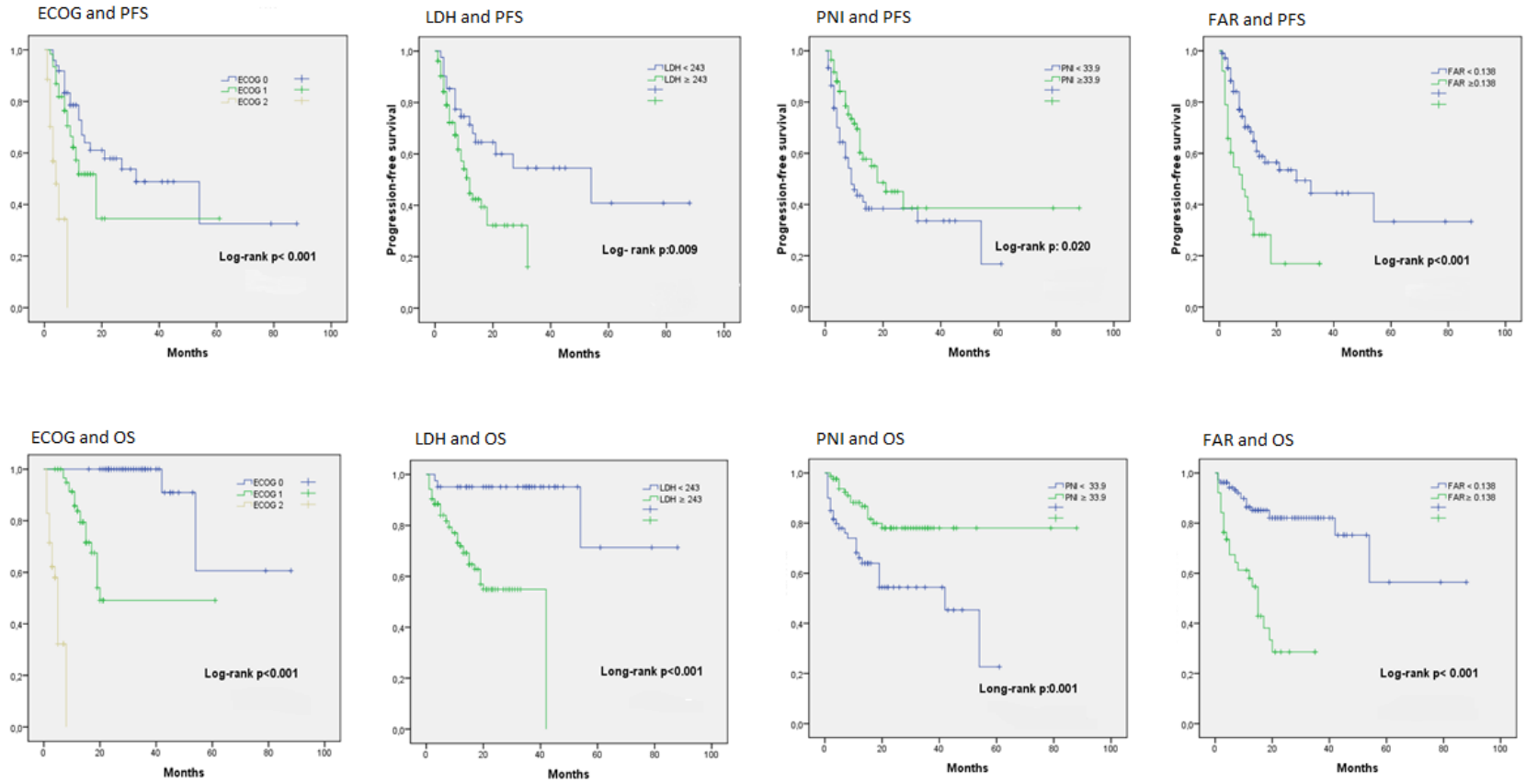

Figure 2. Kaplan-Meier curves for PFS/ OS according to ECOG and markers.

Table 2. Univariate and multivariate cox regression analyses for factors predicting progression-free survival

	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age groups (years)				
> 60 (ref=≤ 60)	0.817 (0.486-1.373)	0.445		
Gender				
Female (ref=male)	0.818 (0.373-1.794)	0.616		
ECOG				
1 (ref=0)	0.110 (0.051-0.236)	**<0.001**	0.204(0.083-0.501)	**0.001**
2	0.183 (0.093-0.361)	**<0.001**	0.195(0.095-0.400)	**<0.001**
Smoking				
Yes (ref=no)	1.149 (0.698-1.891)	0.586		
Comorbidity				
Yes (ref=no)	0.792 (0.485-1.295)	0.353		
TNM Stage				
Extensive (ref=limited)	1.898 (1.142-3.156)	**0.013**	1.154 (0.569-2.342)	0.691
PCI				
No (ref=yes)	0.380 (0.163-0.890)	**0.026**	0.563(0.175-1.812)	0.335
Thoracic RT				
No (ref=yes)	0.510 (0.266-0.978)	**0.043**	1.018(0.400-2.590)	0.971
Palliative RT				
No (ref=yes)	1.840 (0.876-3.864)	0.107		
Extrapulmonary lesion				
1 (ref=0)	0.525 (0.287-0.962)	**0.037**	1.223(0.642-2.329)	0.540
2	0.995(0.530-1.867)	0.988		
LDH				
≥ 243 (ref= < 243)	2.135 (1.180-3.864)	**0.012**	1.988(1.009-3.916)	**0.047**
CAR				
≥ 0.646 (ref= <0.646)	1.705 (1.045-2.779)	**0.032**	0.527(0.208-1.334)	0.176
PCR				
≥6.1(ref= <6.1)	2.005(1.241-3.385)	**0.005**	2.006(0.778-5.172)	0.150
PNI				
< 33.9 (ref= ≥ 33.9)	0.574(0.353-0.932)	**0.025**	0.531(0.302-0.934)	**0.028**
FAR				
≥0.138 (ref=<0.138)	2.685(1.641-4.393)	**<0.001**	2.096 (1.172-3.747)	**0.013**

ECOG Eastern Cooperative Oncology Group performance status, TNM tumor, node, metastasis, PCI prophylactic cranial irradiation, Thoracic RT: Thoracic Radiotherapy, Palliative RT: Palliative Radiotherapy, LDH: lactate dehydrogenase, CAR C-reactive protein/ albumin ratio, PCR procalcitonin/ C-reactive protein ratio, PNI prognostic nutritional index, FAR fibrinojen-to-albumin ratio, Statistically significant (P < 0.05) values are in bold

performance status. Both PFS and OS were shorter in the group with LDH≥243. Both PFS and OS were longer and the difference was significant in the group with PNI ≥ 33.9 compared to low PNI (Figure 2). Only OS was significantly shorter in smoking group (20 months, 61 months, p:0.033). With increasing number of extrapulmonary lesions, both PFS (14 months, 17 months, 41 months, p:0.037) and OS (30 months, 33 months, 62 months, p:0.025) were found to be significantly shorter. Both PFS (16 months, 41 months, p:0.010) and OS (34 months, 62 months, p:0.007) were found as shorter in the group

Table 3. Univariate and multivariate cox regression analyses for factors predicting overall survival

	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age groups (years)				
> 60 (ref=≤ 60)	1.676 (0.772-3.639)	0.192		
Gender				
Female (ref=male)	1.155 (0.355-3.758)	0.811		
ECOG				
1 (ref=0)	0.001 (0.000-0.009)	**<0.001**	0.001(0.000-0.013)	**<0.001**
2	0.024 (0.006-0.094)	**<0.001**	0.019(0.004-0.098)	**<0.001**
Smoking				
Yes (ref= no)	2.006 (1.037-3.884)	**0.039**	0.694(0.299-1.608)	0.394
Comorbidity				
Yes (ref=no)	1.339 (0.680-2.636)	0.398		
TNM Stage				
Extensive (ref= limited)	2.467 (1.239-4.913)	**0.010**	1.255(0.487-3.233)	0.638
PCI				
No (ref=yes)	0.211 (0.050-0.894)	**0.035**	0.249(0.021-2.916)	0.268
Thoracic RT				
No (ref= yes)	0.293 (0.103-0.836)	**0.022**	0.567(0.109-2.960)	0.501
Palliative RT				
No (ref=yes)	1.599 (0.625-4.091)	0.327		
Extrapulmonary lesion				
1 (ref=0)	0.378(0.173-0.825)	**0.015**	1.132(0.482-2.656)	0.776
>1	0.871(0.409-1.854)	0.721		
LDH				
≥ 243 (ref=< 243)	13.421 (3.021-59.613)	**0.001**	8.105(1.374-47.797)	**0.021**
CAR				
≥ 0.646 (ref= < 0.646)	2.786 (1.431-5.427)	**0.003**	0.607(0.214-1.725)	0.349
PCR				
≥6.1(ref=<6.1)	4.036(1.914-8.512)	**<0.001**	2.851(0.872-9.319)	0.083
PNI				
< 33.9 (ref= ≥ 33.9)	0.355(0.187-0.676)	**0.002**	0.331(0.143-0.765)	**0.010**
FAR				
≥0.138 (ref=<0.138)	5.389(2.814-10.320)	**<0.001**	2.875 (1.356-6.099)	**0.006**

ECOG Eastern Cooperative Oncology Group performance status, TNM tumor, node, metastasis, PCI prophylactic cranial irradiation, Thoracic RT: Thoracic Radiotherapy, Palliative RT: Palliative Radiotherapy, LDH: lactate dehydrogenase, CAR C-reactive protein/ albumin ratio, PCR procalcitonin/ C-reactive protein ratio, PNI prognostic nutritional index, FAR fibrinojen-to-albumin ratio, Statistically significant (P < 0.05) values are in bold

with extensive stage compared to the group with limited stage. Both PFS (48 months, 30 months, p:0.018) and OS (70 months, 48 months, p:0.020) were found to be longer in those receiving prophylactic cranial RT compared to those, who did not. Both PFS (21 months, 12 months, p:0.035) and OS (53.4 months, 31.2 months, p:0.014) were found to be longer in those receiving thoracic RT compared to those, who did not. There was no difference for PFS (37.5 months, 12.7 months, p:0.094) and OS (56 months, 33 months, p:0.318) in patients receiving palliative RT. Both PFS (19.5 months vs. 39.8 months, p:0.027) and OS (29.6 months vs. 62.6 months, p:0.001) were shorter in the group with CAR ≥ 0.646. Both PFS (18.5 months vs 42.3 months, p:0.003) and OS (29.1 months vs 65.2 months, p<0.001) were found to be shorter in the group with PCR ≥ 6.1.

As seen in Table 2 and 3, in multivariate analysis, ECOG performance status, PNI and

FAR were found to be independent prognostic factors for both PFS and OS.

Discussion

SCLC, known for its aggressive biological behavior, has a poor prognosis and despite novel treatment modalities, satisfactory survival times can not be obtained. ECOG performance status, PNI and FAR were found as independent prognostic factors both for PFS and OS in SCLC for the first time in this study. According to our best knowledge, this study is the first of its kind, showing prognostic importance of FAR in SCLC patients.

It is known that CAR, one of systemic inflammatory indicators, has a predictive and prognostic importance in many cancers, such as, nasopharyngeal carcinoma and pancreatic cancer, GC [21-23]. There is only one study, involving 367 patients with diagnosis of SCLC, and OS was found to be short and independently prognostic in the group with high CAR (cut-off: 0.441) [24]. In our study, while both PFS and OS were shorter and the difference was significant for patients with high CAR, it could not be deemed as independently prognostic. We think that differences between studies might have been originated from limit values used and differences of analysis times.

Another inflammatory indicator is PCR obtained from the ratio of PCT to CRP. PCT level is an important prognostic factor for survival in malignancies such as HCC, colorectal cancer (CRC), GC and also it was found to be associated with postoperative infections [25-27]. In a study on 147 patients with LC, a high PCT level was found as independently prognostic [28]. In a meta-analysis of 3165 patients with early stage NSCLC, high baseline CRP level had been found to be in significantly correlation with poor prognosis [29]. PCR has been examined only in one study on solid tumors, and it has been demonstrated that it had increased specificity for sepsis and localized infection and that it could have been a safe method to exclude infection, but its correlation with prognosis and mortality has not been examined [30]. Our study is important in the sense that it is the first study, showing the correlation of PCR with prognosis in a solid organ malignancy. In our study, PFS and OS were found to be shorter in the group with high PCR (≥ 6.1), and the difference was significant.

PNI, which is an immune-nutritional indicator, is calculated with serum albumin level and lymphocyte count, and it has been found as independently prognostic in many malignancies such as gynecologic cancers, PC, CRC [31-33]. In a study on limited stage SCLC patients, PNI (≥ 53) had been found as independently prognostic both for PFS and OS [34]. In a study on 97 patients with extensive SCLC, it has been found that while there had been no difference in terms of PFS between groups with high PNI (≥ 44.3) and low PNI, PNI had been found as independently prognostic for OS [35]. In line with other studies, we also found both PFS and OS to be longer in the group with high PNI (≥ 33.9). Also, we found PNI to be an independent prognostic factor both for PFS and OS.

FAR is another parameter reflecting systemic inflammatory balance, and prognostic importance of FAR has been demonstrated in various malignancies such as GC, breast cancer and gallbladder cancer [36-38]. Fibrinogen is an acute phase protein produced by liver, and its level increases in case of malignancy or systemic inflammation, leading to prothrombotic effects [39]. Also, fibrinogen plays an important role in tumor metastasis and angiogenesis [39]. Thrombocyte-fibrin clusters, formed by conversion of fibrinogen into fibrin, surround tumor cells and may help the concealment of

tumor cells from immune system [40]. Moreover, it contribute in the invasive and metastasize ability of tumor cell by causing binding and distribution of tumor cells into vascular wall with an angiogenetic effect [41]. Albumin is a negative acute phase protein, level of which decreases along with release of inflammatory cytokines, such as, TNF-α and IL-6, thereby showing immuno-inflammatory status [42]. It is thought that FAR alone may demonstrate immuno-inflammatory status more extensively compared to plasma fibrinogen or albumin. In a study on 194 patients with lung adenocarcinoma diagnosis, it has been found to be independently prognostic only for PFS, although both PFS and OS were shorter in the group with high FAR [43]. In a study on 270 patients with advanced NSCLC, albumin fibrinogen ratio (AFR) had been examined, and high AFR had been correlated with longer PFS and OS and it had been found to be independently prognostic for both [44]. In a study on 529 patients with NSCLC, who had undergone a resection, pre-operative high AFR measured had been found to be correlated with longer OS and DFS and it had been found as independently prognostic [45]. Our study is the first showing prognostic importance of FAR in SCLC patients, and FAR was found to be independently prognostic both for PFS and OS.

Limiting point of our study is that it was retrospective and included relatively small number of patients. Therefore, studies with prospective and multicenter cohorts including more variables are needed.

Conclusion

FAR can be accepted as a new parameter predicting survival times for patients with SCLC. Due to its useability in daily practice and its low cost, it is an advantageous biomarker.

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Original Article

Evaluation of Patients with Chronic Immune Thrombocytopenic Purpura Treated with Eltrombopag: A Single Center Experience

Eltrombopag Tedavisi Alan Kronik İmmün Trombositopenik Purpura Tanılı Hastaların Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Introduction: The goal of treatment in chronic immune thrombocytopenia is to keep the platelet count within a safe range that can prevent bleeding. Eltrombopag is an oral thrombopoietin receptor agonist for the treatment of thrombocytopenia. We evaluated the demographic characteristics, eltrombopag treatment response and side-effect profile of a total of 79 patients using eltrombopag with follow-up at our center. By comparing our findings with the literature data, we aimed to reveal the differences in response rates and side-effect profiles.

Materials and methods: A total of 79 patients who were diagnosed with chronic immune thrombocytopenia and used eltrombopag, who applied to the hematology outpatient clinic of our center between January 1, 2010 and May 1, 2021, were evaluated in a randomized retrospective manner. Demographic characteristics of the patients, eltrombopag treatment response, and side-effect profile were recorded. Pearson Chi-square test was used to analyze categorical data.

Results: In our study, the data of 79 patients who received eltrombopag treatment were analyzed retrospectively (45 females-34 males, mean age 49±19.1 years). When the basal platelet count of the patients was evaluated before the treatment, the mean value was calculated as 17,000/mm^3. When all platelet values after eltrombopag treatment were examined, the mean maximum platelet value was 127,000/mm^3, and the mean time to reach the maximum platelet value was 30 days. Complete remission was achieved in 46 (58%) patients, partial remission was achieved in 14 (17%) patients, and 19 (25%) didn't respond. Sixteen (20%) patients had a prolonged response

Discussion: While basal platelet count and treatment responses for eltrombopag treatment were similar to those in the literature, prolonged response rates were higher in our study. Although the rate of elevation in liver enzyme follow-ups in our study was higher than the data in the literature, the rates of having to discontinue the drug for this reason were similar.

Keywords: Eltrombopag, chronic immune thrombocytopenic purpura, remission, prolonged response

ÖZET

Giriş: Kronik immün trombositopenide tedavi hedefi trombosit sayısını kanamayı önleyebilecek güvenli bir aralıkta tutmaktır. Eltrombopag, trombositopeni tedavisinde oral bir trombopoietin reseptör agonistidir. Merkezimizde takipli eltrombopag kullanan toplam 79 hastanın demografik özelliklerini, eltrombopag tedavi yanıtını ve yan etki profilini değerlendirdik. Bulgularımızı literatür verileri ile kıyaslayarak özellikle yanıt oranlarındaki ve yan etki profilindeki farklılıkları ortaya koymayı amaçladık.

Gereç ve yöntemler: Çalışmamıza 1 Ocak 2010–1 Mayıs 2021 tarihleri arasında merkezimizin hematoloji polikliniğine başvuran kronik immun trombositopeni tanısı konulan ve eltrombopag kullanan toplam 79 hasta randomize olacak şekilde retrospektif olarak değerlendirildi. Hastaların demografik özellikleri, eltrombopag tedavi yanıtı, yan etki profili kaydedildi. Kategorik verilerin incelenmesinde Pearson Ki-kare testi kullanılmıştır.

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Bulgular: Çalışmamızda eltrombopag tedavisi alan 79 hastanın verileri retrospektif olarak incelendi (45 kadın-34 erkek, yaş ortalaması 49±19,1 yıl). Hastaların tedavi öncesi bazal trombosit sayısı değerlendirildiğinde ortalama değeri 17,000/mm^3 olarak hesaplandı. Eltrombopag tedavisinden sonraki tüm trombosit değerleri incelendiğinde maksimum trombosit değeri ortalaması 127,000/mm^3, maksimum trombosit değerine ulaşılan ortalama süre ise 30 gün şeklindeydi. Hastaların 46'sında (%58) komplet remisyon, 14'ünde (%17) parsiyel remisyon sağlanırken 19'unda (%25) yanıt alınamadığı izlendi. Hastaların 16'sı (%20) uzamış cevaba sahipti.
Tartışma: Eltrombopag tedavi kararı verilen bazal trombosit sayısı ve tedavi yanıtları literatür ile benzerken, uzamış cevap oranlarının bizim çalışmamızda daha fazla olduğu görüldü. Çalışmamızdaki karaciğer enzim takiplerindeki yükselme oranı literatürdeki verilerden daha yüksek bulunmasına rağmen, bu sebepten ilacın kesilmek zorunda kalınmasının oranları benzerdir.

Anahtar kelimeler: Eltrombopag, kronik immün trombositopenik purpura, remisyon, uzamış cevap

Introduction

Immune thrombocytopenia (ITP) is an autoimmune disease in which antiplatelet antibodies accelerate platelet destruction. Most ITP patients are asymptomatic if their platelet count is greater than 50,000/mm^3. However, persistent low platelet count (<20,000 mm^3) is associated with an increased risk of serious bleeding, such as intracranial hemorrhage [1].

The main goal in the management of chronic ITP is to achieve a safe platelet count that can prevent major bleeding in the patient, rather than to normalize the platelet count, thereby reducing treatment-related toxicity as much as possible [2].

Guidelines in the literature recommend corticosteroids as first-line therapy and splenectomy as second-line therapy in ITP. Different options are available for patients who do not or do not respond to splenectomy, such as IVIG (intravenous immunoglobulin), IV (intravenous) anti-D, rituximab, danazol, azathioprine, vinca alkaloids, and cyclophosphamide [3-6].

Eltrombopag is an oral, small molecule, non-peptide thrombopoietin receptor agonist that interacts with the transmembrane domain of the thrombopoietin receptor. The drug interacts with the transmembrane domain of the receptor, initiating thrombopoietin-receptor signaling, thereby inducing proliferation and differentiation of cells in the megakaryocytic lineage. Recent consensus statements and guidelines recommend thrombopoietin-receptor (TPO-R) agonists as second- and third-line therapies [7-11]. Since it does not have as old a history as other drugs used in the treatment of ITP, many international studies are carried out to illuminate the clinical reflections of the drug.

Although headache is the most commonly reported side effect with the use of eltrombopag in ITP, more serious side effects such as increased liver enzymes, cataract development and thrombosis can occur. Such side effects can sometimes lead to discontinuation of treatment [8,9].

In this study, we evaluated the demographic characteristics, eltrombopag treatment response and side effect profile of 79 patients diagnosed with chronic immune thrombocytopenia and using eltrombopag, and aimed to reveal the differences in response rates and side effect profile.

Material and Methods

A total of 79 patients who were diagnosed with chronic immune thrombocytopenia and used eltrombopag, who applied to the Hematology Polyclinic of Eskişehir Osmangazi University Medical Faculty Hospital between January 1, 2010 and May 1, 2021 were included in our study. Demographic characteristics of the patients, eltrombopag treatment response and side effect profile were recorded. In platelet fol-

Table-1: Demographic Characteristics of the Patients

	n: 79(%)
Median age	49±19,1 years
Age at which the drug was started	53±17,2 years
Gender	
Female	45 (57%)
Male	34 (43%)
Etiology	
Idiopathic	58 (73%)
Secondary	21 (27%)
Splenectomy performed	26 (33%)
Prior treatments	
Steroid	79 (100%)
Intravenous immunoglobulin	69 (87%)
Danazol	23 (29%)
Rituximab	7 (8%)
Azathioprine	2 (2,5%)

low-up after use of eltrombopag, those with the highest platelet count above 100,000/mm^3 at any time were considered complete remission, those between 30,000/mm^3 and 100,000/mm^3 were considered partial remission, and those below 30,000/mm^3 were considered non-responders [8-12]. A prolonged response was defined as platelet values ≥50,000/mm^3 for 12 weeks or longer without the need for any treatment after discontinuation of eltrombopag therapy [12]. Patients with partial or complete response to eltrombopag treatment but unresponsive (<30,000/mm^3) during follow-up were considered eltrombopag resistant [12]. Follow-up and overall survival of the patients were recorded.

E25403353-050.99-214165 approval was obtained from the Eskişehir Osmangazi University Non-Interventional Ethics Committee for the study. All procedures performed comply with the ethical standards of the institution and/or the research committee and the 1964 Declaration of Helsinki and subsequent national amendments or comparable ethical standards.

Statistical Analysis: The obtained data were analyzed with SPSS 23.0 (SPSS Inc., Chicago, IL, USA) program. Kolmogorov-Smirnov test was used to evaluate the distribution of data. The distribution of normal data was reported as mean ± standard deviation (SD), non-normally distributed and non-parametric data were reported as the median (median).The Mann-Whitney U test was used for the comparison of two groups for data not normally distributed. Pearson Chi-square test was used to analyze categorical data. In the statistical evaluation, $p<0.05$ was considered significant.

Results

The follow-up period of the patients who were started on eltrombopag ranged from 15 days to 10 years, and the median follow-up period was determined as 18 months. The duration of use of eltrombopag varied between 8 days and 3285 days, with a median of 90 days. Demographic characteristics of 79 patients included in the study are shown in Table 1.

When the etiology of the patients diagnosed with ITP given eltrombopag was examined, it was seen that 58 patients were idiopathic and 21 patients had secondary ITP. Of the patients with secondary ITP, 13 were secondary to hematological malignancy, four were secondary to autoimmune diseases, two were secondary to solid cancer, and two were secondary to drug/vaccine. Prior to the use of eltrombopag, all patients had received steroid therapy. The previous treatments received by the patients are shown in Table 1.

When the basal platelet count of the patients who were started on eltrombopag treatment was evaluated, the median value was calculated as 17,000/mm^3 (2,000/mm^3- 57,000/mm^3). It was

Table-2: Response, prolonged response, and resistance to Eltrombopag therapy

	n: 79(%)
Response (≥50,000/mm^3)	54 (68%)
Complete remission (≥100,000/mm^3)	46 (58%)
Partial remission (30,000/mm^3-100,000/mm^3)	14 (17%)
Unresponsive (<30,000/mm^3)	19 (25%)
Prolonged response[1]	16 (20%)
Resistance[2]	8 (10%)

[1]platelet values ≥50000/mm^3 for 12 weeks or longer on any mild side
[2]partial or complete response but no response (<30000/mm^3) at follow-up

Table-3: Side effect profile

	n: 79(%)
Weakness	8 (10%)
Headache	11 (14%)
Nause	3 (4%)
Liver enzyme elevation	13 (16%)
Major bleeding (gastrointestinal)	2 (2,5%)
Minor bleeding (nose, gums, etc.)	7 (9%)
Thromboembolic event	3 (4%)
Cataract	0 (0%)

observed that 32 (40%) of the patients had a thrombocyte value <15,000/mm^3, 47 (60%) had ≥15,000/mm^3 at treatment baseline. When all platelet values after eltrombopag treatment were examined, the median maximum platelet value was 127,000/mm^3 (3,000/mm^3-913,000/mm^3), and the median time to reach the maximum platelet value was 30 days (1 day-495 days).

In response, it was observed that 60 (75%) patients were responsive to this treatment when the platelet count was 30,000/mm^3 and above at any time, and 54 (68%) patients when the platelet count was 50,000/mm^3 and above. The median day on the first day that patients exceeded 30,000/mm^3 after treatment was day 8 (1 day-45 days), while the median day on the first day when patients exceeded 50,000/mm^3 was day 11 (1 day-58 days).

The response status of the patients to eltrombopag treatment is shown in Table 2. Sixteen (20%) of the patients had a prolonged response and no additional drug requirement developed during their follow-up. Most of the patients with prolonged response are still followed up; The median prolonged response time was found to be 16 months (3.5 months - 64 months).

Eight patients (10%) developed resistance during follow-up. The median time to resistance development was 104 days (23 days -1150 days).

There was no statistically significant difference between the responses of the patients receiving eltrombopag treatment to the treatment, gender and age (p:0.109, p:0.393). Similarly, there was no statistically significant difference between treatment response and initial platelet counts, etiology of ITP, and which line of treatment eltrombopagin was given (p:0.223, p:0.192, p:0.161).

The side effects of patients after eltrombopag are shown in Table 3. Two of the thrombo-embolic events were deep vein thrombosis and one was sinus vein thrombosis. Sixteen (20%) of the patients died during their follow-

up. When the causes of death were examined, it was observed that 9 of them died due to the underlying malignant disease, and three of them died from sepsis. The cause of death of six patients was unknown. Since resistance developed in four of these six patients, it was observed that eltrombopag treatment was discontinued during the follow-up and alternative treatments were started.

Discussion

While the eltrombopag treatment response in our study was 68% similar to the literature, it was observed that the prolonged response rate was 20% higher than the data in the literature. It was observed that only 2.5% of our patients discontinued treatment due to side effects. Although the rate of elevation in liver enzyme follow-ups in our study was higher than the data in the literature, the rates of having to discontinue the drug for this reason were similar.

The median age of patients initiated on eltrombopag was 50 years in the EXTEND study [10], 47 years in the RAISE study [8], Bussel JB. et al. found it to be 47 years [9]. The mean age of onset of eltrombopag in our study was calculated as 53±17.2 years.

The basal platelet value before eltrombopag treatment is lower than 15,000/mm^3 in the literature, which is similar to our study. Percentage of patients with baseline platelet count less than 15,000/mm^3 43% in EXTEND [10], 50% in RAISE [8], Bussel JB. et al. [9], it was found to be 50% in their study, and it was found to be 40% in our study.

In the studies conducted by Cheng et al. in 2011, it was observed that 79% (n=106) of the patients given eltrombopag responded to the treatment [8]. Again, in the experience of 40 patients with eltrombopag from eight different centers in the Aegean Region in our country, the overall response rate was reported to be 87% [13]. Similarly, in our study, a response was observed in 68% of our patients, increasing the platelet count to over 50,000/mm^3.

Saleh MN. et al. In the EXTEND study conducted by [10] with 299 patients, the rate of patients with prolonged response was found to be 4%. In our study, the rate of patients with prolonged response was found to be 20%. It was thought that the existing differences may be due to the fact that the response and effect are affected by many factors such as genetic structure, ethnicity, environmental effects, and the relatively small number of participants in our study.

In our country, the response rate was reported as 77% in the experience of 31 patients with eltrombopag, whose data were scanned in the Ankara Oncology Training and Research Hospital in 2021 [14]. In the same study, the basal platelet count before treatment was determined as 11,000/mm^3, and the median on the first day when it exceeded 50,000/mm^3 was determined as the 17th day [14]. Similarly, in our study, it was observed that 68% of the patients were responsive to treatment. In our study, similar to Ankara data, basal platelet count exceeded 17,000/mm^3 and 50,000/mm^3 and the median of the first day was 11 days.

Saleh MN. et al. Thrombosis developed during treatment in 5% of patients, and treatment was terminated in 2% of patients due to elevated liver enzymes [10]. Similarly, thromboembolic events developed in 4% of patients in our study. Dose reduction was performed in 16% of patients due to liver enzyme elevation. However, only 2.5% of the patients had to discontinue the treatment because the liver enzyme elevation persisted despite the low dose. This situation contributes to the literature in showing that the continuation of the drug is increased with close follow-up and appropriate dose reduction in case of liver enzyme elevation. As a result; Eltrombopag is an effective option in increasing platelet values and reducing

bleeding symptoms in patients with chronic ITP. It has been well tolerated in the short and long term to date, and long-term efficacy and safety studies are still ongoing.

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Original Article

Comparison of Clavien-Dindo and Common Terminology Criteria for Adverse Events Classifications in Postoperative Early-Stage Complications of Patients with Colorectal Cancer

Kolorektal Kanserli Hastaların Postoperatif Erken Dönem Komplikasyonlarında Clavien-Dindo ve Common Terminology Criteria for Adverse Events Sınıflamalarının Karşılaştırılması

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ABSTRACT

Introduction: The present study aimed to compare early complication rates, risk factors for complications, and hospital stay lengths in patients operated on for Colorectal cancer, by using Clavien-Dindo and Common Terminology Criteria for Adverse Events (CTCAE) complication classifications.

Materials and methods: 222 patients who were operated between March 2019 and June 2020 with the diagnosis of colorectal cancer and had early complications were evaluated retrospectively. Complications that developed in the early postoperative period were graded according to Clavien-Dindo and CTCAE classifications.The effects of demographic data, surgical technique, tumor location, neoadjuvant chemoradiotherapy history, preoperative transfusion history, urgency of the operation, additional organ resection, co-morbid diseases, pathological stage and duration of surgery on complications were compared.

Results: According to the Clavien-Dindo classification, the risk of developing complications was 3 times higher in male gender, 8 times higher in open surgical intervention, and 1.7 times higher in diabetes mellitus. According to the CTCAE classification, performing liver resection in the same session increased the risk of complications 5 times, while the use of open surgical technique increased the risk 8 times.

Discussion: Neither classification system is superior to the other in grading postoperative complications, and both can be used to rate surgical complications.

Keywords: Colorectal cancer, surgical,complication,Clavien-Dindo,CTCAE

ÖZET

Giriş: Kolorektal kanser tanısı ile opere edilen hastalarda Clavien-Dindo ve Common Terminology Criteria for Adverse Events (CTCAE) komplikasyon sınıflamaları kullanılarak, erken dönem komplikasyon oranları, komplikasyon oluşmasındaki risk faktörleri ve hastanede kalış sürelerinin karşılaştırılması amaçlandı.

Gereç ve yöntemler: Mart 2019 ve Haziran 2020 tarihleri arasında kolorektal kanser tanısıyla operasyona alınan, erken dönem komplikasyon gelişen 222 hasta retrospektif olarak değerlendirildi. Postoperatif erken dönemde gelişen komplikasyonlar, Clavien-Dindo ve CTCAE sınıflamalarına göre derecelendirildi. Hastaların demografik verilerinin, ameliyat tekniğinin, tümör yerleşiminin, neoadjuvan kemoradyoterapi öyküsünün, peroperatif transfüzyon öyküsünün, operasyonun aciliyeti, ek organ rezeksiyonunun, yandaş hastalıkların, patolojik evre ve ameliyat süresinin komplikasyon üzerine etkisi karşılaştırıldı.

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Bulgular: Clavien-Dindo sınıflamasına göre erkek cinsiyet 3 kat, açık cerrahi girişimde 8 kat ve diabetes mellitusta 1.7 kat komplikasyon gelişme riski daha fazla bulundu. CTCAE sınıflamasına göre aynı seansta karaciğer rezeksiyonu uygulanması komplikasyon riskini 5 kat, açık cerrahi teknikte risk 8 katına çıkmıştır.
Tartışma: Postoperatif komplikasyonları derecelendirirken iki sınıflama sisteminin birbirine üstünlüğü olmayıp, her ikisi de cerrahi komplikasyonları derecelendirmede kullanılabilir.

Anahtar kelimeler: Kolorektal kanser, cerrahi, komplikasyon, Clavien-Dindo, CTCAE

Introduction

Colorectal cancers are both the most common cancer types among gastrointestinal system cancers and the most cured cancer types after treatment [1]. Postoperative complications after colorectal cancer surgery occur in up to 50% of patients.They prolong hospital stay, increase hospital costs, increase mortality, and delay adjuvant treatments.To date, many classification systems have been used for the grading and standardization of postoperative complications in malignant patients.There is a need for an applicable complication classification that standardizes the treatment results of applications between different centers or different clinical applications in the same center. Clavien-Dindo and Common Terminology Criteria for Adverse Events (CTCAE) are frequently used methods and their parameters can be used together if necessary [2,3].

The Clavien classification was first used in 1992 [4].It was updated as the Clavien-Dindo classification in 2004 due to the lack of detailed treatment of complications and the inadequacy of evaluating permanent complications [2]. In the Clavien-Dindo classification, only five grades of post-operative complications are defined.In addition, Clavien-Dindo does not provide an organ-specific classification and does not consider pre-existing conditions and co-morbidities that play an important role in the occurrence of complications.

Standardized and published by the National Institutes of Health (NIH) and the National Cancer Institute (NCI), CTCAE is a classification system used to define the severity of organ toxicity for patients undergoing cancer treatment. This system is widely used to evaluate and describe the toxicity of chemotherapy or radiotherapy. It also describes side effects that result from intraoperative and postoperative complications. In 2009, CTCAE version 4.0 was revised to include significantly more surgical complications. However, it still lacked some common surgical complications [5]. The final version of this system, which also rates complications, was released in April 2018 [3].

In the present study, we grouped complications after colorectal cancer surgery according to Clavien-Dindo and CTCAE classifications. The aim of the study was to investigate the risk factors for complications and the differences between the two classification methods.

Material and Method

Setting and Participants

In the present study, 222 patients were analyzed retrospectively. All of the participants consisted of patients who were operated on with the diagnosis of colorectal cancer between March 2019 and June 2020 at the SBU Ankara Oncology SUAM General Surgery and Surgical Oncology Clinic.

Patients who were operated for colorectal malignancy recurrence, patients younger than 18 years of age, patients who underwent intervention for benign reasons and were considered inoperable and pregnant women were excluded from the study.

Data Collection

Data collected and recorded from patients included: patients' age, gender, comorbidities, body mass index, previous abdominal surgery, preoperative treatments, duration of operation, postoperative stage, operation performed, presence of ostomy, simultaneous liver resection, intraoperative complications, perioperative blood transfusion, early postoperative complications (post-op 30 days), need for reoperation and intensive care, number of days of hospitalization, post-operative 30-day mortality file data. Co-morbidities were divided into five groups as follows: cardiac diseases, diabetes mellitus, chronic obstructive pulmonary disease, other chronic diseases and no comorbidities. The cardiac group consisted of patients with a history of hypertension or previous ischemic cardiac heart disease. Patients receiving treatment for the diagnosis of type I-II diabetes were included in the diabetes group. On the other hand, patients with chronic obstructive pulmonary disease diagnosis in pre-operative evaluation or history formed the COPD group. The patients were divided into 2 groups as 65 years of age and older and under 65 years of age. Body mass index was grouped into two groups as below 30 and above 30. Tumor location was defined as right colon, up to the cecum and distal transverse colon. Tumor localization in the colon segments containing the sigmoid colon from the distal transverse colon was grouped as the left colon. Tumors at a distance of up to 15 cm from the anal canal seen in colonoscopy examination were included in the rectal cancer group. Patients with and without ileostomy and colostomy were considered as two separate groups. Postoperative staging was divided into three groups as stage 0-1-2, stage 3 and stage 4. Postoperative complications were evaluated separately in Clavien-Dindo and CTCAE classifications. Complications of I-II degree, not life-threatening and not requiring surgical or interventional procedures were evaluated in one group in both classifications. Serious complications of III-IV and V degrees, which were operated urgently, required intensive care and resulted in the patient's exitus, were examined under the second group.

Statistical Analysis

SPSS 21 statistical program was used in the statistical analysis of the data. (IBM SPSS Statistics Version 21, International Business Machines Corporation, Armonk, USA).

In the study, mean, standard deviation, median, minimum and maximum values are given for numerical type variables as descriptive statistics, while numbers and percentages are given for qualitative categorical data. Both numerical and categorical variables were compared with each other in terms of the degree of complication. After testing the data for that difference, the homogeneity of the distributions was evaluated. Afterwards, Student's t test and ANOVA were used for numeric variables in independent groups, and chi-square or Fisher exact test was used for categorical variables. A value of $p<0.05$ was accepted as a criterion for statistical significance. A multiple logistic regression model was established to determine the independent parameters affecting the degree of complication, and the odds ratios were given together with the confidence intervals. Our study was conducted in accordance with the Declaration of Helsinki and was approved by ethics committee of SBU Ankara Oncology SUAM (2022-01/32).

Results

The patients who underwent surgery consisted of 131 men (59%) and 91 women (41%). The median age of the patients was 64 (with the youngest being 28 and the oldest being 90). There was tumor localization in the right colon in 41 (18.5%) patients. Left colon group

Table 1. Demographics and clinical characteristics of patients

Age(years)	Median	64
	Range	28-90
	<65	112 (50.5%)
	≥65	110(49.5%)
Sex	Female	91 (41%)
	Male	131 (49.5%)
Body mass index (kg/m^2)	Median	25
	Range	19-32
	<30	180 (81.1%)
	≥30	42 (18.9%)
Tumor location	Right	41 (18.5%)
	Left	79 (35.6%)
	Rectum	102 (45.9%)
Previous abdominal operation		47 (21.2%)
Technique	Laparoscopic	106 (47.7%)
	Open	116 (52.3%)
Ostomy		91(41%)
Liver resection		11 (5%)
Emergency surgery		22 (9.9%)
Preoperative transfusion		9 (4.1%)
Neoadjuvant therapy		69 (31.1%)
Operative time	Median	145
	Range	90-325
	<150 minutes	117 (52.7%)
	≥150 minutes	105 (47.3%)
ASA	1	0
	2	124 (55.9%)
	3	95 (42.8%)
	4	3 (1.4%)
Stage	0-2	135 (60.8%)
	3	73 (32.9%)
	4	14 (6.3%)
Comorbid diseases	Cardiac	68 (30.6%)
	Copd	17 (7.7%)
	Dm	15 (6.8%)

ASA: American Society of Anesthesiologists, COPD: chronic obstructive lung disease dm: diabetes mellitus

consisted of 79 patients (35.6%). There were 102 patients (45.9%) in the rectal group.

Laparoscopic intervention was performed in 106 (47.7%) of the patients. The characteristics of all patients are included in Table 1.

Intraoperative complications occurred in four (1.8%) patients. During the operation, small bowel repair was performed in three patients and ureter repair was performed in one patient. Thirty (13.5%) patients were re-operated due to postoperative complications. Seven of these patients underwent surgical intervention due to surgical site infection. Three patients were re-operated for evisceration. Twelve patients were re-operated due to anastomotic leakage and deterioration in clinical follow-ups.Five patients were operated because complications related to ileostomy or colostomy developed. One patient was operated on due to bleeding the next day after surgery. Two patients were re-operated because of early-stage ileus. Twenty-nine (13.1%) of the patients were followed up in the surgical intensive care unit due to the deterioration of the general condition in their clinical follow-ups. The patient, who was re-operated on the third postoperative day due to the development of anastomotic leakage, was exitus one day later on the day of reoperation. The patient was re-operated on the 20th postoperative day, due to the development of ileus in the clinical follow-ups, which was performed concomitantly with surgery due to liver metastasis of rectum cancer. The patient was exitus on the 21st day of hospitalization due to the development of cardiac arrest. The patient, who was operated for colon cancer and underwent massive intraoperative transfusion, was exitus on the same day after the operation. Three patients (1.4%) were exitus within thirty days post operation.

Wound infection developed in 49 (22%) patients operated for colorectal cancer. 27 patients (12.1%) with complaints of nausea were treated medically. Intravenous or oral replacement was given to 43 patients (19.3%) due to electrolyte imbalance. Medical treatment was given to 34 patients (15.3%) due to pain. Seven patients (3.1%) were treated for high blood pressure. Two patients (0.9%) developed post-surgical mycord infarction. Three patients (1.3%) developed

Table 2. Postoperative complications and their classification

	N (%) median (range)
Patient with intraoperative complications	4 (1.8%)
Re-operated patient	30 (13.5%)
Patients needed ICU care	29 (13.1%)
30-day mortality	3 (1.4%)
Clavien-Dindo classification grade	
1	0
2	161(72.5%)
3A	13(5.9%)
3B	14(6.3%)
4A	20(9%)
4B	11(4.9%)
5	3(1.4%)
CTCAE complication grade	
G1	0
G2	162(73%)
G3	36(16.2%)
G4	21(9.5%)
G5	3(1.4%)
Hospital stay length(days)	
Median	8
Range	1-37

CTCAE: common terminology complication advers event,ICU: intensive care unit

neurological deficits. Two patients (0.9%) experienced delirium. Respiratory distress occurred in five patients (2.4%) during their clinical follow-up. Replacement was performed in eight patients (3.6%) due to low hemoglobin associated with surgery. Acute renal failure developed in five patients (2.4%). Postoperative fistula occurred in four patients (1.8%). Evisceration occurred in three patients (1.3%). Anastomotic leakage occurred in 16 patients (7.2%) after surgery, and 12 of these patients were re-operated. Complications related to ileostomy and colostomy developed in five patients (2.4%), and these patients were re-operated. Post-operative ileus was seen in nine patients (4%) and two patients were re-operated.

Complication rates in complication classification systems are shown in Table 2.

The relationship between the length of hospital stay evaluated in the present study and the degree of complication of the Clavien-Dindo and CTCAE classifications was found to be statistically significant (p=0.0001).It was observed that as the degree of complication increased, the length of stay in the hospital also increased. No difference was observed between the increase in age, BMI and operative time, and the degree of complications (Table 3). The evaluation of the parameters affecting the Clavien-Dindo classification in multivariate analysis showed that the risk of complications is significantly higher in patients with male gender, open surgery and diabetes mellitus. The risk of developing complications was 3 times higher in males, 8 times higher in open surgery, and 1.7 times higher in diabetes mellitus (Table 4).

In the multivariate analysis performed for the CTCAE classification, it was seen that performing liver resection in the same session increases the risk of complications 5 times. Likewise, the risk increased 8 times in the open surgical technique (Table 5).

Table 3. Comparison of complication classifications

	Clavien-Dindo		CTCAE	
	1-2	3-4-5	2	3-4-5
Age (mean±SD)	63.9±11.2	66.5±10.7	63.8±11.2	66.8±10.7
BMI (mean±SD) (kg/m$^{2)}$	25.8±2.7	27.6±3.12	25.8±2.7	25.5±3
Operation time (minute) (mean±SD)	156.2±43.4	165.8±47.8	156.4±44.1	163.5±45.1
Hospital stay (mean±SD) (day)	7.8±2.7*	15.1±7.3*	7.6±2.3*	14.3±7.0*
*p=0.0001				

SD: standart deviation, BMI: body mass index, CTCAE: common terminology complication advers event

Table 4. Multivariate Logistic Regression analysis of risk factors related Clavien-Dindo classification

Parameter	p	OR	95% CI
Male	0.006	3	1.37-6.58
Open Technique	0.0001	8	3.39-19
Diabetes Mellitus	0.014	1.7	1.1-2.7

OR:odds ratio,CI:confidence interval

Table 5. Multivariate Logistic Regression analysis of risk factors related CTCAE classification

Parameter	p	OR	95% CI
Liver resection	0.023	5.1	1.2-21.1
Open Technique	0.0001	8	3.39-19

CTCAE: common terminology complication advers event,OR:odds ratio,CI:confidence interval

Discussion

The present study examined the compatibility and differences of two different complication classification systems in colorectal cancer surgery. 222 patients who were classified for colorectal surgery complications with Clavien-Dindo and CTCAE were analyzed. Complications developed in four patients (1.8%) during the operation. Mortality occurred in three patients (1.4%) during the first 30-day follow-up after surgery. In their clinical follow-up, 30 patients (13.5%) were re-operated. In the study of Zawadki et al., 445 patients who underwent surgery with the diagnosis of colorectal cancer were examined. In this study, 51 patients were re-operated. 20 patients were re-operated for anastomotic leakage, eight patients due to bleeding, five patients due to wound dehiscence. 18 patients who were re-operated were not grouped under a special heading[6].The median length of stay in hospital was eight days. It was determined that, according to both classification systems, the hospitalization time increases as the degree of complication increases. In addition, open surgical technique is a risk factor for the development of complications according to both classification systems. Male gender and diabetes mellitus were found to be additional risk factors in the Clavien-Dindo classification. In the CTCAE classification, the risk of developing complications increased in the liver resection group. It can be said that there are similarities and differences in the two classification systems in examining the factors that cause the development of complications. Age is an independent risk factor for both morbidity and mortality compared to other comorbidities [7].

In this study to rate complications after surgery for colorectal malignancy, the cut-off value for age was 65. In our study, the degree of complications was observed to increase with increasing age. However, there was no statistically significant difference between the degree of complication and age.

Another factor in terms of complications is obesity. Obesity not only makes the procedure more technically demanding and potentially longer, but also increases the risk of developing wound infection. Recent studies have examined the relationship between obesity and surgical site infection after colorectal surgery. These studies reported that patients with a BMI above 30 kg/m^2 had an increased surgical site infection [8]. There are also publications reporting that BMI is an independent risk factor for anastomotic leakage [9]. In the present study, the complication degree of BMI was compared, but no statistically significant result was determined.

One of the factors affecting both the surgery to be performed on the patient and the postoperative follow-up is the existing comorbidities of the patient. Due to comorbidities, the wound healing of the patient changes significantly and the severity of the complication may increase accordingly. Poor glycemic control caused an increase in the incidence of surgical site infections in the early postoperative period in patients undergoing colorectal surgery [10]. In our study, both classification systems were examined and it was observed that diabetes constitutes approximately twice the risk of developing complications in diabetes mellitus, according to the Clavien-Dindo classification. No statistically significant risk for diabetes mellitus was found in the CTCAE classification.

In the literature, it has been reported that anastomotic leakage that develops after colorectal surgery is more common in men. It was thought that this might occur as a result of technical difficulties in male patients due to their narrow pelvis [11]. Studies examining the patient group undergoing LAR have observed that male gender is a risk factor for the development of anastomotic leakage [12]. According to the Clavien-Dindo classification, three times more complications were observed in the male gender, but this inference was not detected in the CTCAE classification.

15-20% of colorectal cancer patients have liver metastases at the time of initial diagnosis. In 70-80% of this patient group, metastasis is limited to the liver only [13-15]. However, some authors stated that simultaneous resection reduces the tumor burden, reduces the economic and psychological burden of patients, and allows patients to undergo a single surgical procedure instead of two [16]. A growing number of authors argue that the optimal operative timing changes gradually from gradual resection to simultaneous resection. In our study, the risk of complications was found to be five times higher in the group with simultaneous liver resection compared to the CTCAE classification. This was not found to be significant in the Clavien Dindo classification.

The use of laparoscopy in surgery for colorectal malignancy is extremely common. Compared to open surgery, laparoscopic surgery has advantages such as smaller incision length, less blood loss and less pain. However, previous studies have shown that laparoscopic surgery has some limitations, such as longer operative time and longer learning curve for surgeons [17, 18]. Laparoscopic surgery is less effective for larger tumors due to traction limitation and consequent insufficient exploration [19]. The incidence of postoperative complications was significantly reduced in the laparoscopic surgery group compared to the open surgery group [20,21]. In our study, open surgery was determined as a risk factor for the

development of complications in the technique.

While some factors that affect the complications that develop after surgery are patient-dependent and cannot be changed, there are also risk factors that can be changed depending on the choice of surgical technique. Laparoscopic surgery performed by experienced colorectal surgeons reduces the postsurgical complication rate.

Conclusion

The present study evaluated complications of colorectal cancer surgery in terms of Clavien-Dindo and CTCAE classifications. It was determined according to both classification systems that as the degree of complication increases, the length of hospital stay also increases. According to both classification systems, open surgery was found to be a risk factor for the development of complications compared to laparoscopic surgery. According to the Clavien-Dindo classification, male gender and diabetes mellitus are other risk factors for the development of complications. According to the CTCAE classification, performing liver resection in addition to open surgery increases the risk of complications. The two classifications have both similarities and differences in revealing the risk factors that cause postoperative complications. There is no superiority between the two classification systems when grading postoperative complications, and both systems can be used to rate surgical complications.

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Original Article

Evaluation of Factors Associated with Retinal Hemorrhage in Patients with Acute Leukemia

Akut Lösemili Hastalarda Retina Kanaması ile İlişkili Faktörlerin Değerlendirilmesi

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ABSTRACT

Purpose: We aimed to investigate the association of retinal hemorrhage and blood parameters in patients with acute leukemia

Material-Methods: We have retrospectively investigated sixty-one acute leukemia patients with and without retinal hemorrhages and analyzed associated factors. Patients underwent a detailed ocular examination. The hematological and coagulation parameters were based on data when the retinal hemorrhages were noticed in the fundus.

Results: The study group consisted of 30 patients with acute myelocytic leukemia (AML) and acute lymphocytic leukemia (ALL) who had retinal hemorrhages and the control group consisted of 31 patients with acute leukemia without retinal hemorrhages. Approximately ½ of the patients had low vision due to retinal hemorrhage, while the other half were detected by meticulous eye examination. AML diagnosis was statistically more frequent in patients with retinal hemorrhage (p=0.02). Active disease was statistically more common in the patients with retinal hemorrhage (p=0.03). In the retinal hemorrhage group, patients had significantly lower hemoglobin, hematocrit, and platelet levels than those without hemorrhages (p=0.001, p=0.001 and p=0.001 respectively). There was no statistically significant difference in leukocytes values between two groups (p=0.634).

Conclusion: In present study we found correlation between the hematological parameters and retinal hemorrhages. In patients with active AML and profound thrombocytopenia, a visual examination should be prioritized since ocular problems may go unnoticed since many patients are asymptomatic.

Key Words: Leukemia, retina, retinal hemorrhage, leucocyte, thrombocytopenia

ÖZET

Amaç: Akut lösemili hastalarda retina kanaması ile kan parametreleri arasındaki ilişkiyi araştırmayı amaçladık

Gereç ve Yöntem: Retina kanaması olan ve olmayan 61 akut lösemi hastasını geriye dönük olarak araştırdık ve ilişkili faktörleri analiz ettik. Hastalara detaylı göz muayenesi yapıldı. Hematolojik ve pıhtılaşma parametreleri, fundusta retina kanamalarının fark edildiği andaki verilere dayanıyordu.

Bulgular: Çalışma grubunu retina kanaması olan akut miyelositik lösemili (AML) ve akut lenfositik lösemili (ALL) 30 hasta, kontrol grubunu ise retina kanaması olmayan 31 akut lösemi hastası oluşturdu. Hastaların yaklaşık ½'sinde retina kanamasına bağlı az görme mevcutken, diğer yarısı titiz bir göz muayenesi ile tespit edildi. AML tanısı retina kanaması olan hastalarda istatistiksel olarak daha sıktı (p=0,02). Retina kanaması olan hastalarda aktif hastalık istatistiksel olarak daha yaygındı (p=0.03). Retinal kanama grubunda, hastaların hemoglobin, hematokrit ve trombosit düzeyleri kanaması olmayanlara göre anlamlı derecede daha düşüktü (sırasıyla p=0,001, p=0,001 ve p=0,001). İki grup arasında lökosit değerlerinde istatistiksel olarak anlamlı fark yoktu (p=0,634).

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Sonuç: Bu çalışmada hematolojik parametreler ile retinal kanamalar arasında korelasyon bulduk. Aktif AML ve derin trombositopenisi olan hastaların göz problemlerinin çoğu asemptomatik olduğundan bunların gözden kaçmaması için göz muayenesine öncelik verilmelidir.

Anahtar Kelimeler: Lösemi, retina, retinal kanama, lökosit, trombositopeni

Introduction

Leukemic retinopathy was first described by Liebreich in 1861 [1]. Since that time, ophthalmic manifestations of leukemia have been observed commonly by ophthalmologists, and the prevalence of ocular involvement in patients with leukemia reported in the literature ranges from 9 to 90% [2-5]. Leukemic retinopathy typically refers to the intraretinal hemorrhages, white-centered hemorrhages, and cotton-wool spots seen in patients with leukemia. The term 'leukemic retinopathy' is used to describe the retinal manifestations of anemia, thrombocytopenia and hyperviscosity, rather than leukemic infiltration by neoplastic cells. Controversy exists concerning the relationship between fundus findings in leukemic retinopathy and hematologic parameters such as platelet count, hematocrit level, and leukocyte count. Several studies implicate anemia, thrombocytopenia, or leukocytosis in the pathogenesis of leukemic retinopathy, but other reports show no association between fundus findings and blood profiles [7-18]. This retrospective study was conducted to evaluate the relationship between retinal hemorrhage and hematological parameters in patients with acute leukemia.

Patients and Methods

Between the years 2018 October-2022 February the medical records of the acute leukemic patients collected retrospectively and analyzed in tertiary hospital ophthalmology clinic of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey.

Collected data included as age, gender, clinical features, acute leukemia type and disease activation, ophthalmology examinations and laboratory parameters. The eye examination consisted of measurement of visual acuity, a slit-lamp examination for ambulatory patients or a penlight examination for patients under protective isolation, and direct and indirect ophthalmoscopy after dilation of fundus. Fundus camera was used for color photodocumentation for ambulatory patients. Patients with intraretinal hemorrhages, white-centered hemorrhages, and cotton-wool spots-like retinal hemorrhages were scored as absent or present based upon the clinical examination findings. Blood parameters included white blood cell counts, hemoglobin levels, hematocrit, platelet counts, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and C-reactive protein (CRP) levels. These values were based on data obtained when the retinal hemorrhages were noticed in the fundus. Active disease was defined as the presence of more than 5% blasts in the bone marrow.

Exclusion criteria: Patients with direct infiltration of neoplastic cells presenting as leukemic infiltrates and white centered retinal hemorrhages. Patients with retinal hemorrhages due to another diseases such as aged macular degeneration or diabetic retinopathy.

Ethical consideration: The Ethics Commitee of Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (Ankara,

Table 1: Comparison of demographic and clinical characteristics of the groups

	Retinal Hemorrhage Group	Control group	P value
Age(mean±SD)	40±14.6	32±14.6	0.2
Male/Female	19/11	20/11	0.9
AML/ALL	23/7	16/15	0.02*
Active disease	11 (36.7%)	4 (13%)	0.03*
Visual acuity (logMar)	1.3	0.035	0.001*

SD: Standard deviation, AML: acute myelocytic leukemia, ALL: acute lymphocytic leukemia
* p<0.05, statistically significant.

Turkey) approved the protocol, dated December 2021, number 11/1. All subjects provided written informed consent. Data of the patients were treated according to the Declaration of Helsinki Guidelines.

Statistical Analysis

Statistical analyses were performed using with SPSS software (Version 26.0. Armonk, NY: IBM Corp). The numerical data were expressed as mean±standard deviation and categorical data displayed as ration (percentage). Normality assumption were tested with Shapiro wilk test and histograms. Independent T test and chi-square tests were utilized to compare groups. A p value of <0,05 was considered statistically as significant in all analyses.

Results

A total of 61 patients with acute leukemia were included in the study. Study group consisted of 30 patients who had retinal hemorrhage; 23 had myelocytic leukemia (AML) and seven had lymphocytic leukemia (ALL). Nineteen (63.3%) were male and 11 (36.6%) were female; ages ranged from 19 years to 70 years (mean ± SD, 40±14.6). In the control group 16 patients had AML and 15 patients had ALL. Of the 31-control group, 20 (64.51%) were male, and 11 (35.4%) were female. The mean age was 32±14.6 years (range, 19-65 years).

In the study group retinal hemorrhage was seen bilateral in 22 (73.3%) of 30 patients. While 16 of the patients complained of decreased vision due to retinal hemorrhage, hemorrhage was detected during eye examination in the remainder. The mean visual acuity of the patients with retinal hemorrhage was 1.3 (min/max 1.5/0) according to the logMar visual chart. The mean visual acuity of the patients without retinal hemorrhage was 0.035 (min/max 0.2/0) according to the logMar visual chart (p<0.001).

AML diagnosis was statistically higher in patients with retinal hemorrhage (p=0.02). Active disease was statistically more frequent in the patients with retinal hemorrhage (p=0.03) (Table 1).

When the groups were analyzed for laboratory parameters, the patients with AML and ALL with retinal hemorrhages had significantly lower hemoglobin, hematocrit and platelet levels than those without hemorrhages (p=0.001, p=0.001 and p=0.001 respectively) (Table 2). There was no statistically significant difference in leukocytes values between two groups (p=0.63).

Patients with retinal hemorrhages had significantly higher PT levels than those without hemorrhages (p=0.001). On the other hand, no difference was found in APTT and

Table 2: Blood parameters in AML and ALL patients with and without retinal hemorrhages

	Study group Mean ± SD	Control group Mean ± SD	P value
Complete blood count			
Hemoglobin(g/dL)	8.5±1.8	9.83±2.3	0.001
Hematocrit (%)	25.45± 5.8	29.85±7	0.001
Leukocyte (× 10^3 per µL)	3.915±3.9	4.405±2.2	0.63
Platelet (× 10^3 per µL)	46.50±39	174.50±136	0.001
Coagulation			
PT (s)	12.05± 2.2	11.1±0.9	0.001
aPTT (s)	25.4±5.21	25±3.5	0.15
Fibrinogen (g/L)	404±29.9	360.2±27.2	0.28
Biochemistry values			
Creatinine (mg/dL)	0.67±0.35	0.59±0.22	0.21
BUN (mg/mL)	13.15±8.12	11.11±3.99	0.25
AST (U/L)	18.6±21.33	21.4±13.52	0.19
ALT (U/L)	25.2±27.82	23.95±32.013	0.31
CRP (mg/dL)	16.6±68.9	5.0±14	0.001

PT: prothrombin time, aPTT: partial thromboplastin time, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, SD: Standard deviation

fibrinogen levels (p=0.15 and p=0.28, respectively). CRP was the only biochemical parameter which was found to be statistically higher in the retinal hemorrhage group (Table 2).

Discussion

This retrospective study of retinopathy in acute leukemia analyzed the relationship between the retinal hemorrhages and hematologic parameters. 76% of patients with retinal hemorrhage had AML, suggesting that AML patients were more prone to retinal hemorrhage. Approximately ½ of the patients had low vision due to retinal hemorrhage, while the other half were noticed in the ophthalmologic evaluation. Retinal hemorrhage was seen bilateral in 22 (73.3%) of 30 patients. Active disease was found statistically more frequent in the patients with retinal hemorrhage. In this study, the patients with either acute leukemia or acute lymphocytic leukemia who had retinal hemorrhages had significantly lower hemoglobin, hematocrit and mean platelet count than did patients without such hemorrhages.

Many recent clinical studies of patients with acute leukemia have discussed the relationship of retinal hemorrhages, hematocrit, and platelet count. Guyer and coworkers, in a prospective study of retinopathy in leukemia, also found a lower hematocrit in patients with ALL and retinal hemorrhages than those without [19]. Cullerlo observed that the patients with low platelet counts and extreme anemia were more likely to have retinal hemorrhages [10]. Rubenstein et al also found that thrombocytopenia alone was not associated with an increased incidence of retinal hemorrhage [12]. They found that patients with both anemia and thrombocytopenia frequently had retinal hemorrhages. Similar to these studies, our results showed a strong association between the presence of intraretinal hemorrhages and both thrombocytopenia and anemia in patients with acute leukemia.

In contrast to our findings, Abu El-Asrar et al reported that platelet counts did not differ in patients with and without retinal hemorrhages [20]. Another study done by Leonardy and

associates also noted the similar platelet counts like Abu El-Asrar et al [21]. Robb and colleagues, on the other hand, stated that there was no correlation between the presence of retinal hemorrhages and the hematologic parameters in patients with acute leukemias [11].

The correlation between the retinal findings and the leucocyte count has been the subject of much debate. Parallel to some studies, we did not observe any significant difference in leukocyte levels in patients having or those not having retinal hemorrhage [19-21]. On the other hand, Karesh et al. (1989) found that their patients with retinopathy had a non-significantly lower mean white blood cell [22]. In contrast, Jackson and associates found that high leukocyte levels were associated with retinopathy in patients with leukemia but stated that anemia and thrombocytopenia were not associated with retinal hemorrhage [23].

The limitation of the study was that the number of ALL was less than AML. The strength was that all eye examinations were performed by the same clinician at the same center.

In conclusion, our findings suggest that anemia and thrombocytopenia are an important factor in retinal hemorrhages in acute leukemia and leukocyte count is not associated with the retinal hemorrhages. Considering that retinal hemorrhage is detected incidentally during eye examination in half of the patients, it is important to evaluate the patients with active disease, anemia and thrombocytopenia for retinal hemorrhage.

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Case Report

Inflammatory Myofibroblastic Tumor of the Breast in 64–Year–Old Women

64 Yaş Kadın Hastada Memede İnflamatuar Miyofibroblastik Tümör

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ABSTRACT

Introduction: The inflammatory myofibroblastic tumor is rarely located in the breast and, surgical resection is enough for the diagnosis and treatment.

Case Report: The patient, a 64-year-old female, was referred to our centre palpable mass in the right breast. Mammography demonstrated a mass of smoothed contour with calcification in the right breast. After three months, segmental mastectomy was planned as the mass grew. Pathological features, micromorphological and immunohistochemical staining have confirmed the lesion as being breast inflammatory myofibroblastic tumor.

Conclusion: Inflammatory myofibroblastic tumor of the breast is a rare and intermediate (rarely metastasizing) malignant potential tumor. Due to recurrence and metastasis risk, complete excision with negative margins and regular follow up plays a critical role in treating of inflammatory myofibroblastic tumors.

Key words: Breast, mammography, inflammatory myofibroblastic tumor

ÖZET

Giriş: İnflamatuar miyofibroblastik tümör memede nadir olarak yerleşir ve cerrahi rezeksiyon tanı ve tedavi için yeterlidir.

Olgu Sunumu: 64 yaşında kadın hasta sağ memede kitle ile merkezimize başvurdu. Mamografide, sağ memede kalsifikasyon ile birlikte düzgün konturlu bir kitle mevcuttu. Üç ay sonra, kitlenin büyümesi nedeniyle segmental mastektomi planlandı. Patolojik özellikler, mikromorfolojik ve immünohisto-kimyasal boyama lezyonun İnflamatuar miyofibroblastik tümör olduğunu doğrulamıştır.

Sonuç: Memenin inflamatuar miyofibroblastik tümörleri nadir ve orta (nadiren metastaz yapan) malign potansiyel bir tümördür. Nüks ve metastaz riski nedeniyle negatif sınırlarla eksizyon ve düzenli takip inflamatuar miyofibroblastik tümör tedavisinde kritik bir rol oynamaktadır.

Anahtar Kelimeler: Meme, mamografi, inflamatuar myofibroblastik tümör

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Introduction

According to the World Health Organization (WHO) classification, inflammatory myofibroblastic tumor (IMT) is an intermediate malignant potential tumor with potential recurrence and rarely metastasis. IMT is located in any part of the body, and it is usually detected in children and young adults. IMT is reported rarely in the breast [1].

Case report

A 64-year-old woman was referred to our center with a hard, palpable mass in the right breast. The patient is taking medicine for hypertension and hypothyroidism. Also, the patient has been in menopause for ten years and has never had hormone therapy. She had no family history of cancer. There was a palpable mass of approximately 2 centimeters in the upper outer quadrant of the right breast. A lobulated mass lesion with a contoured smooth contour with calcification of 23x17 millimeters in the right breast was observed in mammography. The lesion was reported as BIRADS 0 (Figure 1), and ultrasonography (USG) evaluation was suggested. 20x16 millimeters multilobulated heterogeneous hypoechoic lesion was measured on the upper outer quadrant of the right breast without any other abnormality of the contralateral breast or both axillary regions, and histopathological diagnosis was recommended. USG, guided core needle biopsy performed. Myxoid stroma containing spindle stromal cells with low cellularity and a few breast ducts were observed on histopathologic examination. The patient was admitted three months later due to the growth of the mass. After clinical and radiological re-evaluation, a rebiopsy is recommended. After three months later, on control USG, a 27x20 mm multilobular heterogeneous hypoechoic lesion was observed in the upper outer quadrant of the right breast, and lesion size increased. Segmental mastectomy was planned for the patient to have negative surgical margins. A well-circumscribed, white-tan coloured mass was measuring about 3,5 cm × 2,7 cm × 2,5 cm was identified in the macroscopic examination of the segmental mastectomy specimen. Microscopic examination showed a well-circumscribed tumor (Figure 2A, 2B) composed of spindle cells arranged in fascicles mixed with an inflammatory infiltrate containing lymphocytes and plasma cells (Figure 2 C). The stroma showed focal myxoid to hyalinized collagenous fibrovascular tissue. A multilayered concentric proliferation of spindle cells around blood vessels was observed (Figure 3A). Obliterative phlebitis was not observed. Nuclear atypia was not seen. Three typical mitoses were seen in 10 high power fields. There was no atypical mitosis. Immunohistochemical analysis showed focal positive staining for smooth muscle actin (Cell Marque, 1A4, monoclonal) (Figure 3 B), CD34 (Ventana, QBEnd/10, monoclonal) (Figure 3C) and ER receptor (Ventana, SP1, monoclonal) (Figure 3D). Immunohistochemistry showed negative staining for anaplastic lymphoma kinase (ALK) (Ventana, ALK01, monoclonal), S100 (Ventana, 4C4.9, monoclonal), pan CK (Cell Marque, AE3, monoclonal), MUC4 (Cell Marque, 8G7, monoclonal), HHF35 (Cell Marque, monoclonal), desmin (Ventana, DE-R-11, monoclonal), B catenin (Cell Marque, 14, monoclonal) and C-kit (Ventana, 9.7, monoclonal). The surgical resection margins were tumor-free. Inflammatory myofibroblastic tumors were diagnosed based on the morphology and the immunohistochemical features. The patient was called for control 6 months later. No pathology was detected in the examination.

Discussion

IMT is a mesenchymal neoplasm composed of spindle cells with myofibroblasts' morphologic features and intermingling with plasma cells and other inflammatory cells.

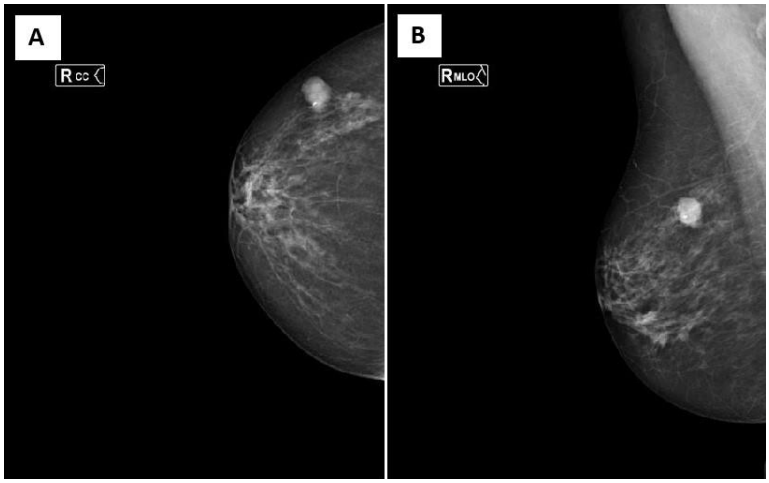

Figure 1. On mammography a lobulated mass lesion with a smooth contour with calcification was observed. (A) Craniocaudal view; (B) mediolateral view.

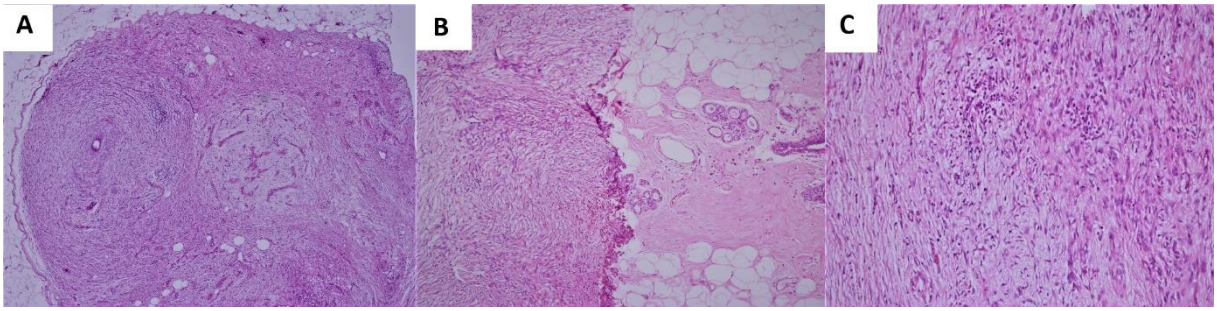

Figure 2. (A)- A well- circumscribed tumor composed of spindle cells in the breast (H-E, x40) (B)- A well- circumscribed tumor with breast parenchyma (H-E, x100) (C)- Tumor shows fascicular growth pattern and is composed of spindle cells admixed with aggregates of inflammatory infiltrate containing lymphocytes and plasma cells (H-E, x200).

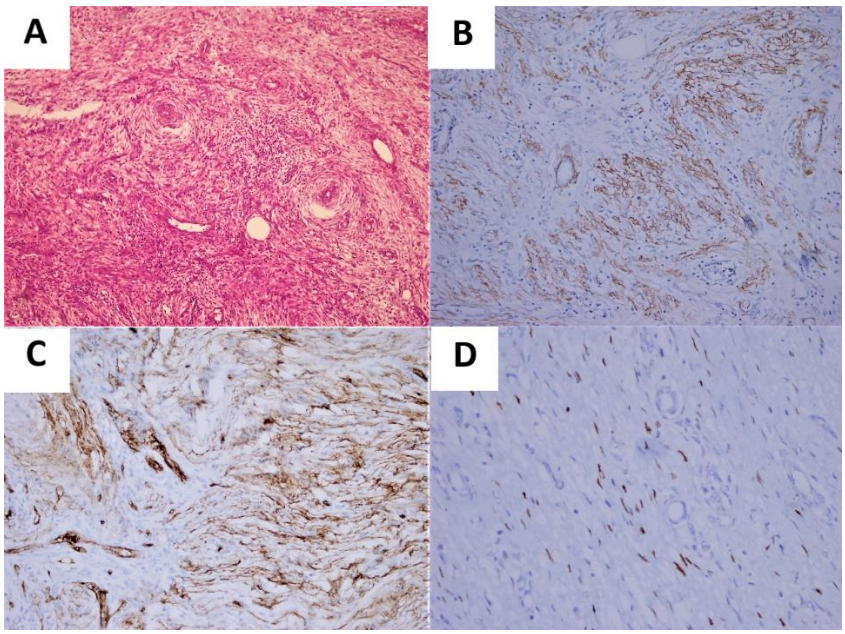

Figure 3. (A)- A multilayered concentric proliferation of spindle cells around blood vessels (H-E, x 200) (B)- Focal smooth muscle actin positivity in tumor cells (C)- Focal CD34 positivity in tumor cells (D)- ER receptor positivity in tumor cells.

The aetiology of IMT is unknown [1,2]. At first, researchers thought that IMT was an autoimmune or reparative postinflammatory condition. Currently, IMT is defined a neoplastic process with potential recurrence and rarely metastasis.[3]. Recent molecular studies showed that chromosome 2p23 of anaplastic lymphoma kinase (ALK) rearrangements in 50% of IMTs patients [4].

IMTs have been encountered virtually in any anatomical location. The most common site of involvement is in the lung. Extrapulmonary sites include the mesentery and omentum, soft tissue, pelvis, mediastinum, bone, larynx, central nervous system [5]. IMTs rarely occur in the breast [2].

Most patients with IMT on the breast present with a palpable mass, which is sometimes detected in screening mammography [5, 6]. IMT on the breast is primarily seen in women, sometimes in men [4]. IMT can be observed in both breasts simultaneously [7]. In addition, it has been reported that the same patient may be located in different organs with the breast [7]. Mammography and ultrasonography showed nonspecific features of IMT's of the breast. IMT can see as hypo-hyperechoic, smooth or irregularly circumscribed lesions on ultrasonographic images [5, 8, 9,10]. It has also been reported to co-occur in patients with breast cancer [6]. In our case, it was described a multilobulated heterogenous hypoechoic lesion in ultrasonography.

IMTs of the breast are lack typical clinical and radiological characteristics. It was diagnosed at pathological examination after resection of the mass. IMTs are diagnosed based on their pathological appearance and, breast IMTs have the same morphological features arising in other sites. Breast IMT should be differentiated from other spindle cell lesions of the breast ranging from reactive tumor-like lesions to high-grade malignant tumors. The distinction may be challenging in small biopsies. Histomorphological features and immunohistochemistry facilitate the correct diagnosis of an excised specimen. Diagnostic features are α-smooth muscle actin positive spindle cells admixed with inflammatory cells composed of plasma cells and lymphocytes and ALK expression by immunohistochemistry or ALK gene rearrangement. Nevertheless, approximately 50% of IMT patients have ALK gene rearrangement. There is a good correlation between ALK immunohistochemistry and the ALK gene rearrangement by FISH analysis [4,6]. In our case, ALK was negative.

Previous studies have indicated that ALK-negative IMTs are more diagnosed at a higher age, associated with metastases and histological differences from ALK-positive IMTs. There s a higher degree of nuclear pleomorphism, atypical atypia mitoses detected in ALK-negative IMTs [4,11]. IMT is more commonly seen in children and young adults, but a broad age range has been documented [4]. Our case was 64 years old. Nuclear atypia and atypical mitoses were not identified.

IMTs recurrence rate is 2% for pulmonary tumors and 25% for extrapulmonary lesions [11]. The recurrence rate depends on ill-defined morphology, tumor size, multi-focality, the success of the surgical resection [11]. Also, a high degree of atypia, the presence of ganglion-like cells, increased mitotic figures, high Ki-67 proliferative index, the absence of ALK reactivity, onco-genetic protein overexpression (p53) is associated with potential aggressive growing, recurrence and malignancy [11,12]. For this reason, complete surgical resection of IMTs is mandatory. [3] Distant metastasis of IMTs is 5% of the cases [1, 13]. The metastatic IMTs cases are characterized by a broad range of age and primary sites, metastases typically developed in the lungs, brain, liver and bone [12]. In addition to this, metastasis to the lymph nodes or the mediastinum were detected only two cases [13].

IMTs of the breast are unusual conditions and can be confused with malignancy [9]. Malignant course, recurrence and metastasis of IMTs are also rare [8]. Until today a few cases of IMT has been reported in the male breast [4]. Surgical margin negative wide excision is sufficient. Cases that developed recurrence despite negative surgical margins have been reported [12]. Wide excision with negative margins or simple mastectomy is recommended for a patient with IMT of the breast [6, 8]. In this case, excision was made with a negative surgical margin. Incomplete resection is associated with a high risk for recurrence of IMT. IMT recurrence rate was detected at 25% in the other anatomical location [12]. In this case, recurrence was not detected in the eight month follow up periods. Axillary lymph node management is unclear in the cases of breast IMT. If axillary lymph node metastasis suspicion exists, wide local excision with sentinel lymph node biopsy or modified radical mastectomy should be performed [6]. However, some research suggests that routine SNLB is unnecessary because of lymphatic spread of the lesion is unusual [8]. A case of breast inflammatory myofibroblastic tumor with internal lymph node and supraclavicular lymph node metastasis has been reported [14]. Other treatment options for IMTs of the breasts in the literature are corticosteroids, chemotherapy, radiotherapy and immunomodulation. Some reports show that corticosteroids are helpful with treatment [15]. There are sporadic cases treated with chemotherapy and anti-inflammatory agents in two studies [10]. Although this results, more investigation is needed for treatment strategy for IMTs of the breasts.

Conclusion

IMTs of the breast is a rare and intermediate (rarely metastasizing) malignant potential tumor. Due to recurrence and metastasis risk, complete excision with negative margins and regular follow up plays a critical role in treating IMTs.

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