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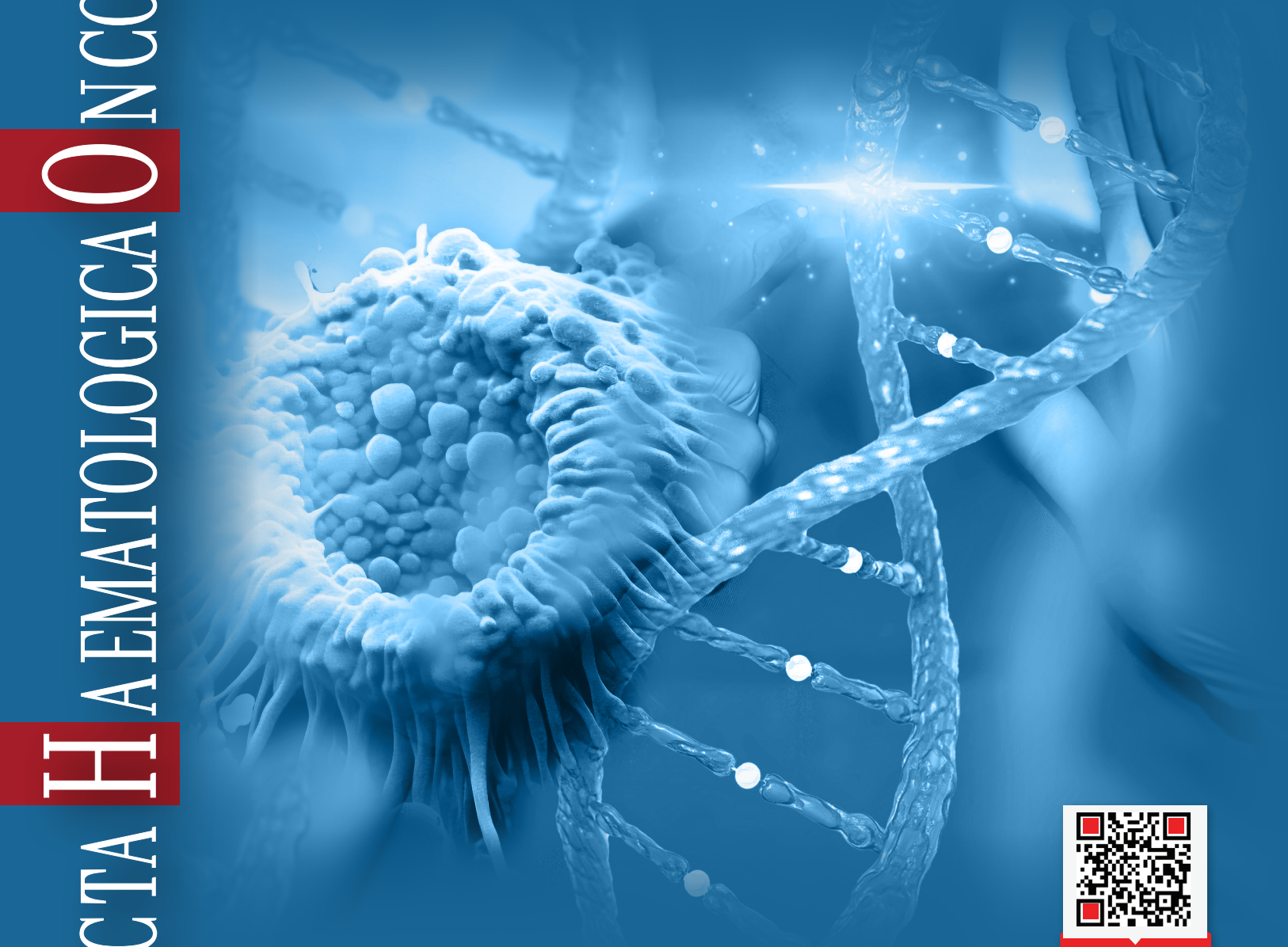

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VOLUME 57 / ISSUE 3

CONTENTS

AHOT | Acta Haematologica Oncologica Turcica

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Original Article

Impact of Primary Tumor Diameter and SUV_{max} on Pathological Lymph Node Involvement in Non-small Cell Lung Cancer

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ABSTRACT

Aim: The aim of our study was to determine the role of preoperative primary tumor diameter (PTD) and maximum standardized uptake (SUV_{max}) values on preoperative ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in predicting regional lymph node (LN) involvement, lymphatic invasion (LI), vascular invasion (VI), and pleural invasion (PI) in patients with non-small cell lung cancer (NSCLC) who were operated without receiving neoadjuvant therapy.

Methods: A total of 70 patients diagnosed with NSCLC who underwent surgery after ^{18}F-FDG PET/CT but did not receive neoadjuvant therapy were retrospectively examined. The effects of PTD and SUV_{max} on postoperative LN involvement, LI, VI, and PI in patient groups below and above the determined threshold value on preoperative ^{18}F-FDG PET/CT were compared. Since an optimal cut-off value for specificity and sensitivity was not obtained with the receiver operating characteristic curve for both the PTD and SUV_{max} of the primary tumor, patients were grouped based on the median values for the two parameters.

Results: The median PTD was 32 mm. The median SUV_{max} of 12.55 was obtained, and patients were grouped according to these median values. No significant difference was found in the primary tumor diameters ≥32 mm and <32 mm in terms of pathological LN involvement (p=0.322), VI (p=0.122), LI (p=0.122) and PI (p=1.000). Again, no significant difference was found in the patient groups with SUV_{max} values of the primary tumor ≥12.55 and <12.55 regarding pathological LN involvement (p=0.621), VI (p=0.122), LI (p=0.122), and PI (p=1.000). A low positive correlation (p=0.000, r=0.447) was found between the PTD and SUV_{max} values.

Conclusion: ^{18}F-FDG PET/CT alone is not a reliable noninvasive method for predicting LN metastasis in patients with early-stage NSCLC for whom curative treatment is planned.

Keywords: Lung cancer, ^{18}F-FDG PET/CT, invasion, lymph node involvement

Introduction

Non-small-cell lung cancer (NSCLC) accounts for 85% of all lung cancer cases. Approximately 40% of cases are metastatic upon diagnosis [1,2]. Curative treatment modalities (surgery, chemoradiotherapy) are chosen based on the stage of the remaining non-metastatic patients.

The precise staging of NSCLC, particularly preoperative identification of lymph node (LN) metastasis, is critical for treatment planning and prognosis determination.

LN metastasis is a significant prognostic factor in patients with NSCLC because it is associated with a worse prognosis. This is because LN metastases often indicate that the cancer has spread beyond the lung to other parts of the body.

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Patients with NSCLC who have larger tumors have an increased risk of LN metastasis. This is because larger tumors are more likely to invade the lymphatic system, which is a network of vessels containing white blood cells and other immune cells throughout the body.

LN metastasis can be determined by invasive or non-invasive methods. Non-invasive imaging methods, such as computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography-CT (^{18}F-FDG PET/CT), are widely used to identify involvement of the ipsilateral (N2) or contralateral mediastinal LNs (N3). Mediastinoscopy and endobronchial ultrasound-guided transbronchial needle aspiration are two invasive staging procedures that are frequently used after non-invasive staging results from CT and ^{18}F-FDG PET/CT scans. ^{18}F-FDG PET/CT using ^{18}F-FDG, a glucose analog shown to be useful in detecting malignancy, is an extremely important imaging method in the staging of NSCLC. Here, the maximum standardized uptake value (SUV_{max}) of the primary tumor and primary tumor diameter (PTD) can be used to predict the risk of nodal metastasis, and the threshold SUV_{max} value is between 2.5 and 4.0 [3].

Although invasive methods remain the gold standard for mediastinal nodal staging, they come with disadvantages, such as the risk of complications, delay in treatment, and high cost. Hence, the correct use of non-invasive mediastinal nodal staging will help in selecting patients who will benefit most from invasive staging and preventing unnecessary invasive procedures. However, in patients clinically staged as N0 (no nodal involvement) on preoperative ^{18}F-FDG PET/CT, the incidence of histologically proven occult nodal metastasis after surgery has been found to range between 8% and 58% in various stages [4,5].

The relationship between PTD and LN metastases in clinical staging and the proper selection of treatment methods has been investigated in many previous studies. Some studies have revealed a close relationship between these two factors, suggesting that PTD could be used to predict positive LN metastases [6,7]. However, others have concluded that there is no such specific correlation between these two factors [8,9]. It is believed that combining the PTD and SUV_{max} values may provide a more sensitive method for detecting pathological LN metastasis.

In this study, we aimed to determine the role of the PTD and SUV_{max} in preoperative ^{18}F-FDG PET/CT in predicting regional LN involvement, lymphatic invasion (LI), vascular invasion (VI), and pleural invasion (PI) in patients with NSCLC who were operated on without neoadjuvant therapy.

Methods

The computer registration system of our hospital was reviewed, and the archive file records of 70 patients who were diagnosed with NSCLC at the medical oncology clinic between October 2014 and February 2023 and who underwent surgery (segmentectomy, lobectomy, bilobectomy, pneumonectomy) after ^{18}F-FDG PET/CT without receiving neoadjuvant therapy were retrospectively examined. The effects of PTD and SUV_{max} on postoperative LN, lymphatic, vascular, and PI in patient groups below and above the determined threshold value on preoperative ^{18}F-FDG PET/CT were compared. Since an optimal cut-off value for specificity and sensitivity was not obtained with the receiver operating characteristic (ROC) curve for both the PTD and SUV_{max} of the primary tumor, patients were grouped based on the median values for the two parameters.

The demographic and clinical characteristics of the patients included in the study are presented in Table 1. Parameters such as PTD and SUV_{max} in preoperative ^{18}F-FDG PET/CT and histopathological diagnosis of the tumor in postoperative pathology reports, LN involvement, LI, VI, and PI were recorded. The effects of PTD and SUV_{max} on pathological LN involvement, LI, VI, and PI were compared between patient groups below and above the determined threshold value. The median follow-up period was 30.4 (0.17-112.7).

This study was planned and conducted in accordance with Good Clinical Practices and the Declaration of Helsinki, and it was approved by the Ethics Committee of Aydın Adnan Menderes University Hospital (approval no: E-53043469-050.04.04-346879, date: 11.05.2023).

Table 1. Demographics and clinical characteristics of all patients

		n	%
Gender	Male	60	85.7
	Female	10	14.3
Age	Median (min-max)	68 (48-91)	
Smoking	Never	5	7.1
	Current or ex-smoker	65	92.9
Smoking duration (pack years)	Median (min-max)	40 (0-100)	
ECOG	0	28	40.0
	1	42	60.0
Localization	Right	47	67.1
	Left	23	32.9
Surgery	Segmentectomy	7	10.0
	Lobectomy	52	74.3
	Bilobectomy	3	4.3
	Pneumonectomy	8	11.4
Histological type	SCC	38	54.3
	Adeno	32	45.7
Adjuvant chemotherapy	Did not receive	22	31.4
	Received	48	68.6
Adjuvant radiotherapy	Did not receive	60	85.7
	Received	10	14.3

ECOG: Eastern Cooperative Oncology Group, SCC: Squamous cell cancers, Min-max: Minimum-maximum

Statistical Analysis

Data were summarized using descriptive statistics, such as mean, standard deviation, median, minimum, maximum, frequency, and ratio. The distribution of variables was assessed using the Kolmogorov-Smirnov test. Independent quantitative data were analyzed using independent sample t-tests and Mann-Whitney U tests. The chi-square test was employed for qualitative independent data, with the Fisher's test used when conditions for the chi-square test were not met. ROC curve analysis was performed to maximize the sensitivity, specificity, and accuracy for assessing the cut-off value for PTD and SUV_{max}. A p value of less than 0.05 was considered statistically significant. Statistical Package for the Social Sciences 22.0 software was used for the analyses.

Results

For the PTD and SUV_{max} values of the primary tumor, since a cut-off value could not be obtained with the ROC curve with optimal specificity and sensitivity, patients were divided into 2 groups based on the median values.

There was no significant difference in age between patients with a PTD of ≥32 mm and <32 mm (p=0.073). In the group with ≥32 mm, the male gender was found to be more predominant (p=0.040) (Table 2).

The number of patients who smoked (p=0.164), the smoking duration (p=0.506), Eastern Cooperative Oncology Group (ECOG) status (p=0.329), tumor localization (p=0.203), and histological subtype (p=0.150) did not significantly differ between the groups. The number of patients who received adjuvant chemotherapy was significantly higher in the group with a PTD of ≥32 mm (p=0.000). There was no significant difference in the number of patients who received adjuvant radiotherapy (p=0.495, Table 2).

Age was not significantly different (p=0.073) in the groups of patients with SUV_{max} values ≥12.55 and <12.55 for the primary tumor. Regarding gender distribution, male sex was more predominant (p=0.040) in the group with SUV_{max} ≥12.55 (Table 3).

No significant differences were observed between the groups in the number of patients who smoked (p=0.643), duration of smoking (p=0.948), ECOG status (p=0.626), tumor localization (p=0.203), or histological subtype (p=0.055). In the group with a primary tumor SUV_{max} value ≥12.55, the number of patients who received adjuvant chemotherapy was significantly higher (p=0.002). Adjuvant radiotherapy was not significantly different between the number of patients who received it (p=1.000) (Table 3).

Pathological LN involvement (p=0.322), VI (p=0.122), LI (p=0.122), and PI (p=1.000) were not significantly different between the two groups according to PTD (Table 4).

Regarding the SUV_{max} values of the primary tumor, no significant difference was found between the two groups in terms of the pathological LN involvement (p=0.621), VI (p=0.122), LI (p=0.122) and PI (p=1.000) (Table 5).

A low positive correlation was observed between the PTD and SUV_{max} values (p=0.000, r=0.447) (Figure 1).

Table 2. Demographic and clinical characteristics of patients according to tumor diameter

		Tumor diameter <32 mm				Tumor diameter ≥32 mm				p	
		Mean±SD			Median	Mean±SD			Median		
Age		67.43	±	8.68	69 (48-88)	67.97	±	10.48	68 (43-91)	0.073	t
Gender	Male	27		77.1%		33		94.3%		***0.040***	x^2
	Female	8		22.9%		2		5.7%			
Smoking	Never smoked	4		11.4%		1		2.9%		0.164	x^2
	Smoked	31		88.6%		34		97.1%			
Smoking duration (pack years)		38.09	±	18.23	40.00	40.43	±	22.31	35.00	0.506	m
ECOG	0	16		45.7%		12		34.3%		0.329	x^2
	1	19		54.3%		23		65.7%			
Localization	Right	21		60.0%		26		74.3%		0.203	x^2
	Left	14		40.0%		9		25.7%			
Histological type	Squamous carcinoma	16		45.7%		22		62.9%		0.150	x^2
	Adenocarcinoma	19		54.3%		13		37.1%			
Adjuvant chemotherapy	Did not receive	18		51.4%		4		11.4%		***0.000***	x^2
	Received	17		48.6%		31		88.6%			
Adjuvant radiotherapy	Did not receive	29		82.9%		31		88.6%		0.495	x^2
	Received	6		17.1%		4		11.4%			

t: Independent samples t-test, m: Mann-Whitney U test, x^2: Chi-square test, ECOG: Eastern Cooperative Oncology Group, SD: Standard deviation

Table 3. Demographic and clinical characteristics of patients by SUV_{max} value

		SUV_{max} value <12.55				SUV_{max} value ≥12.55				p	
		Mean±SD			Median (min-max)	Mean±SD			Median (min-max)		
Age		65.7	±	9.7	67 (43-88)	69.7	±	9.1	70 (48-91)	0.073	t
Gender	Male	27		77.1%		33		94.3%		***0.040***	x^2
	Female	8		22.9%		2		5.7%			
Smoking	Never smoked	3		8.6%		2		5.7%		0.643	x^2
	Smoked	32		91.4%		33		94.3%			
Smoking duration (pack-years)		37.1	±	16.4	40 (0-70)	41.4	±	23.5	40 (0-100)	0.948	m
ECOG	0	15		42.9%		13		37.1%			x^2
	1	20		57.1%		22		62.9%		0.626	
Localization	Right	21		60.0%		26		74.3%		0.203	x^2
	Left	14		40.0%		9		25.7%			
Histological type	Squamous carcinoma	15		42.9%		23		65.7%		0.055	x^2
	Adenocarcinoma	20		57.1%		12		34.3%			
Adjuvant chemotherapy	Did not receive	17		48.6%		5		14.3%		***0.002***	x^2
	Received	18		51.4%		30		85.7%			
Adjuvant radiotherapy	Did not receive	30		85.7%		30		85.7%		1.000	x^2
	Received	5		14.3%		5		14.3%			

t: Independent samples t-test, m: Mann-Whitney U test, x^2: Chi-square test, ECOG: Eastern Cooperative Oncology Group, SD: Standard deviation, Min-max: Minimum-maximum, SUV_{max}: Maximum standardized uptake

Table 4. Relationship between tumor size and microscopic tumor spread in pathological samples

		Tumor diameter <32 mm		Tumor diameter ≥32 mm		p	
		n	%	n	%		
Pathological N factor	N0	24	72.7%	20	57.1%	0.322	x^2
	N1-3	11	33.3%	15	42.9%		
Venous invasion	Absent	14	42.4%	8	22.9%	0.122	x^2
	Present	21	63.6%	27	77.1%		
Lymphatic invasion	Absent	14	42.4%	8	22.9%	0.122	x^2
	Present	21	63.6%	27	77.1%		
Pleural invasion	Absent	23	69.7%	23	65.7%	1.000	x^2
	Present	12	36.4%	12	34.3%		

x^2: Chi-square test

Discussion

Our study showed that the preoperative PTD and SUV_{max} on ^{18}F-FDG PET/CT were insufficient to predict pathological LN involvement in patients with NSCLC.

In clinical stage 1A patients, the prevalence of LN metastasis is low, and because of high false-positive rates, the role of ^{18}F-FDG PET/CT is limited [10,11]. Additionally, a study has shown that the utility of ^{18}F-FDG PET/CT in predicting LN metastasis in subsolid lesions significantly decreases, with a sensitivity of 11.1%, specificity of 86.1%, and accuracy of 81.9% for LN staging in patients with subsolid adenocarcinomas (AC) with a PTD ≤3 cm [12].

This study showed that the incidence of LN metastasis in lung cancer increased with tumor size. Seok et al. [13] found that when patients were split into six groups based on tumor diameter: ≤0.5, 0.6-1, 1.1-1.5, 16-2.0, 2.1-2.5, and 2.6-3 cm, the rates of LN metastasis were 0%, 0%, 7%, 14%, 27%, and 31%. However, our study has shown similar results in terms of PTD among patients with NSCLC.

^{18}F-FDG PET/CT is a valuable tool in oncology practice because it can be used to measure increased glucose metabolism in tumor cells. This is because tumor cells typically have a higher metabolic rate than normal cells, and they take up more glucose to fuel their growth. A SUV_{max} >2.5 is generally used as a cut-off value for malignancy. This indicates that lesions or tissues

with an SUV_{max} >2.5 are more likely to be cancerous than those with an SUV_{max} 2.5. However, some benign conditions can also cause high ^{18}F-FDG uptake, and there are some cancers that may have an SUV_{max} below 2.5.

Tuberculosis, obstructive pneumonia, anthracosis, or immune reactions resulting from granulomatous inflammation can lead to false-positive results. Low-grade malignancies can also result in false negatives [14,15]. However, it is important to note that using a higher SUV_{max} cut-off value can also increase the false positive rate. This means that more patients will be identified as having metastasis even if they do not actually have metastasis. This can lead to unnecessary additional testing and procedures.

Some authors have claimed that using a higher SUV_{max} than the traditional 2.5 can increase the accuracy of metastasis presence. This is because a high SUV_{max} is more likely to indicate malignant tissue. However, it is important to note that no single SUV_{max} value is universally accurate for all cancer types. The optimal cut-off value varies depending on the specific type of cancer, tumor location, and other factors [16].

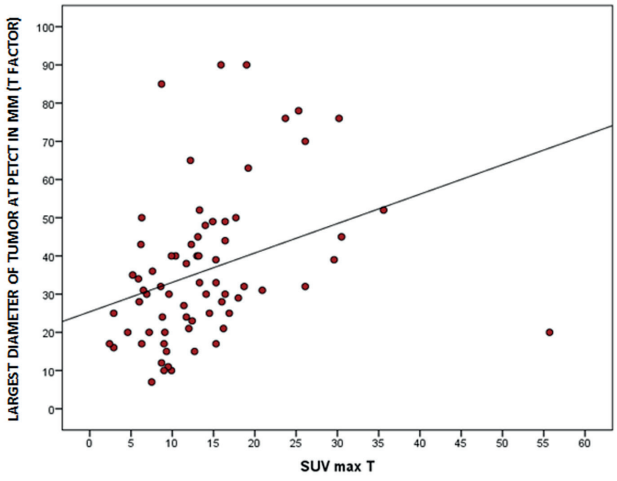

Figure 1. Positive correlation between primary tumor diameter and SUV_{max} value (p=0.000, r=0.447)
SUV_{max}: Maximum standardized uptake, PET/CT: Positron emission tomography/computed tomography

The SUV_{max} value was also a good indicator of tumor aggressiveness [17]. However, a study conducted in patients with resected stage 1 NSCLC found that the cellular components in the tumor varied widely and therefore did not correlate with 18F-FGD activity [18].

Tumor size and the presence of necrosis are other factors affecting a tumor's SUV_{max}. Previous studies have shown a positive correlation between PTD and SUV_{max} [19,20]. Similarly, in our study, a positive correlation was found between the PTD and SUV_{max}. However, there was no significant difference in pathological LN involvement between the two groups based on the SUV_{max} of the main tumor.

It is known that the likelihood of necrosis increases with tumor size, which is associated with a lower SUV_{max}. However, the relationship between SUV_{max} and necrosis was not evaluated in our study.

Tumor histologic type has also been identified to be associated with LN metastasis in patients with NSCLC. It is known that squamous cell cancers (SCC) have shorter doubling times and grow faster than AC, and therefore have higher glucose metabolism [21]. Moreover, glucose transporter-1 expression is higher in SCCs. Accordingly, previous studies have shown that SUV_{max} values are higher in SCC [22-24]. Kim et al. [25] found that the SUV_{max} was 10.8±4.4 for SCC and 8.8±3.2 for AC.

However, contrary to this, our study showed no significant difference in PTDs and SUV_{max} values according to histological subtype.

In studies involving patients with early-stage NSCLC, a high primary tumor SUV_{max} was found to be a strong indicator of lymphovascular invasion (LVI) and LN metastasis [23,26]. In a study conducted by Koksal et al. [27], it was found that the SUV_{max} of the tumor did not correlate with the nodal (N) stage, and the median SUV_{max} did not show a significant difference between groups with and without LN metastasis. Similarly, in our study, the tumor SUV_{max} was insufficient to predict pathological LN metastasis. Additionally, no significant relationship was observed between SUV_{max} and LVI or PI.

Table 5. Relationship between SUVmax and microscopic tumor spread in pathological samples

		Primary tumor SUV_{max} <12.55		Primary tumor SUV_{max} ≥12.55		p	
		n	%	n	%		
Pathological N factor	N0	23	65.7%	21	60.0%	0.621	x^2
	N1-3	12	34.3%	14	40.0%		
Venous invasion	Absent	14	40.0%	8	22.9%	0.122	x^2
	Present	21	60.0%	27	77.1%		
Lymphatic invasion	Absent	14	40.0%	8	22.9%	0.122	x^2
	Present	21	60.0%	27	77.1%		
Pleural invasion	Absent	23	65.7%	23	65.7%	1.000	x^2
	Present	12	34.3%	12	34.3%		

x^2: Chi-square test, SUV_{max}: Maximum standardized uptake

Study Limitations

The important limitations of our study are its non-randomized and retrospective nature. In addition, the small number of patients might have affected the study outcome. Therefore, we believe that prospective studies with large cohorts are needed to evaluate the utility of preoperative ^{18}F-FDG PET/CT in predicting LN involvement.

Conclusion

Ultimately, the decision to use a higher SUV_{max} cut-off value should be made on a case-by-case basis in consultation with a medical oncologist.

Ethics

Ethics Committee Approval: The study was approved by the Aydın Adnan Menderes University Hospital of Ethics Committee (approval no: E-53043469-050.04.04-346879, date: 11.05.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.A., B.D., S.B., Y.Y., Concept: A.A., S.B., Design: A.A., S.B., Data Collection or Processing: A.A., B.D., Analysis or Interpretation: A.A., B.D., S.B., Y.Y., Literature Search: A.A., B.D., Writing: A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Fibrinolytic Activity in Patients with Newly Diagnosed Multiple Myeloma

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ABSTRACT

Aim: Coagulation and fibrinolysis are in balance in the normal hemostatic system, and disruption of this balance can result in bleeding disorders or thrombotic events. Studies on the fibrinolytic system in patients with multiple myeloma (MM) are few in number and have yielded conflicting results. Impaired fibrinolysis may contribute to the development of thrombotic complications in these patients.To measure levels of the fibrinolysis activator, tissue plasminogen activator (tPA) and the major fibrinolysis inhibitors, plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI) in MM patients and compare with a control group.

Methods: The study group included 48 newly diagnosed, previously untreated MM patients who presented to the Hematology Outpatient Clinic of Zonguldak Bülent Ecevit University Faculty of Medicine for 20 months. The control group consisted of 20 individuals with no systemic disease who presented to the general internal medicine outpatient clinic for routine check-ups.

Results: Mean plasma tPA level was 9 (6.58-15.36) ng/mL in the patient group and 12.35 (8.4-19.7) ng/mL in the control group (p=0.221). Plasma PAI-1 level was 9.36 (1.28) ng/mL in the patient group and 9.56 (0.26) ng/mL in the control group (p=0.057). Plasma TAFI level was significantly lower in the patient group [7.6 (6.2-9.19) µg/mL] compared to the control group [9.46 (8.83-13.02) µg/mL] (p<0.001) but was not correlated with disease stage. There was no statistically significant difference in plasma D-dimer levels between the MM patients and the control group (p=0.406).

Conclusion: While impaired fibrinolytic activity is expected in MM patients, our results demonstrated that MM patients had low TAFI levels without significant changes in tPA and PAI-1 levels. Decreased TAFI levels may play a role in other mechanisms that can cause bleeding in MM patients.

Keywords: Multiple myeloma, fibrinolytic system, tPA, TAFI, PAI-1

Introduction

Multiple myeloma (MM) is one of the most common hematological malignancies, accounting for approximately 1% of all human cancers. It is characterized by strong and abnormal proliferation of malignant plasma cells that secrete monoclonal immunoglobulins or light chains and is associated with bone destruction, suppressed bone marrow function, and renal dysfunction [1,2]. As with other lymphoproliferative diseases, MM is associated with hemostasis disorders that cause both thrombosis and hemorrhage [3,4].

The reported risk of thromboembolism in patients with MM, especially those receiving multi-agent chemotherapy, is as high as 30% [5]. Hemorrhage is observed in less than 10% of patients with MM. The interaction between plasma paraprotein and platelets and coagulation factors is the most common pathophysiological mechanism [6]. Other risk factors for bleeding include thrombocytopenia caused by plasma cell replacement of bone marrow, renal failure, invasive procedures, and treatment-related toxicities [7].

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Clot dissolution is mediated by the fibrinolytic system (plasminogen-plasmin). Tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) are the main activators of the fibrinolytic system, whereas plasminogen activator inhibitor-1 (PAI-1), α2-antiplasmin (α2-AP), and thrombin activatable fibrinolysis inhibitor (TAFI) are the main inhibitors. Disruptions in the fibrinolytic system may cause thrombosis or hemorrhage. Patients with impaired fibrinolytic activity are more susceptible to thrombosis. Increased fibrinolysis with bleeding has been reported in several cases, including patients with MM and amyloidosis. Impaired fibrinolytic activity may occur due to decreased synthesis and/or release of plasminogen activators or increased concentrations of PAIs [3,8,9].

In the literature, different results have been reported on the fibrinolytic system in patients with MM. Several studies have suggested that disruption of the fibrinolytic system contributes to the development of thrombosis [3,4,6,7,9]. Carr et al. [10] reported that myeloma protein concentration was associated with the formation of abnormally thin fibrin fibers, resulting in impaired fibrinolysis. However, fibrinolysis activator and inhibitor levels were not analyzed in this study. Very few studies have investigated fibrinolytic system activators and inhibitors in this disease. Therefore, in this study, we aimed to evaluate fibrinolytic system activity by measuring tPA, TAFI, and PAI-1 levels in patients with MM and comparing them with healthy controls.

Methods

A total of 48 newly diagnosed patients with MM aged 51-80 years who were admitted to the Hematology Outpatient Clinic of Zonguldak Bülent Ecevit University between July 2009 and February 2011 were included in this study. Patients previously treated for MM, those diagnosed with thyroid and/or coagulation disorders, and those with chronic liver disease and those or controls using anticoagulant drugs were excluded from the study. The control group included 20 individuals aged 53-80 years who presented to the general internal medicine outpatient clinic for routine checkups, had no known systemic disease, and were not diagnosed with any disease as a result of examinations. Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Zonguldak Karaelmas University Local Ethics Committee (date: 29.06.2009, decision no: 2009/09).

Blood was collected from all patients and healthy controls at 8:00 in the morning into 5 mL biochemistry tubes for analysis of urea, creatinine, total protein, albumin, calcium, and β2 microglobulin levels. At the same time, blood was collected in 5 mL 3.8% citrate tubes for the measurement of plasma fibrinogen, D-dimer, tPA, PAI-1, and TAFI. After centrifugation, plasma samples were stored at -80 °C until analysis.

Determination of plasma tPA, TAFI, PAI-1, and D-dimer levels:

- Quantitative measurement of tPA was performed by enzyme-linked immunosorbent assay (ELISA) using the Asserachrom® tPA kit (Diagnostica Stago, France) according to the manufacturer's instructions (normal range, 2-12 ng/mL).

- Quantitative measurement of plasma PAI-1 was performed by sandwich ELISA using the Asserachrom® PAI-1 kit (Diagnostica Stago, France) according to the manufacturer's instructions (normal range: 4-43 ng/mL).

- TAFI was measured using the Asserachrom® TAFI ELISA kit (Diagnostica Stago, France). A normal range of 0.1-25 µg/mL was used, as stated in the commercial kit.

- D-dimer was analyzed using an Amax D-dimer kit (Trinity Biotech, USA) in an AMAX 200 device. Values <147 ng/mL were accepted as normal.

Statistical Analysis

The Statistical Package for Social Science 26 package program was used for the statistical evaluation of the data obtained in the study. The Shapiro-Wilk test was used to evaluate whether the measured variables were suitable for normal distribution. Student's t-test was used for normally distributed data, and Mann-Whitney U and Kruskal-Wallis tests were used when the assumption was not met. In order to summarize group comparisons and demographic characteristics, mean and standard deviation values for parametric data, median and interquartile range for non-parametric data, and measures of dispersion were used as descriptive statistics. Spearman's correlation analysis was used to explain the relationship between the parameters. $P<0.05$ was accepted as the statistical significance level.

Results

The study included 48 newly diagnosed patients with MM in the study group and 20 healthy subjects in the control group. There were 27 male (56.2%) and 21 female (43.8%) in the patient group and 9 male (45.0%) and 11 female (55.0%) in the control group. 18.15% (n=9) of the patient group were diabetic and 41.66% (n=20) were hypertensive. The mean ages in the patient and control groups was 68±9.9 years (51-80 years) and 63.9±7.5 years (53-80 years), respectively. There were no significant differences in age or sex between the control and patient groups. Myeloma protein type was IgG in 64.6% of the patients (n=31), IgA in 29.2% (n=14), lambda light chain in 4.2% (n=2), and IgM in 2.1% (n=1) (Table 1). MM disease stage determined at the time of diagnosis according to the international staging system was stage 3 in 27 patients (56.3%), stage 2 in 14 patients (29.2%), and stage 1 in 7 patients (14.6%). The demographic and clinical characteristics of both groups are presented in Table 1.

Serum total protein, urea, and creatinine levels were significantly higher in the patient group than in the control group ($p<0.001$, $p<0.001$, $p=0.001$, respectively), and albumin levels were significantly lower in the patient group than in the control group ($p<0.001$). However, there was no statistically significant difference in serum calcium levels between the groups ($p=0.319$) (Tables 2, 3).

In the comparisons of fibrinolytic system factors between patients with MM and the control group, no significant differences were detected in the mean plasma tPA, PAI-I, or D-dimer levels (p>0.05 for all). The mean plasma TAFI level was significantly lower in the patient group [7.6 (6.2-9.19) µg/mL] than in the control group [9.46 (8.83-13.02) µg/mL] (p<0.001). The relationship between diabetes, hypertension, and TAFI was evaluated using the Spearman correlation test, but no significant correlation was found. Levels of plasma tPA, TAFI, PAI-I, and D-dimer measured in the patient and control groups are presented in Tables 2 and 4. In the post-hoc analysis, the G*Power value was found to be 0.584.

Discussion

MM is a malignant plasma cell disease that accounts for 1% of all cancers and approximately 10% of all hematological malignancies. Thrombotic and hemorrhagic events are common complications of MM [11]. Numerous independent mechanisms are believed to be responsible for hypercoagulability in patients with myeloma. The main causes of hypercoagulability include the effects of abnormal and increased immunoglobulins on fibrin polymerization; the production of procoagulant antibodies; activation of the coagulation system by inflammatory cytokines; disorders

Table 1. The demographic and clinical characteristics of the patient and control groups

	Patients (n=48)	Controls (n=20)	p
Age (years), mean±SD	68±9.9	63.9±7.5	0.099
Sex, n (%) Female Male	 21 (43.7) 27 (56.2)	 11 (55) 9 (45)	0.562
Comorbidity DM, n (%) HT, n (%)	 16 (33) 23 (47.9)	- - -	
Paraprotein type, n (%) IgG IgA IgM Lambda	 31 (64.6) 14 (29.2) 1 (2.1) 2 (4.2)	 - - - -	
ISS stage, n (%) Stage 1 Stage 2 Stage 3	 7 (14.6) 14 (29.2) 27 (56.3)	 - - -	

SD: Standard deviation, DM: Diabetes mellitus, HT: Hypertension, ISS: International scoring system, Ig: Immunoglobulin

Table 2. Comparison of biochemical test results between the patient and control groups

Biochemical markers	Patients	Control	p
	Mean (SD)	Mean (SD)	
Albumin (g/dL)	3.56 (0.7)	4.25 (0.18)	<0.001
Total protein (g/dL)	9.36 (2.04)	7.02 (0.4)	<0.001
Calcium (mg/dL)	9.36 (1.28)	9.56 (0.26)	0.319
D-dimer (ng/mL)	110.39 (16.12)	106.8 (16.27)	0.406

Mean values of biochemical parameters between patient and control groups, measured by Student's t-test.
SD: Standard deviation

Table 3. Comparison of biochemical test results between the patient and control groups

Biochemical markers	Patients	Control	p
	Median (IQR)	Median (IQR)	
Urea (mg/dL)	23 (17.25-31.75)	14.5 (12.25-19.5)	<0.001
Creatinine (mg/dL)	1.2 (0.9-1.6)	0.9 (0.8-1)	<0.001
β2-microglobulin	58.41 (3890-9141)		

Median values of biochemical parameters between patient and control groups, measured by Mann-Whitney U test.
IQR: Interquartile range

Table 4. Comparison of tPA, PAI-1 and TAFI levels between the patient and control groups

Biochemical markers	Patients	Control	p
	Median (IQR)	Median (IQR)	
tPA (ng/mL)	9 (6.58-15.36)	12.35 (8.4-19.7)	0.221
TAFI (µg/mL)	7.6 (6.2-9.19)	9.46 (8.83-13.02)	<0.001
PAI-I (ng/mL)	9.36 (1.28)	9.56 (0.26)	0.057

Median values of biochemical parameters between patient and control groups, measured by Mann-Whitney U test.
tPA: Tissue plasminogen activator, PAI-1: Plasminogen activator inhibitor-1, TAFI: Thrombin-activatable fibrinolysis inhibitor, IQR: Interquartile range

of the natural anticoagulation mechanisms; and an increase in adhesion molecules caused by both tumor cells and chemotherapy [6,8]. The causes of bleeding in patients with MM are also multifactorial. Hemorrhage can occur for various reasons, including decreased factor X and α2-AP levels; amyloid accumulation in vessel walls; and inhibition of fibrin polymerization, factor VIII, and Von Willebrand factor, and disruption of platelet function by paraprotein [6].

The fibrinolytic system plays a role in many physiological and pathological events. The major activators of the fibrinolytic system are tPA and uPA, whereas PAI-1 and PAI-2 are its inhibitors [12]. TAFI is another recently identified fibrinolysis inhibitor that acts by separating carboxy terminal lysine residues from fibrin after activation by thrombin [13].

In the present study, we compared tPA, PAI-1, TAFI, and D-dimer levels between 48 patients newly diagnosed with MM and a healthy control group. Our patients had comparable tPA levels to healthy controls. In contrast, although the difference did not quite reach statistical significance, the PAI-1 level was lower in the patients with MM than in controls. Interesting finding was that the patients with MM had significantly lower TAFI levels than the controls.

In a study by Spicka et al. [3] involving 49 patients with monoclonal gammopathy (44 patients with MM, 3 patients with Waldenstrom macroglobulinemia, and 2 patients with monoclonal gammopathy of undetermined significance), increased tPA activity was the most common abnormality, although increased PAI-1 levels were also reported. Anticoagulant system defects were detected in 26.5% of the same patient group. The risk of venous thromboembolism was higher in the group with anticoagulant and/or fibrinolytic system abnormalities, but not significantly. Yağci et al. [9] published one of the most comprehensive studies investigating fibrinolytic system activator and inhibitor levels and their relationship with cytokines in patients with MM. In their study, tPA, PAI-1, interleukin (IL)-6, IL-1β, and IL-11 levels and global fibrinolytic capacity were compared between 66 patients with MM and a healthy control group. Levels of tPA were similar between the two groups. However, patients with MM were found to have significantly higher PAI-1 levels and resulting lower fibrinolytic activity, and a positive correlation was observed between PAI-1 and IL-6 levels. TAFI levels were not analyzed. Shortened clot lysis time, increased fibrinolysis characterized by increased levels of fibrin degradation products, and consequent bleeding have also been reported in patients with MM and amyloidosis [6].

TAFI levels have been studied in patients with solid tumors and hematological malignancies. Higher TAFI levels were observed in patients with non-small-cell lung cancer compared with the control group, suggesting that this antigen may be secreted by cancer cells themselves [14]. In the same study, increased TAFI was proposed to play a role in the pathogenesis of venothrombotic events in patients with lung cancer. In another study comparing levels of TAFI and TAFIa (active enzyme) between patients with antiphospholipid syndrome (APS) and a control group, APS patients had higher TAFI and TAFIa levels than controls, and patients with arterial thrombosis had higher TAFIa levels than those with other APS phenotypes. The authors concluded that TAFIa could be a new biomarker of arterial thrombosis in APS patients [15]. In contrast, the Hypercoagulability and Impaired Fibrinolytic Function Mechanisms Predisposing to Myocardial Infarction study suggested that increased TAFI antigen levels could protect against myocardial infarction [16].

In the first study to investigate TAFI in patients with MM, TAFI levels measured in 27 patients with newly diagnosed myeloma were significantly higher than those in the control group [17]. The authors reported that TAFI level was associated with disease activity and suggested a link between the higher TAFI level in myeloma and thrombotic complications in these patients. Similar results were obtained in another subsequent study [18]. Misiewicz et al. [19] compared the relationship between certain rotational thromboelastometry parameters and tPA and PAI-1 levels in newly diagnosed patients with MM and a healthy control group and detected high PAI-1 levels indicative of hypofibrinolysis in patients with MM. In a study investigating the effect of induction therapy on fibrin clot properties in patients with MM, Undas et al. [20] observed ischemic stroke in 2 patients and venous thromboembolism in 10 patients despite thromboprophylaxis and determined that these patients had high TAFI and PAI-1 levels before treatment. In contrast to these data, the TAFI levels in the present study were significantly lower in patients with MM than in the control group.

Increased TAFI levels have also been reported as the cause of hypofibrinolysis in various endocrine disorders, such as obesity and diabetes [21,22]. There are also many studies in the literature that investigated plasma TAFI Ag or TAFIa levels in patients with overt hypothyroidism. Erem et al. [23] reported no significant correlation between TAFI Ag and thyroid hormone levels, and another study determined higher plasma TAFI Ag levels in hypothyroid patients [24].

Ermantas et al. [25] found that TAFI and TAFIa levels were higher in hypothyroid patients than in the control group, and they suggested that thyroid insufficiency may have affected circulating TAFI Ag levels. However, we detected no correlation between TAFI levels and disease stage, diabetes, and hypertension. One of the limitations of the study was that we could not access the patients' body mass index and lipid panel. Since obvious thyroid dysfunctions were excluded from our patient population, fibrinolytic system-thyroid disorders are outside the scope of this study.

In our study, clinical bleeding was observed in 4 of the MM patients. There were no significant differences between patients with MM and controls in terms of the levels of D-dimer, an *in vivo* coagulation marker. Therefore, we do not believe coagulation activation or subsequent secondary fibrinolysis. However, less than 10% of patients with MM, Waldenstrom macroglobulinemia, and primary amyloidosis present with bleeding complications. We believe that the decreased TAFI levels detected in our study may also contribute to increased fibrinolysis, especially in patients with myeloma who have bleeding. In patients with acute leukemia, it was reported that TAFI activity was lower than that of the control group but inversely proportional to the severity of bleeding [26]. In various studies, low TAFI was associated with hyperfibrinolysis. Van Thiel et al. [27] reported that plasma TAFI levels were quite low in patients with advanced hepatocellular liver disease. Colucci et al. [28] showed that clots obtained from patients with cirrhosis were more sensitive to exogenous tPA at physiological concentrations. They stated that TAFI deficiency is the main cause of hyperfibrinolysis. Denorme et al. [29] examined the inhibition of TAFI and PAI-1 in a mouse model of transient middle cerebral artery occlusion. Inhibition of TAFI or PAI-1 significantly reduced cerebral infarct size by 50% at 24 hours after stroke. On the contrary, an experimental agent (DS-1040) has recently been shown to inhibit the activated form of TAFI but to have no effect on bleeding time [30]. Although it was difficult to determine the cause of the low plasma TAFI levels, it may be related to the different laboratory methods used in the studies.

Study Limitations

The main limitation of our study was that plasmin-AP complex level, which is a direct indicator of *in vivo* fibrinolysis and TAFI gene polymorphisms, could not be examined due to technical reasons.

Conclusion

In conclusion, although impaired fibrinolytic activity is generally expected in patients with MM, the present study demonstrated that these patients had low TAFI levels without significant changes in tPA and PAI-1 levels. Decreased TAFI levels may play a role in other mechanisms that can cause bleeding in patients with MM. However, further clinical studies with a large number of patients measuring plasmin-AP levels are needed.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the Zonguldak Karaelmas University Local Ethics Committee (date: 29.06.2009, decision no: 2009/09).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.Ö.T., F.C.S., Concept: M.K., Design: H.Ş., M.K., Data Collection or Processing: M.K., H.Ş., Analysis or Interpretation: İ.Ö.T., F.C.S., Literature Search: M.K., H.Ş., Writing: M.K., H.Ş.

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Original Article

Role of PET/CT in T-cell Lymphoma

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ABSTRACT

Aim: This study aimed to investigate the impact of post-treatment positron emission tomography-computed tomography (PET/CT) findings on predicting disease prognosis in patients with T-cell lymphoma.

Methods: Patients diagnosed with T-cell lymphoma and admitted to the Medical Oncology Clinic of Gazi University Medical Faculty Hospital between 2004 and 2014 were retrospectively evaluated. The study included 24 patients who underwent PET/CT for staging. The correlation between post-treatment PET/CT findings and progression-free survival (PFS) and overall survival (OS) was analyzed.

Results: The 1- and 2-year PFS rates were 78.6% and 50% in the PET-negative group and 40% and 0% in the PET-positive group (p=0.007). No statistically significant difference was found between the two groups regarding 1- and 2-year OS rates (p=0.113). As a result of multivariate cox regression analyses, only age was found to be effective for OS and PFS, and the risk of progression and death increased with older age.

Conclusion: Post-treatment PET/CT findings were not independent predictors of PFS and OS in T-cell lymphomas. However, the small sample size and retrospective design of the study warrant further research with larger patient cohorts.

Keywords: Lymphoma, T-cell, positron emission tomography, prognosis

Introduction

Hodgkin's lymphoma (HL) and non-HL (NHL) are clonal lymphoproliferative diseases arising from immune system cells, each with distinct clinical presentations. Approximately 90% of all lymphomas are NHL and 10% are HL. According to the World Health Organization (WHO) 2008 classification, NHL is categorized into two main groups: B-cell lymphoma and T/NK cell lymphoma [1]. The prevalence of NHL increases with age and is more common in men than in women. Infections, environmental factors, and chronic inflammation have been shown to have an etiology [2]. Immunosuppression is the most clearly defined factor in the etiology of NHL and increases the risk of lymphoma by 50-100 times [3]. Lymphomas are classified based on their morphological appearance based on immune phenotype and genetic characteristics. In 2008, this classification was updated by the WHO. A tissue biopsy sufficient to reveal a large area of cells that exhibit the morphology is essential for a definitive lymphoma diagnosis [4]. Excisional diagnostic biopsy is recommended.

About 10-15% of all lymphomas in Western countries are T-cell NHLs, a diverse group of neoplasms with distinct morphological, immunophenotypic, and clinical characteristics. However, they are more prevalent in Asia [5]. Treatment usually consists of chemotherapy and radiotherapy, but high-dose therapy, autologous stem cell transplantation, and new agents are also used.

Positron emission tomography (PET) is a noninvasive nuclear imaging technique based on introducing a positron-emitting radiopharmaceutical into the body, followed by imaging the distribution and kinetics of the radioactive tracer. PET and computed tomography (CT) are combined in PET/CT and have been used to detect areas of involvement more effectively than CT, especially in aggressive lymphomas [6]. Although there is evidence that using PET in lymphoma staging is effective for progression-free survival (PFS), there is no evidence-based data showing that it increases overall survival (OS), but studies have shown that PET/CT is more sensitive than CT and other conventional methods for identifying lymphoma

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involvement [7-10]. PET also showed metabolic activity in the lesions. Fluorine-18-2-fluoro-2-deoxy-D-glucose PET (F18-FDG-PET) is a functional imaging modality used for initial and posttreatment staging. F18-FDG uptake before and after treatment is essential for determining treatment response and prognosis [11]. According to the PET result, it may be possible to direct the patient to more aggressive treatment modalities.

This study aimed to evaluate the relationship between post-treatment PET/CT findings and both PFS and OS in individuals diagnosed with T-cell lymphoma.

Methods

Patients diagnosed with T-cell lymphoma and admitted to the Medical Oncology Clinic of Gazi University Hospital between 2004 and 2014 were retrospectively evaluated. The study included 24 patients who underwent PET/CT for staging. Patients who had received chemotherapy or radiotherapy prior to F18-FDG PET/CT were excluded from the study. PET/CT was used to evaluate treatment responses in conjunction with conventional CT and magnetic resonance imaging methods. PET/CT performed following the completion of treatment was referred to as PET2. PET/CT was performed at least 3-4 weeks following the end of chemotherapy and at least 8 weeks following the end of radiotherapy. The Deauville criteria were used for the response evaluation. Complete response, partial response, stable disease, and progressive disease (PD) were the classifications used to describe treatment responses.

All PET scans were performed according to the standard F18-FDG PET/CT imaging protocol at Gazi Faculty of Medicine, Department of Nuclear Medicine.

Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital on November 11, 2015 (protocol number: E-15-596).

Statistical Analysis

The Statistical Package for the Social Sciences software for Windows 11.5 was used to analyze the data. We provided descriptive statistics for numerical variables as mean±standard deviation or median (minimum-maximum), while categorical variables were represented as number of cases and percentages (%). The Kaplan-Meier method was used to evaluate the survival data, and univariate survival analysis was performed via the log-rank test. Independent prognostic factors were identified by multivariate Cox regression analysis. PFS was defined as the duration from treatment initiation to the occurrence of disease progression, death, or most recent follow-up. OS was defined as the duration from treatment initiation until death or recent follow-up. All tests were conducted in a one-sided manner, and $p<0.05$ was considered statistically significant.

Results

The study included 24 patients diagnosed with T-cell lymphoma. Median age was 45 years (range 19-84 years). 75% of the patients were male (n=18). Splenic involvement was present in 20.8%, extranodal involvement in 45.8%, and B symptoms in 37.5%. 29.2% (n=7) of patients had stage 1, 25% (n=6) stage 2, 25% (n=6) had stage 3, and 20.8% (n=5) had stage 4 disease. Table 1 provides additional details about the patients' clinical and demographic characteristics.

Table 1. Demographic and clinical characteristics of patients

	n=24
Age, mean±SD	45.7±17.7
Sex, n (%)	
Male	18 (75.0)
Female	6 (25.0)
The type of lymphoma, n (%)	
NK/T HL	9 (37.5)
PTHL	6 (25.0)
AITL	5 (20.8)
T-cell lymphoblastic leukemia/lymphoma	2 (8.3)
Cutaneous anaplastic lymphoma	1 (4.2)
ALK + ALCL	1 (4.2)
IPI, n (%)	
0	4 (16.7)
1	8 (33.3)
2	5 (20.8)
3	7 (29.2)
Stage, n (%)	
1	7 (29.2)
2	6 (25.0)
3	6 (25.0)
4	5 (20.8)
Splenic involvement, n (%)	5 (20.8)
B symptoms, n (%)	9 (37.5)
Performance status, n (%)	
0	21 (87.5)
1	3 (12.5)
High LDH level, n (%)	11 (45.8)
Extranodal involvement, n (%)	11 (45.8)
Extranodal involvement site, n (%)	
Subcutaneous	4 (36.4)
Liver	1 (9.1)
Bone marrow	3 (27.3)
Meninx	1 (9.1)
Nazal cavity	2 (18.2)
Chemoteraphy type, n (%)	
CHOP	11 (45.8)
SMILE	4 (16.7)
R-CHOP	2 (8.3)
HCVAD	2 (8.3)
CHOEP	1 (4.2)
CVP	1 (4.2)

Table 1. Continued

	n=24
Other variables, n (%)	2 (8.3)
Number of chemotherapy applications, median (min-max)	5 (1-8)
Salvage regime, n (%)	9 (37.5)
Stem cell transplantation rate, n (%)	9 (37.5)
Radiotherapy, n (%)	9 (37.5)
Response, n (%)	
Complete response	16 (66.7)
Partial response	4 (16.7)
Progressive disease	4 (16.7)
PET1 positivity, n (%)	23 (95.8)
SUV 1, median (min-max)	9.2 (3.8-25.9)
PET3 positivity, n (%)	5 (25.0)
SUV 3, median (min-max)	5.1 (2.8-6.7)
Last response, n (%)	
Complete response	8 (33.3)
Partial response	2 (8.3)
Stable disease	2 (8.3)
Progressive disease	12 (50.0)
Relapse, n (%)	12 (50.0)
Exitus (n (%)	12 (50.0)

HL: Hodgkin lymphoma, PTHL: Peripheral T-cell lymphoma, AITL: Angioimmunoblastic T-cell lymphoma, ALK: Anaplastic lymphoma kinase, ALCL: Anaplastic large cell lymphoma, LDH: Lactate dehydrogenase, PET: Positron emission tomography, SUV: Standardized uptake value, CHOP: Cyclophosphamide, vincristine and doxorubicin, SMILE: Dexamethasone, methotrexate, ifosfamide, l-asparaginase and etoposide, R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, HCVAD: Cyclophosphamide, vincristine, doxorubicin, dexamethasone, CHOEP: Cyclophosphamide, doxorubicin, vincristine, prednisolone, etoposide, CVP: Cyclophosphamide, prednisolone, vincristine, SD: Standard deviation, IPI: International Prognostic Index, min-max: Minimum-maximum

All patients underwent PET/CT before primary chemotherapy (PET1), and a positive result due to lymphoma was found in 23 patients. All chemotherapy completers (n=20) underwent PET/CT (PET2). Four patients did not undergo PET/CT because of the mortality of PD. PET2 was negative in 15 patients after the end of treatment. A total of 12 patients developed relapse/progression during follow-up. Among these patients only 4 of them had a positive PET result, while 8 of them had complete remission according to PET2.

Survival analyses were performed using the PET (PET2) result after the primary chemotherapy.

A statistically significant difference was observed in PFS between the PET2-negative and PET2-positive patient groups and between the groups divided according to the International Prognostic Index (IPI) score (p=0.007, p=0.045). No statistically significant discrepancy in OS was observed between patient groups classified as PET2-negative or PET2-positive, as well as among different IPI score categories (Figures 1-4).

Factors such as stage, high lactate dehydrogenase levels, and extranodal involvement did not significantly affect OS or PFS (Table 2).

As a result of univariate statistical analyses, the combined effects of all possible risk factors that are effective or thought to be effective on PFS and OS were investigated. IPI, PET2, and age variables were included in the baseline model. When the combined effects of all three factors were analyzed, none of these factors were found to be statistically significant predictors of PFS, whereas age was found to be predictive of OS independent of IPI and PET2, and the risk of death increased with increasing age [HR=1.106; 95% confidence interval (CI): 1.015-1.205 and p=0.022]. On the other hand, when retrospectively analyzed, only age was found to be effective for PFS and OS (HR=1.060; 95% CI: 1.012-1.110, p=0.013; HR=1.070; 95% CI: 1.014-1.129, p=0.013).

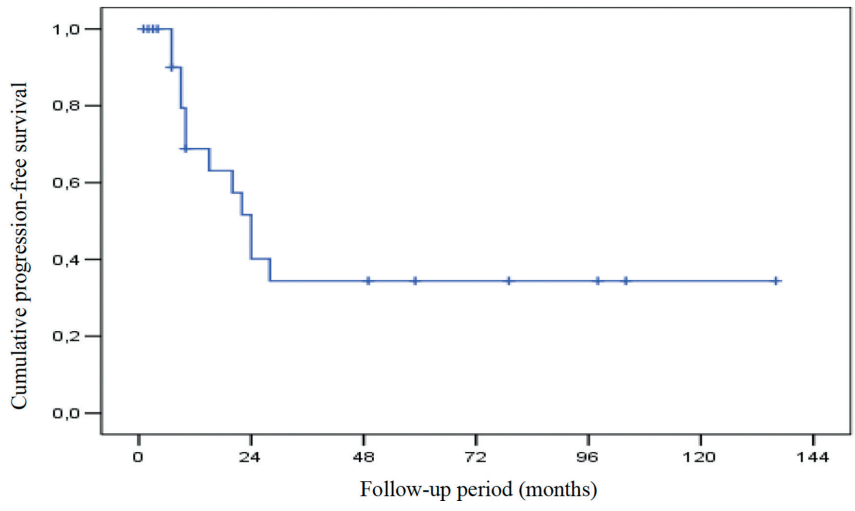

Figure 1. Progression-free survival

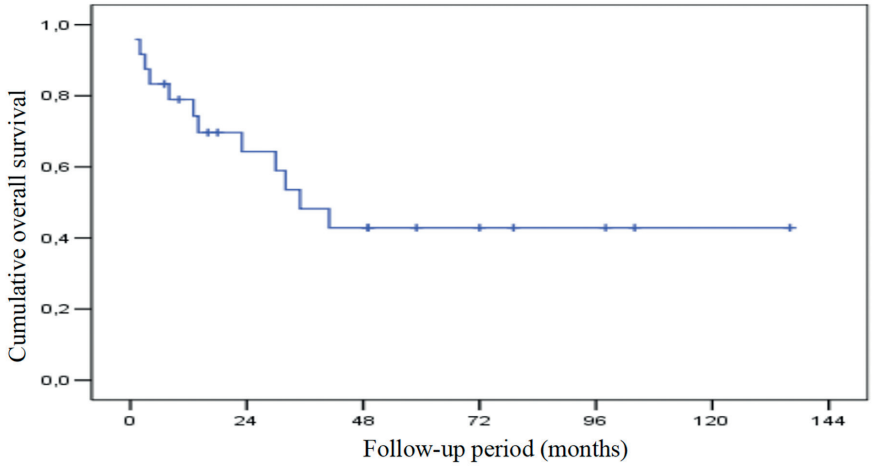

Figure 2. Overall survival in all patients

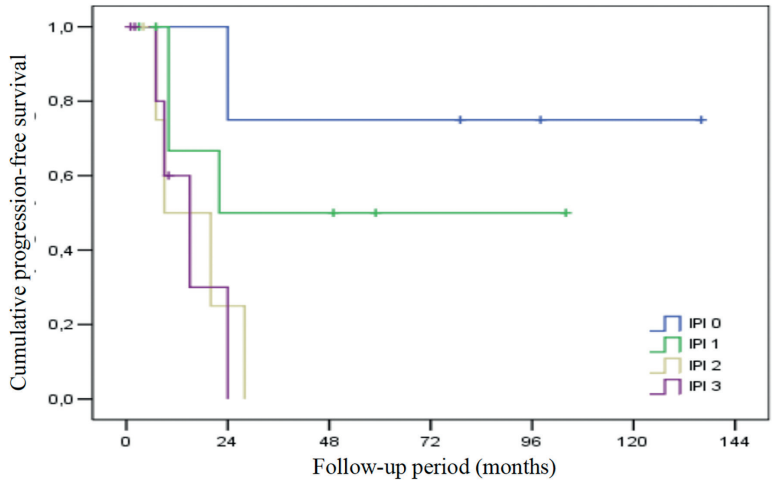

Figure 3. Relationship between IPIs and progression-free survival
IPI: International prognostic Index

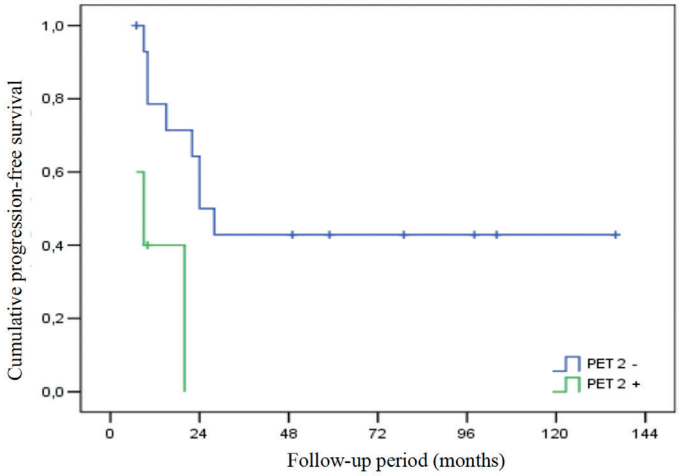

Figure 4. Relationship between PET2 and progression-free survival
PET: Positron emission tomography

Discussion

In this study, 24 patients with T-cell lymphoma were assessed with post-treatment F18-FDG-PET/CT. After a median follow-up period of 26.5 months (range 1-136 months), PET/CT was performed in 83.3% of patients at the end of treatment. PET scans were negative in 15 patients post-treatment, with progression/relapse occuring in 4 patients who remained PET2-positive. Relapse/progression was observed in 8 of the 15 patients with negative PET results post-treatment. PET positivity predicted relapse/progression in 80% of the patients, which is consistent with the literature, whereas 46% of PET-negative patients remained in remission.

Tomita et al. [12] retrospectively evaluated the predictive value of F18-FDG-PET (post-PET) after first-line treatment for peripheral T-cell lymphomas (PTHL). Thirty-six patients were included. Sixteen patients presented with PTHL-not otherwise specified (PTHL-NOS) and 20 with angioimmunoblastic T-cell lymphoma (AITL). Post-PET results were positive in 31% (11/36) and negative in 69% (25/36) of the patients. In the groups with positive and negative PET results, the 3-year PFS rates were 18% and 62%, respectively ($p<0.001$). Patients with positive post-PET results developed PD in 9 of 11 patients (positive predictive value 82%). In comparison, 16 of 25 patients in the negative post-PET group did not develop PD (negative predictive value 64%). The 3-year OS rates were 44% for PET-positive patients and 84% for PET-negative patients ($p=0.03$). These findings suggest that post-PET can predict prognosis in patients with PTHL. In the study by Cahu et al. [13], a total of 54 T/NK cell lymphoma patients (15 PTHL-NOS and 11 AITL patients) were evaluated using PET/CT before (n=44) and after (n=31) treatment. Interim evaluation by PET/CT was negative in 25 of 44 patients, whereas 19 of 31 patients achieved complete remission on PET/CT after treatment. In patients with anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma, a 4-year PFS rate of 80% was observed, with post-treatment PET/CT showing a negative predictive value of 83% (n=9). In ALK T/NK lymphomas, patients with a negative interim PET/CT evaluation exhibited a 4-year PFS rate of 59%, whereas those with a positive interim PET/CT evaluation showed a PFS rate of 46% ($p=0.28$, n=35). Similarly, no statistically significant disparity was observed in 4-year PFS between patients with negative and positive PET/CT after treatment (51% and 67%, respectively, $p=0.96$). The 4-year cumulative relapse incidence in ALK-T/NK lymphomas was 53% among patients who had negative post-treatment PET/CT. Despite F18-FDG uptake upon diagnosis, negative interim or posttreatment PET/CT scans do not exhibit a significant association with improved PFS in ALK-positive T/NK lymphomas.

In this study, patients with negative PET2 results had 1- and 2-year PFS rates of 78.6% and 50%, respectively, and a mean PFS of 68.4 months. In contrast, the 1- and 2-year PFS rates for PET2-positive patients were 40% and 0%, respectively, with a mean PFS of 12.6 months. A statistically significant disparity in PFS was observed between the groups ($p=0.007$). There were no statistically significant differences in 1- and 2-year OS between PET2-negative and PET2-positive patients.

Unlike the studies by Tomita et al. [12] and Cahu et al. [13], Li et al. [14] examined interim PET scans and post-PET outcomes in a cohort of 88 patients with T/NK cell lymphomas (23 PTHL-NOS and 3 AITL), who underwent treatment with CHOP and various anthracycline-free chemotherapy protocols. The study found that both interim and posttreatment PET results were independently associated with PFS and OS in patients with T/NK cell lymphoma. However, it is important to note that in this study, only 13 patients with PTHL (all PTHL-NOS) underwent post-PET evaluation. The contradictory results of these investigations might be attributable to variations in treatment protocols and histological types.

Study Limitations

This study has some limitations, including the retrospective nature of our investigation, the limited number of patients included in the study, the inhomogeneity of histological tumor distribution, differences in first-line chemotherapy regimens, and differences between the completion of chemotherapies (1-8 cycles).

Conclusion

In this study, post-treatment PET/CT findings were not found to be independent predictors of PFS and OS in T-cell lymphomas. Although numerous studies have demonstrated the role of PET/CT in diagnosing and staging T-cell NHL, further prospective randomized clinical trials are needed to confirm the value of interim evaluation and post-treatment PET/CT in predicting disease prognosis.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Ethics Committee of University of Health Sciences Turkey, Haydarpaşa Numune Training and Research Hospital on November 11, 2015 (protocol number: E-15-596).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.Ç., M.B., Surgical and Medical Practice: E.Ç., M.B., Concept: E.Ç., M.B., Design: E.Ç., M.B., Data Collection or Processing: E.Ç., Analysis or Interpretation: E.Ç., M.B., Literature Search: E.Ç., M.B., Writing: E.Ç., M.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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AHOT | Acta Haematologica Oncologica Turcica

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Original Article

Acinetobacter baumannii in Hematology Practice: Clinical Factors Affecting the Course of Infection

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ABSTRACT

Aim: Hematological malignancies are inherently risk factors for *Acinetobacter baumannii (A. baumannii)* infection. In this study, we aimed to reveal the clinical features of *A. baumannii* infection in patients with hematological malignancies and identify factors affecting the course of the infection.

Methods: The data of 49 subjects who were diagnosed and followed-up at the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Hematology between October 2014 and July 2019 were analyzed retrospectively.

Results: Twenty-two (44.9%) subjects were diagnosed with acute myeloid leukemia, 15 (3.6%) subjects with lymphoma, 9 (18.4%) subjects with ALL, and 3 (6.1%) subjects were diagnosed with other hematological malignancies. Thirty-nine (79.6%) patients died during follow-up. Thirty-five (71%) subjects required intensive care unit (ICU) and were transferred to the ICU. Twenty-two (95.7%) of the subjects with neutrophil count <100/mm^3 and seventeen (65.4%) of the subjects with neutrophil count >100/mm^3 died (p=0.009). In the univariate analysis, neutrophil count <100/mm^3 had an impact on the occurrence of death in subjects with *A. baumannii* infection (p=0.026, HR=11.64). The number of patients who died was comparable between those treated with or without colsitin/tigecycline (p=0.253). The number of subjects who died was comparable between those who were treated with or without a carbapenem-type antibiotic (p=0.076).

Conclusion: Further studies are needed to identify factors affecting the course of *A. baumannii* infection in patients with hematological malignancies.

Keywords: *Acinetobacter baumannii (A. baumannii),* hematology, mortality, prognosis

Introduction

Acinetobacter baumannii (*A. baumannii*) is a Gram-negative pathogen that can spread easily by clinging to surfaces and can be a severe infectious agent in clinical practice due to its strong virulence factors [1]. Carbapenems, beta-lactam antibiotics, and polymyxins are frequently used, but multidrug-resistant *A. baumannii* can be a severe infection agent with difficulties that can be experienced during treatment [2-6].

A. baumannii-related mortality has been reported to range between 30% and 73% among critically ill patients [7,8]. Septic shock and mortality are quite high, especially within 30 days of the onset of infection [9]. Some mortality factors associated with *A. baumannii* infection include but are not limited to, advanced age, recent surgery, presence of immunosuppressive treatment, presence of invasive procedures such as catheterization and mechanical ventilation, presence of comorbidities such as acute renal failure, acute respiratory failure, septic shock, inappropriate use of antibiotics, and low platelet and albumin levels [10,11]. It is also important to determine whether there is an infectious agent due to colonization, especially in patients with a history of intensive

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care unit (ICU) admission, which may lead to the unnecessary use of antibiotics [11].

Hematological malignancies are inherently risk factors for *A. baumannii* infection [10]. Data on the course of infection in hematologic malignancies, factors influencing the course of infection and mortality are limited. In this study, we aimed to reveal the clinical features of *A. baumannii* infection in patients with hematological malignancies and to identify factors affecting the course of the infection, as observed in our clinic.

Methods

Patients with co-existing hematological malignancies and *A. baumannii* infection were included in this study. The data of 49 patients who were diagnosed and followed at the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Hematology, between October 2014 and July 2019, were analyzed retrospectively. Patients diagnosed with urinary infection, ventilator-associated pneumonia, or catheter-related bloodstream infection were included in the study. The only exclusion criterion was A. *baumannii* infection-related septic shock.

Bactec plus aerobic and anaerobic medium (BD; USA) were used and incubated in the Bactec FX (BD, USA) automated blood culture system. After obtaining the culture signal, Gram-stained microscopic examination of the positive blood culture bottle was performed. Microscopic examination revealed Gram-negative coccobacilli. The blood samples were then inoculated in 5% sheep blood (Oxoid, UK), eosin methylene blue (EMB, Oxoid, UK), and chromogenic *Candida* agar (AEM Medical, Turkey). The cells were incubated for 24 h at 37 °C under aerobic conditions. Species-level identification was performed in line with the manufacturer's recommendations using the VITEK-2 Compact (bioMérieux, France) system. A 0.5 McFarland (DensiChek Plus, bioMérieux, France) bacterial suspension from pure bacterial colonies was used for identification. All isolates in this study were identified as *A. baumannii using* the VITEK-2 Compact (bioMérieux, France) system, and their antimicrobial susceptibility was determined. Antibiotherapy was revised according to the antibiogram results.

The data, including age, diagnosis, antibiotic treatment, and ICU history, of the subjects were reviewed through the hematology department's database. Laboratory tests performed to assess the biochemical and metabolic status of the subjects included measurements of complete blood count and kidney and liver function.

The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital of Local Ethics Committee (approval date and number: 09/08/2019-1949).

The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations. Informed consent to publish the article was obtained from the subjects.

Statistical Analysis

The Statistical Package for the Social Sciences 24 package was used for statistical analysis. Data were presented as numbers and percentages or median and range, as appropriate. x^2 Fisher's exact test was used to analyze categorical values in subject groups. Regression analysis was used to evaluate the effect of neutrophil count on the occurrence of death. All p values were 2-sided with statistical significance at 0.05

Results

The characteristics of the participants are summarized in Table 1. The median age of the subjects was 49 years (range 19-76), with 39 males and 10 females. Twenty-two (44.9%) subjects were diagnosed with acute myeloid leukemia, 15 (3.6%) subjects with lymphoma, nine (18.4%) subjects with acute lymphoblastic leukemia and three (6.1%) with other hematological malignancies. The median numbers of white blood cells and neutrophils were 3,961/mm^3 (range, 100-32,200) and 2,417/mm^3 (range, 0-2,005). The number of

Table 1. The characteristics of the subjects

Patients' characteristics	N=49
Age, years, median (range)	49 (19-76)
Gender, n (%)	
Female	10 (20%)
Male	39 (80%)
Diagnosis, n (%)	
Acute myeloid leukemia	22 (44.9%)
Acute lymphoblastic leukemia	9 (18.4%)
Lymphoma	15 (30.6%)
Other	3 (6.1%)
WBC, mm^3, median (range)	3.961 (10-32,200)
Platelet count, mm^3, median (range)	43.977 (1.000-315,000)
Neutrophil count, mm^3, median (range)	2417 (0-20,050)
Hemoglobin, gr/dL, median (range)	8.4 (5.5-13.7)
C-reactive protein, mg/L (range)	99 (1.8-452)
Procalcitonin, µg/L, median (range)	9.8 (0.04-158)
Number of neutrophil count, n (%)	
<100 mm^3	23 (47%)
>100 mm^3	26 (53%)
Number of neutrophil count, n (%)	
>1,000 mm^3	16 (32%)
500-1,000 mm^3	3 (6%)
100-500 mm^3	7 (14%)
<100 mm^3	26 (53%)
Intensive care requirement, n (%)	
Present	35 (71%)
Absent	14 (29%)
Use of colistin/tigecycline	
Present	13 (26.5%)
Absent	36 (73.5%)
Use of a carbapenem	
Present	28 (57.1%)
Absent	21 (42.9%)

WBC: White blood cell count

subjects with neutrophil count >1,000/mm^3 was 16 (32%), between 500-1,000/mm^3 was three (6%), between 100-500/mm^3 was seven (14%), and the number of subjects with neutrophil count <100/mm^3 was 23 (47%). The number of subjects with neutrophil counts >100/mm^3 was 26 (53%). The median C-reactive protein level was 36.6 mg/L (range, 1.8-452), and the median procalcitonin level was 0.975 µg/L (0.04-158) (Table 1).

Thirty-nine (79.6%) patients died during follow-up. Thirty-five (71%) subjects required ICU and were transferred to the ICU (Table 1). Although all subjects (100%) in the ICU died, four (28.6%) of the subjects not requiring ICU also died (p=0.000). Twenty-two (95.7%) of the subjects with neutrophil count <100/mm^3 and seventeen (65.4%) of the subjects with neutrophil count >100/mm^3 died (p=0.009) (Table 2). In the univariate analysis, neutrophil count <100/mm^3 had an impact on the occurrence of death in subjects with *A. baumannii* infection (p=0.026, HR=11.64).

When the subjects were analyzed based on their antibiotherapy, the number of subjects treated with either colistin or tigecycline was 13 (26.5%) and that treated with a carbapenem-type antibiotic was 28 (57%). The number of subjects who died was comparable between those who were treated with colsitin/tigecycline or not (p=0.253). The number of subjects who died was comparable between those who were treated with a carbapenem-type antibiotic and those who did not (p=0.076) (Table 2).

Discussion

Real-life data on *A. baumannii* infection and its course in patients with hematological malignancies are limited, and the factors affecting the course of infection are not clear in this patient group. In this study, we aimed to determine the factors that influence the course of *A. baumannii* in patients with hematologic malignancies.

Table 2. Comparative characteristics of subjects who died and survived

	Dead patients N=39	Alive patients N=10	p value
Number of neutrophil count, n (%) <100 mm^3 >100 mm^3	22 (56.4%) 17 (43.6%)	1 (10%) 9 (90%)	0.009
Intesive care requirement, n, (%) Present Absent	35 (89.7%) 4 (10.3%)	0 (0%) 10 (100%)	0.000
Use of colistin/tigecycline Present Absent	12 (30.8%) 27 (60.2%)	1 (10%) 9 (90%)	0.184
Use of a carbapenem Present Absent	25 (64.1%) 14 (35.9%)	3 (30%) 7 (70%)	0.052

In a multicenter study examining the clinical characteristics and prognostic factors of *A. baumannii* infection in patients with hematological malignancies, a total of 40 patients with bacteremia were identified; 62.5% of them were diagnosed with acute leukemias. Neutropenia was detected in 67.5% of subjects, and neutropenic subjects had higher Acute Physiology and Chronic Health Evaluation Scores (APAHCE) and 30-day mortality than non-neutropenic subjects [12]. Carbapenem-resistant *A. baumannii* infection, neutropenia, high APAHCE, and Pitt bacteremia scores, and inappropriate antibiotic therapy were associated with 30-day mortality compared with carbapenem-susceptible infections [12]. In another multicenter study conducted on 46 patients with hematological malignancies, carbapenem-resistant *A. baumannii* cases were examined; a high SOFA score was associated with 7-day mortality, and appropriate antibiotic therapy was found to be protective in the first 48 hours [13].

Clinical data on *A. baumannii* and its course in patients with hematological malignancies have also been published. In a study that included critically ill hematological patients, 39 subjects with *A. baumannii* infection were included. Advanced age, aminoglycoside exposure, central venous catheterization, and nasogastric tube use were independent risk factors for *A. baumannii* infection [14]. In the multivariate analysis, low Glasgow coma score, neutropenia and immunosuppressive therapy, invasive mechanical ventilation, and severe sepsis were associated with mortality [14]. *A. baumannii* bacteremia was defined in 6% of subjects with hematologic malignancies, and 50% of these cases were fatal; all cases were carbapenem-resistant in another study [15]. In a study involving 154 patients with hematologic malignancies, nosocomial Gram-negative bacteremia was evaluated. Pitt bacteremia score, presence of aplastic anemia, bacteremia caused by glucose non-fermenting Gram-negative bacillus, inappropriate antibiotic therapy, presence of severe sepsis or septic shock, difficulty obtaining a microbiological culture, and need for ICU were associated with mortality. In the multivariate analysis, only bacteremia requiring ICU was associated with mortality [16].

In our study, *A. baumannii* infection was most frequently observed in the acute leukemia subgroup. Thirty-one (61%) of the subjects included in our study were diagnosed with acute leukemia, which was in accordance with the literature findings. Neutrophil count <100/mm^3 was found to have an impact on the occurrence of death in subjects with *A. baumannii* infection. Our study also showed that acute leukemia was the riskiest malignancy and that profound neutropenia was one of the most important risk factors. Although carbapenem administration did not have a significant effect on mortality, colistin/tigecycline administration did not have a significant effect. The need for ICU was associated with mortality, which is consistent with the literature.

Study Limitations

There are important limitations to our study. The most significant limitation of this study is that it was based on data from a single center. A further limitation is the retrospective

mortality prediction scores of subjects who were not included in the statistical analysis due to a lack of recorded data. In addition, antimicrobial susceptibility was not evaluated statistically.

Conclusion

In conclusion, in our study, we investigated the clinical features of *A. baumannii* infection in patients with hematological malignancies and the factors affecting the course of the infection in our clinic. Univariate analysis showed that neutrophil count <100/mm^3 had an impact on the occurrence of death in subjects with *A. baumannii* infection. The number of patients who died was comparable between those who were and were not treated with carbapenem-type antibiotic and those who were not. The need for ICU was associated with mortality. Further studies are needed to identify factors affecting the course of *A. baumannii* infection in patients with hematological malignancies.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital of Local Ethics Committee (approval date and number: 09/08/2019-1949). The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

Informed Consent: Retrospective study.

Acknowledgments

We respectfully remember all the colleagues we lost in the fight against COVID-19.

Footnotes

Authorship Contributions

Data Collection or Processing: A.K., İ.S., M.H.D., Analysis or Interpretation: A.K., İ.S., M.H.D., Writing: A.K., İ.S., C,A., M.H.D., E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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Drug-related Problems in Elderly Patients with Hematologic Malignancies: A Single-center Study on Inappropriate Medication Use and Drug-drug Interactions

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ABSTRACT

Aim: Medication-related issues are prevalent among elderly patients diagnosed with hematological malignancies. The present study aimed to evaluate the prevalence and characteristics of polypharmacy, potentially inappropriate medication use (PIM), and drug-drug interactions (DDI) among patients with polypharmacy.

Methods: This cross-sectional study included elderly patients (≥65 years) with hematological malignancies who attended a geriatric outpatient clinic between April and September 2024. Sociodemographic data, medical history, medication use, and chemotherapy status were collected from electronic records. Polypharmacy, PIM, and the DDI were analyzed. PIM was evaluated using the Turkish Elderly Inappropriate Medication (TIME) criteria, whereas the DDI was classified according to the Lexi-Interact database.

Results: In an analysis of 219 patients (mean age 73.9±6.0), 27.8% (n=61) had received chemotherapy. Polypharmacy was observed in 64.4% (n=141) of patients, rising to 70.5% (n=43) in the chemotherapy group. PIM was listed in 63.0% (n=138) of patients, with 77.1% (n=185) of PIMs based on TIME-to-STOP criteria and 22.9% (n=55) on TIME-to-START. Antihypertensives and proton pump inhibitors were most frequently discontinued, whereas calcium and vitamin D were most commonly initiated. DDIs were detected in 73.1% (n=160) of the patients, and 21.9% had at least one major DDI.

Conclusion: Polypharmacy, PIM, and DDI are common in elderly patients with hematological malignancies. The prominence of specific drug groups in inappropriate use and the significant occurrence of major DDIs highlight the need for careful medication management in this population.

Keywords: Hematological malignancy, geriatric patient, polypharmacy inappropriate medication use, drug-drug interactions

Introduction

Hematological malignancies are more common in elderly individuals, and this group also has an important role in the prevalence of cancer. The decrease in physiological reserves with age, increase in comorbidities and pharmacokinetic-pharmacodynamic changes make the treatment process more complicated. In patients with hematological malignancies, the use of multiple drugs because of both the existing malignancy and other chronic diseases is common [1,2]. As expected, drug-related problems, such as polypharmacy, potential inappropriate medication (PIM), and drug-drug interactions (DDI), are more prominent in this patient group [3-5].

Polypharmacy refers to the simultaneous use of 5 or more drugs and is more common in elderly patients and makes clinical patient management difficult [6]. Studies have shown that polypharmacy in geriatric patients is closely associated with adverse outcomes, such as side effects, drug incompatibilities, and clinical complications [7]. The frequency of polypharmacy, especially in patients with hematological malignancies, increases due to the nature of the treatment.

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This may increase the risk of PIM use and DDI in vulnerable patients, leading to increased incidence of adverse drug events, hospitalization, and mortality [8,9].

Polypharmacy does not always indicate inappropriate medication use. PIM encompasses multiple problems, such as medication use without a valid reason, failure to prescribe needed medications, and ineffective doses of appropriate medications [10]. Various tools have been developed to assess PIM. These tools, which include criteria for the need to discontinue and/or start medication, such as the STOPP/START, Beers, and Turkish Elderly Inappropriate Medication (TIME) criteria, provide a comprehensive set of recommendations for inappropriate medication use [11-13]. PIM is common among patients with cancer, including those with hematological malignancies, and some studies have reported prevalence rates as high as 50% (39.9-54%) [3,14,15]. In addition, polypharmacy is associated with DDIs associated with drug toxicity, treatment failure, morbidity, and mortality. Various online tools are used to guide the clinical significance of interactions and predict potential adverse effects by comprehensively assessing DDIs [16-18]. DDIs, which occur when one drug affects the pharmacokinetics or pharmacodynamics of another, are common among patients with hematologic malignancies because of complex treatment regimens that include chemotherapy agents, supportive care medications, and medications for preexisting conditions [5,19]. This study aimed to provide a comprehensive understanding of drug-related problems commonly encountered in this patient population by evaluating polypharmacy, PIMs, and DDIs in elderly patients with hematologic malignancies. The findings will provide guidance for identifying high-risk drug groups and clinically significant interactions that should be considered in clinical practice.

Methods

Study Design

This cross-sectional study included adults aged 65 years and older who were registered in a tertiary outpatient geriatric clinic. Between April 2024 and September 2024, 492 patients with hematological malignancies were admitted to the outpatient clinic. Among these patients, those with advanced dementia, delirium, severe metabolic disorder, sensory disability, communication limitation, and nursing home stay were excluded from the study. Informed consent forms were obtained from all participants, and 219 patients who volunteered to participate in the study were included in the study. This study was conducted in accordance with the Declaration of Helsinki, and the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee approved the study (no: 2024-03/27, date: 14.03.2024).

Assessment of Medications

All prescription and non-prescription medications used by the patients were evaluated and recorded in detail. Polypharmacy was defined as the use of 5 or more drugs, and hyper-polypharmacy was defined as the use of 10 or more drugs [6,20]. PIM was defined by a geriatrician using the TIME criteria determined based on national and international guidelines. TIME criteria is a tool defined in 2020, including 112 criteria for drug discontinuation (TIME-to-STOP) and 41 criteria for drug initiation (TIME-to-START). Although the relevant criteria tool included the nutrition and vaccination sections in addition to medication in patient evaluations, they were not included in the numerical results in the drug initiation and discontinuation evaluation during the analysis. In the DDI evaluation, the Lexi-Interact tool, which provides a comprehensive database to determine the clinical importance and management of interactions, was used [21]. The severity of DDIs was also categorized into risk classes as minor, moderate, and major in accordance with this tool [21].

Patient Characteristics

The participants' age, gender, body mass index, and current diseases were recorded. The patient's hematological malignancy diagnosis was noted by evaluating the patient's history, electronic records, and diagnostic codes. Other accompanying comorbid diseases (hypertension, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, cerebrovascular disease and hypothyroidism) were recorded. The presence of 2 or more diseases other than malignancy was defined as multimorbidity [22]. The estimated glomerular filtration rate (eGFR) was evaluated using the Modification of Diet in Renal Disease formula, and patients with a value <60 mL/minute/1.73 m^2 were additionally determined. The functional performances of the patients were evaluated using the Katz Activities of Daily Living Scale [23]. Six points were categorized as full function, 3-5 points as moderate impairment and 1-2 points as severe impairment [23].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) (IBM SPSS Inc., IL, Chicago, U.S.). The numerical variables comprise absolute numbers and percentages, average standard deviation, and median (minimum-maximum). The Student's t-test or the Mann-Whitney U test was used for continuous data comparison. The Kolmogorov-Smirnov test was used to analyze data distribution. The comparison of categorical variables was conducted using the chi-square test. A statistically significant result was accepted when the p value was less than 0.05.

Results

Baseline Characteristics

A total of 219 patients with hematological malignancies were included in the study. The mean age of the participants was 73.9 (±6.0) years, and 55.3% were male. The most common malignancies were multiple myeloma (19.2%), non-Hodgkin lymphoma (15.1%), and chronic lymphoid leukemia (11.9%). The most common comorbidity was hypertension (57.1%),

followed by cardiovascular disease (34.2%) and diabetes mellitus (23.7%). More than half of the patients (64.8%) were functionally fully independent. Of the total patient population, 27.8% (61 individuals) were undergoing chemotherapy at the time of the study. The detailed characteristics of the patient groups that received and did not receive chemotherapy are presented in Table 1.

Medication Properties

In total, 1,327 medications from all patients were evaluated. The median number of medications used by the patients was 6 (0-18) and all patients except 4 were using at least 1 medication. More than half of the patients (64.4%) had polypharmacy and 35 (16.0%) had hyper-polypharmacy. Polypharmacy was more common in those receiving chemotherapy (70.5%), and the rate of hyper-polypharmacy was approximately 2 times higher in the chemotherapy group than in those not receiving chemotherapy (12.7 vs. 24.6) (Table 2). Forty-seven (77.0%) of the patients in this group were using prophylactic treatments because they were receiving chemotherapy, and the median number of prophylactic medications used was 2 (0-4). A total of 63.0% of the patients (138 individuals) were using one or

Table 1. Comparison of baseline sociodemographic and clinical characteristics according to chemotherapy status

Variables	Total (n=219)	Not receiving chemotherapy (n=158)	Receiving chemotherapy (n=61)	p value
Age > years, mean (SD)	73.9 (6.0)	74.2 (5.8)	72.6 (6.2)	0.080
Age group, n (%)				
65-74	128 (58.4)	92 (58.2)	36 (59.0)	0.628
75-84	82 (37.4)	58 (36.7)	24 (39.3)	
≥85	9 (4.1)	8 (5.1)	1 (1.6)	
Sex, male, n (%)	121 (55.3)	86 (54.4)	35 (57.4)	0.762
BMI, mean, mean (SD)	26.9 (5.0)	27.01 (4.9)	26.4 (5.3)	0.523
Hematologic malignancies, n (%)				
Myeloma and plasma cell dyscrasia	42 (19.2)	21 (13.3)	21 (34.4)	**0.024**
Hodgkin lymphoma	6 (2.7)	4 (2.5)	2 (3.3)	
Non-Hodgkin's lymphoma	33 (15.1)	24 (15.2)	9 (14.8)	
Acute myeloid leukemia	12 (5.5)	2 (1.3)	10 (16.4)	
Chronic myeloid leukemia	8 (3.7)	5 (3.2)	3 (4.9)	
Chronic lymphoid leukemia	26 (11.9)	21 (13.3)	5 (8.2)	
Myelodysplastic syndrome	12 (5.5)	9 (5.7)	3 (4.9)	
Other	80 (36.5)	72 (45.6)	8 (13.1)	
Comorbidities, n (%)				
Hypertension	125 (57.1)	94 (59.5)	31 (50.8)	0.287
Diabetes mellitus	52 (23.7)	39 (24.7)	13 (21.3)	0.724
Cardiovascular disease	75 (34.2)	55 (34.8)	20 (32.8)	0.874
Chronic obstructive pulmonary disease	16 (7.3)	13 (8.2)	3 (4.9)	0.565
Cerebrovascular disease	3 (1.4)	2 (1.3)	1 (1.6)	0.831
Hypothyroidism	26 (11.9)	21 (13.3)	5 (8.2)	0.358
Number of comorbidities, *median (range)	2 (0-7)	2 (0-7)	1 (0-4)	**0.014**
Multimorbidity, n (%)	141 (64.4)	111 (70.3)	30 (49.2)	**0.005**
eGFR <60, n (%)	17 (7.8)	11 (7.0)	6 (9.8)	0.574
Katz ADL score, mean (SD)	5.39 (1.08)	5.49 (0.9)	5.11 (1.3)	0.046
Functional category, n (%)				
Full function	142 (64.8)	108 (68.4)	34 (55.7)	0.061
Moderate impairment	68 (31.1)	45 (28.5)	23 (37.7)	
Severe impairment	9 (4.1)	5 (3.2)	4 (6.6)	

Values with p<0.05 are indicated in bold.
*Excluding hematologic malignancy.
ADL: Activities of daily living, BMI: Body mass index, eGFR: Estimated glomerular filtration rate, SD: Standard deviation

Table 2. Evaluation of drug-related characteristics according to chemotherapy status

Variables	Total (n=219), n (%)	Not receiving chemotherapy (n=158), n (%)	Receiving chemotherapy (n=61), n (%)
Number of medications	6 (0-18)	5 (0-16)	7 (1-18)
None	4 (1.8)	4 (0.6)	0 (0.0)
≥1	215 (98.2)	154 (99.4)	61 (100)
≥5	141 (64.4)	98 (62.0)	43 (70.5)
≥10	35 (16.0)	20 (12.7)	15 (24.6)
Number of PIM[†]	1 (0-7)	1 (0-7)	1 (0-5)
PIM use			
None	81 (37.0)	58 (36.7)	23 (37.7)
≥1	138 (63.0)	100 (63.3)	38 (62.3)
Number of total PIMs	240	189	51
TIME-to-STOP	185	141	44
TIME-to-START	55	36	19
DDI			
Number of DDI[†]	2 (0-27)	2 (0-24)	3 (0-27)
None	59 (26.9)	47 (29.7)	12 (19.7)
≥1	160 (73.1)	111 (70.3)	49 (80.3)
Number of total DDIs	939	651	288
Severity of the DDI			
None	9	2	7
Minor	158	96	62
Moderate	692	497	195
Major	80	56	24

[*]Excluding chemotherapeutic agents, [†]median (range).
ADL: Activities of daily living, DDI: Drug-drug interaction, PIM: Potentially inappropriate medication, TIME: Turkish Elderly Inappropriate Medication

more PIMs. Of the 240 PIMs detected in the entire group, 185 (77.1%) were listed as requiring drug discontinuation (TIME-to-STOP) and 55 (22.9%) were listed as requiring drug initiation (TIME-to-START) (Table 2). When evaluated as sections, according to TIME-to-STOP, the most frequent discontinuations were those that met cardiovascular system (A) criteria (n=46, 24.9%), followed by central nervous system (B, n=37, 20.0%) and endocrine system (G, n=26, 14.1%) drugs. According to TIME-to-START, the most frequently started drugs were musculoskeletal system and analgesic group (E) drugs (n=38, 69.1%), followed by cardiovascular system (A, n=9, 16.4%) and central nervous system (B, n=6). The most frequently stopped drugs were antihypertensive drugs in patients with inappropriately tight blood pressure control (A11, n=27), followed by patients with inappropriate proton pump inhibitor (PPI) addition due to multiple drug use (C5, n=21). The most frequently started drugs were Ca and vitamin D preparations in patients with inadequate dietary intake (E1, n=28), followed by the necessity of starting anti-resorptive or anabolic agents in patients with documented osteoporosis (E2, n=10) (Figure 1). Although proportionally more drugs were stopped in the group that did not receive chemotherapy, more drugs were started in the group that received chemotherapy. On the other hand, in both groups, the most frequently intervened drug groups remained unchanged (Figure 1). The median number of DDIs was 2, and only 26.9% (n=59) of patients did not list any drug interactions with Lexi-interact. At least 1 DDI was detected in 73.1% of patients, and this rate was even higher in patients receiving chemotherapy (80.3%). In total, 939 drug interactions were identified with the relevant vehicle. Of the listed interactions, the most frequently detected interaction was level C interaction (n=687, 73.2%), indicating that the relevant interaction may be clinically significant and that careful monitoring and dosage adjustments should be made if necessary (Figure 2). The majority of the interaction severities were at the "moderate" level (n=692), which is defined as "may require medical intervention", while 80 (8.5%) of these interactions were at the major level (potentially leading to serious outcomes such as treatment failure, hospitalization, permanent damage, or death). The number of patients with at least one major DDI was 48 (21.9%). Other evaluations of the drug properties are presented in Table 2.

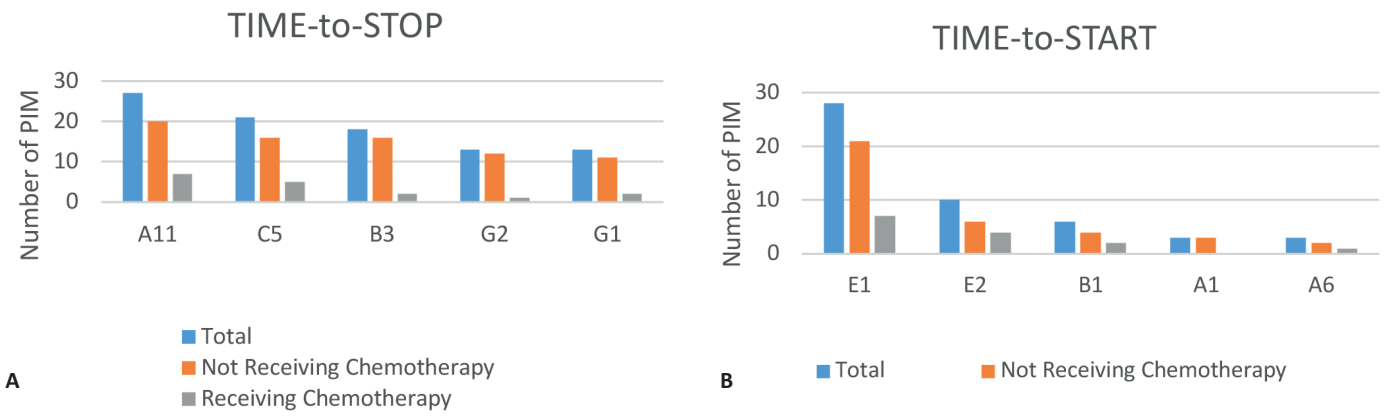

Figure 1. A, B) The five most commonly identified potentially inappropriate medications based on TIME criteria
EF: Ejection fraction, eGFR: Estimated glomerular filtration rate, MI: Myocardial infarction, PIM: Potentially inappropriate medication, PPIs: Proton pump inhibitors, TIA: Transient ischemic attack, SSRIs: Selective serotonin reuptake inhibitors, Na: Sodium, TIME: Turkish Elderly Inappropriate Medication

A11. Strict blood pressure control (<140/90 mmHg) in patients with orthostatic hypotension, cognitive impairment (e.g. dementia) / functional limitation/low life expectancy (<2 years) / high risk of falling.
B3. SSRIs with current or recent significant hyponatremia i.e. serum Na <130 mEq/L (risk of intensifying or precipitating hyponatremia).
C5. PPIs for multiple indications (no benefit, potential harm).
G1. Intensive glycemic control (HbA1c <7%) in patients with limited life expectancy (<5 years) or a history of falls or cognitive impairment.
G2. Metformin if eGFR <30 mL/min/1.73 m^2 (risk of lactic acidosis).
A1. Antiplatelet therapy (aspirin or clopidogrel) for secondary prevention in patients with documented atherosclerotic coronary artery disease (previous acute coronary syndrome/coronary artery angioplasty or stenting/coronary artery bypass grafting/abdominal aortic aneurysm), documented atherosclerotic cerebrovascular disease (presence of ischemic stroke/TIA/previous carotid endarterectomy or stenting) or symptomatic lower extremity artery disease.
A6. Beta-blockers for ischemic heart disease (antianginal effect in chronic ischemic heart disease/mortality reduction effect in post-MI era) or systolic heart failure (EF<=40%) (bisoprolol/prolonged release metoprolol succinate/carvedilol/nebivolol in systolic heart failure; any beta blocker in ischemic heart disease).
B1. Antidepressant treatment in patients with major depressive disorder.
E1. Bone anti-resorptive (bisphosphonate, denosumab) or anabolic therapy (parathormone analog) in patients with documented osteoporosis [fragility fracture and/or bone mineral density T-scores (femur total, femoral neck or total lumbar) <-2.5].
E2. Bisphosphonates in patients who started long-term systemic corticosteroid therapy (an anticipated duration of ≥3 months): i) if >=7.5 mg/day prednisolone or equivalent dose is given, ii) at any dose if T score is <-1.

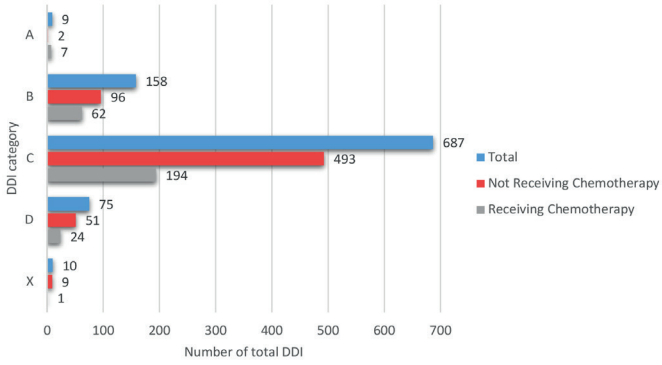

Figure 2. Drug-drug interaction numbers by categories
DDI: Drug-drug interaction, A: No known interaction, B: Action needed, C: Monitor therapy, D: Consider therapy modification, X: Avoid combination

Discussion

Our cross-sectional and descriptive cohort study examined the characteristics of medication use in detail in terms of polypharmacy, PIM use and DDI in elderly individuals with geriatric hematological malignancies. When the frequency of hematological malignancies was evaluated in our study, it was found to be largely consistent with studies conducted for patients of similar ages [23,24]. The median number of drug use was 6 (0-18), and polypharmacy was detected in 64.4%. When studies in the literature were examined, the average number of drugs was found to be between 3 and 10, whereas the frequency of polypharmacy was found to be between 32% and 80%, similar to our study [1,9,25]. The fact that the polypharmacy rate was higher in patients receiving chemotherapy and the hyper-polypharmacy rate was approximately 2-fold higher compared with the other groups can be attributed to the necessity of additional drugs for the management of supportive treatments and side effects used due to the nature of cancer treatment. In particular, antiemetics, opioids, or non-steroidal anti-inflammatory drugs for pain management, gastrointestinal system protectors, antibiotic or antifungal prophylaxis against infection risk, and growth factors used to manage hematological toxicities are frequently added to the treatment [26,27]. The fact that

the rate of prophylactic drug use in this group who received chemotherapy in our study was 77.0% supports this finding. This multidrug use, which is more notable in individuals receiving chemotherapy but is detected in the entire patient population, increases the risks of treatment-related complications and drug interactions, indicating that a more careful approach to patient management is required.

Polypharmacy is not always synonymous with PIM. In patients with hematological malignancies, the use of several medications is necessary not only for malignancy treatment and management but also for patients with past comorbidities. However, striking a balance between necessary and inappropriate medication use is of great importance, especially in the elderly population. In our study, at least one PIM use was detected in approximately two out of every three patients (63.0%). This rate was observed to be higher when compared with studies in the literature, both in the general elderly population and in the limited number of studies on elderly patients with hematological malignancies [3,28]. This increase in PIM rates could be attributed to methodological differences in the assessment tools used for PIM detection and the effects of the malignancy-specific medication burden. The vast majority of these PIMs (77.1%) indicated medication discontinuation (TIME-to-STOP), and this necessity was seen to be particularly prominent among cardiovascular system medications. Discontinuation of antihypertensive medications was the most common intervention. Age-related physiological changes, effects of malignancy, and drugs used during treatment may affect blood pressure or cause drug interactions, resulting in unnecessary drug use in this area [29-31]. In addition, since blood pressure targets adapted to physical performance are in question in elderly patient practice [32], and this is especially taken into consideration by a geriatrician's evaluation, this drug group may have come to the forefront as a PIM. Another group of drugs that should be discontinued is inappropriate PPIs added to the treatment of patients using multiple drugs. Since long-term use of PPIs in elderly patients may lead to various negative outcomes, such as vitamin and mineral deficiencies, increased risk of gastrointestinal infection, and deterioration in renal function, it is important to carefully evaluate the use of these drugs [33,34]. On the other hand, drugs that are considered appropriate to start according to TIME-to-START among PIMs are frequently included in the "Musculoskeletal System and Analgesics" group, and the most needed ones were calcium (Ca) and vitamin D preparations (69.1%). These drugs were followed by agents that should be initiated for osteoporosis treatment. This situation may be associated with both nutritional problems and hematological malignancies in the relevant patient group, and the agents used in the treatment of these malignancies affect Ca and vitamin D metabolism and reduce bone mineral density [35,36]. These findings emphasize the need for a more careful evaluation and regular drug review during the treatment process regarding PIM use, which is frequently observed in elderly patients with hematological malignancies. Correct management of this fine line between polypharmacy and inappropriate drug use can improve patients' quality of life and minimize the risk of complications.

DDI are an important clinical problem in elderly patients with hematological malignancies. In our study, at least one DDI was detected in 73.1% of patients. In another study conducted on 122 elderly patients with hematological malignancies, although a different methodology was used to determine the DDI, the rate was found to be similar to that of our study (71.3%) [3]. DDI rates were higher among patients receiving chemotherapy (80.3%), as expected. Although chemotherapy agents were not included in drug interactions in our study, agents used for prophylaxis and management of secondary side effects of treatment in this patient group can be considered highly responsible for these interactions. The fact that most of the DDIs in our study were in category C (73.2%) indicates that there are risks in the concomitant use of these drugs, but they are clinically manageable. In such cases, potential adverse effects can be prevented with regular monitoring and dose adjustments. Moderate interactions detected in most patients who require medical intervention are not as serious as major interactions. One of the striking findings of our study is that 8.5% of the DDIs were at the major level, and at least one major interaction was found in almost one in every five patients. Major interactions can reduce treatment efficacy or increase toxicity and have the potential to cause serious adverse outcomes, such as hospitalization or death. Therefore, early detection of such interactions in patients with geriatric hematological malignancies and meticulous monitoring and management during the treatment process are of vital importance.

Study Limitations

This study has some important strengths and limitations. First, having a cross-sectional design limits the full revealing of causal relationships. In addition, the fact that the data were obtained from a single center and only from patients who applied to the outpatient clinic limits the generalizability of the results to a large population. Although our sample size is consistent with similar studies in the literature, the variety of malignancy diagnoses and stages prevented the comparability of drug use behaviors among different subgroups and did not allow for more information on this subject. In addition, although there are alternatives to the tools used for the definition of PIM and DDI in our study, it should be considered that some drug-related problems that may be listed in other tools may not have been identified in this analysis. However, our study provides important data that can guide clinical decisions for this population by focusing on the use and management of drugs in elderly patients with hematological malignancies. By making evaluations based on real-world data, inferences for clinical practice have become more meaningful. Considering the limited number of studies on medication management in elderly patients with hematological malignancies, this study can make significant contributions to the existing literature and form the basis for more comprehensive studies to be conducted in the future.

Conclusion

Our study demonstrated the prevalence of medication-related problems, such as polypharmacy, PIM, and DDI, in elderly patients with hematological malignancies. In particular, certain medications were found to be responsible for a significant portion of medication-related problems in this patient group. These findings suggest that regular medication review and the implementation of evidence-based medication management protocols can play critical roles in preventing potential adverse effects and complications. In the future, larger-scale prospective studies are needed to evaluate the effects of medication-related problems on long-term patient outcomes.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, and the Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Ethics Committee approved the study (no: 2024-03/27, date: 14.03.2024).

Informed Consent: Informed consent forms were obtained from all participants, and 219 patients who volunteered to participate in the study were included in the study.

Footnotes

Authorship Contributions

Concept: N.K.S., B.U.U., Design: N.K.S., B.U.U., Data Collection or Processing: N.K.S., Analysis or Interpretation: B.U.U., Literature Search: N.K.S., B.U.U., Writing: N.K.S., B.U.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

Proton Pump Inhibitors: Effects on Magnesium and Arterial Stiffness in Renal Transplant Recipients

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ABSTRACT

Aim: Hypomagnesemia predicts cardiovascular outcomes in renal transplant recipients (RTRs). Proton pump inhibitors (PPIs) and H_2 receptor blockers (H_2RBs) are the most commonly used agents in RTRs. Previous studies have detected an association between hypomagnesemia and PPIs in patients undergoing ongoing hemodialysis. The current study aimed to evaluate the effects of PPIs on serum magnesium levels and arterial stiffness in RTRs.

Methods: We retrospectively analyzed 354 maintenance RTRs (mean age: 38.6±10.7 years) with stable allograft function who had undergone transplantation at least 36 months previously. All acute cellular and humoral rejections were excluded. According to the use of stomach-protecting agents (SPAs), patients were divided into the following three groups: PPIs (group 1, n=164), H_2RBs (group 2, n=96), and a control group that did not receive SPAs (group 3, n=94). Clinical and laboratory parameters (complete blood count, creatinine, calcium, phosphorus, magnesium, vitamin B12, folic acid, lipid profile) were noted from recorded data. The estimated glomerular filtration rate (eGFR) was calculated using the MDRD4 equation. The pulse-wave velocity (PWv) was determined by pressure tracing over the carotid and femoral arteries using the SphygmoCor system.

Results: The groups were similar in terms of demographic characteristics (age, gender, duration of dialysis before transplantation) and biochemical parameters (serum calcium, phosphorus, parathyroid hormone, C-reactive protein, lipid profile, and eGFR). The mean serum magnesium level was significantly lower in group 1 but similar in groups 2 and 3. The PWv values were significantly higher in group 1 but similar in groups 2 and 3. In the linear regression analysis; types of SPA, serum calcium, and magnesium were detected as predictors of PWv.

Conclusion: We concluded that PPIs inhibit magnesium absorption independent of calcium metabolism in RTRs. Moreover, PPIs increase arterial stiffness and cardiovascular risk in RTRs. Thus, physicians should be aware of the side effects of PPIs to reduce cardiovascular morbidity and mortality.

Keywords: Biochemistry, cardiovascular risk, hypomagnesemia, kidney transplantation

Introduction

Cardiovascular disease is frequently observed in patients with end-stage renal disease (ESRD), and the risk of mortality among cardiac diseases in these patients has been shown to be 10-20 times grater than general population [1]. Renal transplantation (RT) is the standard treatment for patients with ESRD because it significantly prolongs patient life, largely by decreasing the progression of cardiovascular disorders. Renal transplant recipients (RTRs) have up to a 10-fold reduced rate of cardiac death compared with dialysis recipients [2].

Magnesium depletion is considered the missing link between cardiovascular risk factors and atherosclerosis in ESRD. Magnesium modulates calcium uptake and distribution in vascular smooth muscle cells and directly affects the vascular tone, thereby reducing peripheral resistance [3]. Hypomagnesemia predicts cardiovascular morbidity and mortality in the general population and accelerated loss of kidney function in RTRs [4].

Proton pump inhibitors (PPIs) are frequently used both to prevent and treat various gastrointestinal disorders after radiotherapy (RT) [5].

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Previous studies have highlighted the association between hypomagnesemia and PPIs in healthy individuals and patients undergoing ongoing hemodialysis. It is assumed that these observations are due to possible effects of hypomagnesemia on left ventricular size, hypertension, endothelial function, and insulin resistance [6].

The current study aimed to evaluate the effects of PPIs on serum magnesium levels and arterial stiffness in RTRs.

Methods

We performed a retrospective study of 354 maintenance RTRs (mean age: 38.6±10.7 years) with stable allograft function who had received their transplant at least 36 months previously were selected cross-sectionally according to the following exclusion criteria; 1) lack of regular follow-up data 2) malignant, rheumatologic or chronic inflammatory disease of unknown origin, systemic vasculitis history, 3) acute rejection 4) heart failure (ejection fraction <50%) or diastolic dysfunction of the heart 5) ischemic heart disease history (myocardial infarction, need for cardiac revascularization) or coronary bypass before or after transplantation, 6) peripheral artery disease, 7) tobacco use. The study was approved by the Ankara Bilkent City Hospital Ethics Committee (decision no: 2-24-69, date: 20.03.2024).

According to the use of stomach-protecting agents (SPAs), patients were divided into the following three groups: PPIs (group 1, n=164), H2RBs (group 2, n=96), and a control group that did not receive SPAs (group 3, n=94).

Immunsuppressive Treatment Protocol

In most patients, maintenance immunosuppressive treatment included prednisone with a gradual tapering, mycophenolate mofetil, and cyclosporine or tacrolimus. Target through levels at 3 months were 150-200 ng/mL for cyclosporine and 8-10 ng/mL for tacrolimus. All patients were under 5 mg prednisolone treatment within the maintenance immunosuppressive regimen.

Biochemical Parameters

The standard clinical and biochemical parameters of all patients were analyzed. Physical examination and routine laboratory measurements (complete blood count and biochemical parameters as described below) were examined. In all participants, venous blood samples were collected after an overnight fast to measure the biochemical parameters.

The estimated glomerular filtration rate was calculated based on the CKD-Epi formulas; $141 * \min(Scr/\kappa,1)^{\alpha} * \max(Scr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] *1.159 [if black] [7].

Pulse-wave Velocity

The aortic pulse-wave velocity (PWv) was measured with the same device by sequentially recording electrocardiogram-gated carotid and femoral artery pressure waves using the intersecting tangent algorithm to determine the characteristic points. The PWv was calculated as the path length divided by the transit time (m/s) [8].

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences software (v 15.0, IBM, Armonk, NY, USA). All numerical data are expressed as the mean±standard deviation. Data normality was analyzed using the Kolmogorov-Smirnov test. Normally distributed numeric variables were compared with independent-samples Student's t-test, and skew distributed numeric variables were compared using the Mann-Whitney U test. A p value of 0.05 was considered statistically significant.

Results

Demographic characteristics and laboratory data for the study population and data classified by group are summarized in Tables 1 and 2, respectively.

The mean daily PPI dose was 24±8.4 mg. The median duration of PPI use was 47±4.4 months. There were no significant differences between the two groups in terms of age, duration of transplantation, and presence of comorbid conditions.

The mean serum magnesium levels were significantly lower in group 1, but were similar in groups 2 and 3 (1.1±0.4 mg/dL, 1.7±0.2 mg/dL and 1.6±0.1 mgdL, respectively) ($p<0.05$) (Figure 1). The PWv values were significantly higher in group 1 ($p<0.05$), whereas they were similar in groups 2 and 3 (7.3±0.2 cm/sec, 6.3±0.1 cm/sec and 6.2±0.1 cm/sec, retrospectively) (Figure 2).

Using linear regression analysis with serum Mg as the dependent variable, PPI use was significantly associated with serum Mg ($p=0.008$) after adjusting for age, dialysis duration, and plasma albumin.

Table 1. Demographic and clinical characteristics of the study population

Gender (male/%)	196 (55%)
Age Mean±SD (years)	38.6±10.7
Etiology of ESRD [number (%)] Diabetes mellitus Hypertension PCKD Glomerulonephritis Unknown	 173 (49) 95 (27) 21 (6) 14 (4) 51 (14)
Duration of transplantation (months)	38.2±0.8
Fasting glucose, mean±SD (mg/dL)	88.7±12.4
Total cholesterol, mean±SD (mg/dL)	244.0±32.0
LDL- cholesterol, mean±SD (mg/dL)	128.8±24.5
Triglyceride, mean±SD (mg/dL)	189.7±12.5
Serum creatinine, mean±SD (mg/dL)	1.2±0.7

ESRD: End stage renal disease, LDL: Low-density lipoprotein, SD: Standard deviation, PCKD: Polycystic kidney disease

Discussion

The metabolism of magnesium is regulated by gastrointestinal absorption and renal excretion. It has been shown that PPI use is associated with impaired intestinal absorption of dietary Mg by disrupting active transport by TRPM 6/7 channels [9]. Moreover, hypomagnesemia is known to predict cardiovascular outcomes in both the general population and RTRs [4]. To our knowledge, this is the first in the literature that showed PPIs are linked to increased arterial stiffness and cardiovascular risk by decreasing Mg levels in RTRs.

A study by Recart et al. [10], which included 236 patients on PPI treatment, showed that patients on long-term PPI use were frequently prone to hypomagnesemia. On the other hand, some studies have reported that PPI use does not affect serum magnesium levels. Biyik et al. [11] detected serum magnesium levels of outpatients receiving long-term PPI treatments to be within the normal range in the absence of other factors affecting serum magnesium levels. The serum magnesium levels of outpatients who have and have not been using PPIs were found to be similar. However, the situation in patients undergoing ongoing hemodialysis is slightly different from the general population. Hypomagnesemia was reported to be linked to PPI use among patients undergoing hemodialysis. In a previous study, the dialysate magnesium level was 0.5-0.375 mmol/L. They reported that hypomagnesemia might occur with PPI use in hemodialysis patients with dialysate magnesium level was 0.5-0.375 mmol/L [12]. Another cross-sectional study of patients on ongoing hemodialysis showed that serum Mg levels among patients receiving PPIs were significantly lower than those who were not on PPIs [13,14]. Besides, by multivariate analysis, they found that the use of PPIs was a strong and independent predictor of low Mg levels, similar to the present study.

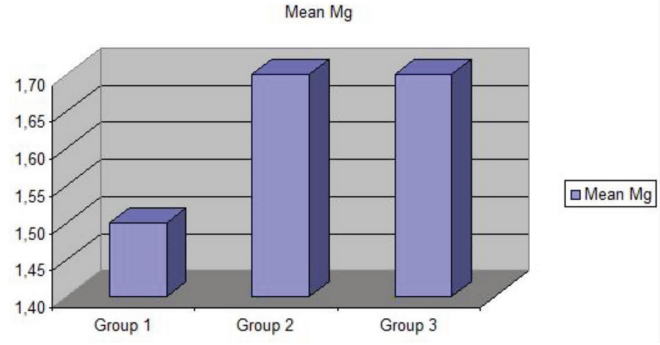

Figure 1. Mean serum magnesium level in group 1

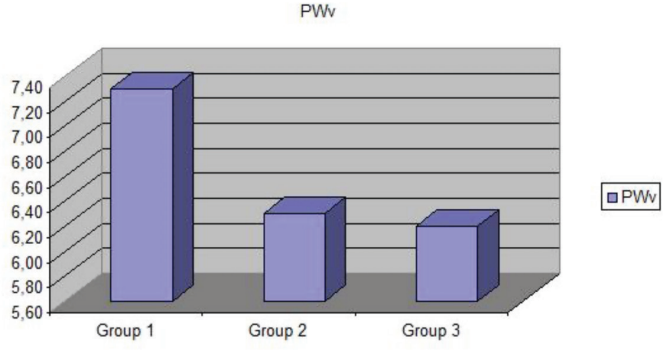

Figure 2. Mean PWv was significantly higher in group 1 than in group 2
PWv: Pulse-wave velocity

Vascular calcification is highly prevalent in patients who are on ongoing hemodialysis and continue after RT [15]. Previous studies have shown that hypomagnesemia may be related to atherosclerosis and arterial stiffness. The underlined mechanism may be associated with mitochondrial dysfunction and Ca transient suppression. A retrospective study on patients undergoing ongoing hemodialysis detected that serum Mg level was an independent factor for arterial stiffness [16]. Similar to our study, the relationship between hypomagnesemia and vascular stiffness was investigated in a previous study on RTRs. Our results were consistent with those of a previous report, as serum Mg level was an independent risk factor for arterial stiffness [17].

A previous study demonstrated that PPIs directly damage vascular endothelial cells [18]. Yepuri et al. [19] demonstrated that PPIs result in impaired endothelial function. Another recent study reported that PPIs decrease the levels of anti-atherogenic molecules in endothelial cells [20]. The present study, we showed PPI are associated with increased arterial stiffness and cardiovascular risk by decreasing Mg levels

Table 2. Demographic and clinical characteristics of the study groups

	Group 1 (n=164)	Group 2 (n=96)	Control group (n=94)	p value
Age, mean±SD (years)	38.4±4.6	41.1±3.1	39.7±9.7	NS
Duration of dialysis before tx, mean±SD (months)	76.4±1.8	83.2±1.6	77.6±2.4	NS
Duration of transplantation (months)	38.1±9.4	37.6±8.7	39.6±7.6	NS
Hemoglobin (g/dL) mean±SD	11.6±1.7	11.2±2.4	11.8±0.9	NS
Serum albumin (g/L) mean±SD	3.8±0.7	3.6±0.4	3.8±1.1	NS
Serum phosphate (mg/dL) mean±SD	4.2±0.4	4.6±0.6	4.4±0.7	NS
Serum creatinine (mg/dL) mean±SD	1.24±0.1	1.22±0.2	1.30±0.1	NS
Serum magnesium level (mg/dL) mean±SD	1.1±0.4	1.7±0.2	1.6±0.1	**<0.05**
PWv, mean±SD (m/sec)	7.3±0.2	6.3±0.1	6.2±0.1	***<0.01***

NS: Not significant, PWv: Pulse wave velocity, tx: Transplantation, SD: Standard deviation

in RTRs. These findings suggest that PPIs may increase calcification induced by vascular endothelial injury.

Study Limitations

The limitations of the present study include, first, we studied serum Mg levels, but did not specifically look at the ionized Mg fraction and we did not give information on PPI duration and baseline magnesium levels prior to PPI initiation, second, the lack of pretransplant measurements of PWv in recipients, third, we did not measure dietary Mg intake, markers of nutritional status, and finally, we did not distinguish the PPI types and we did not specify immunosuppressive drug levels.

Conclusion

In conclusion, we detected that PPIs may inhibit magnesium absorption independent of calcium metabolism in RTRs. Moreover, PPIs are linked to increased arterial stiffness and cardiovascular risk in RTRs. Thus, physicians should be aware of the side effects of PPIs to reduce cardiovascular morbidity and mortality. On the other hand, because of its cross-sectional design, this study has limited the ability to assess the long-term effects of PPI use on magnesium levels and cardiovascular risk, and prospective studies are needed to assess long-term impacts.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Bilkent City Hospital Ethics Committee (decision no: 2-24-69, date: 20.03.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.Ş.K., Concept: M.Ş.K., Design: M.Ş.K., Data Collection or Processing: B.G.D., Analysis or Interpretation: B.G.D., Literature Search: B.G.D., Writing: B.G.D.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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Original Article

The Role of the T790M Mutation in Lung Cancer: A Molecular Perspective Based on Genetic Data

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ABSTRACT

Aim: Lung cancer is one of the most common types of cancer, with non-small cell lung cancer (NSCLC) being the most prevalent subtype, accounting for approximately 85% of all cases. Tyrosine kinase inhibitors (TKIs) improve progression-free survival in patients with NSCLC and activating epidermal growth factor receptor (*EGFR*) mutations. However, the development of resistance has increasingly reduced the long-term efficacy of these treatments. Third-generation TKIs are designed to target drug resistance mutations, such as the T790M mutation, and have been approved as first-line treatment for advanced-stage *EGFR*-mutant NSCLC. In advanced-stage patients, obtaining tissue samples can be challenging. Thus, liquid biopsy for T790M mutation detection is a suitable alternative. Due to its high sensitivity, droplet digital PCR (ddPCR) is a prominent method for the detection of this protein. This study aimed to share our experience with T790M mutation analysis using ddPCR with liquid biopsy and emphasize the significance of this mutation.

Methods: This study analyzed liquid biopsy data from 183 patients diagnosed with NSCLC and referred from various centers with suspected progression under first- or second-generation EGFR-TKI treatment. Using approximately 10 mL of blood samples, cell-free tumor DNA was extracted from plasma and evaluated for *EGFR* T790M mutation using ddPCR.

Results: The T790M mutation was detected in 29 patients, including 14 male patients (15.2%) out of 92 and 15 female patients (16.48%) out of 91. In addition, other accompanying *EGFR* mutations were observed in 85 patients (46.45%). Among these patients, 17 (9 male and 8 female) were also found to harbor the T790M mutation.

Conclusion: The ddPCR method using liquid biopsy has high sensitivity and accuracy for the molecular diagnosis of *EGFR* T790M mutations. Based on these combined data, this study demonstrated that ddPCR is a robust alternative method for detecting *EGFR* T790M mutations in plasma samples from patients with NSCLC.

Keywords: Non-small cell lung cancer, liquid biopsy, T790M, droplet digital PCR

Introduction

Lung cancer is one of the most frequently diagnosed cancers and remains the leading cause of cancer-related mortality worldwide [1]. Among the various lung cancer types, non-small-cell lung cancer (NSCLC) is the most prevalent histological subtype, accounting for approximately 85% of all lung cancer cases [2].

One of the notable advancements in the management of NSCLC associated with activating epidermal growth factor receptor (*EGFR*) mutations has been the development of targeted therapies known as tyrosine kinase inhibitors (TKIs). These agents are designed to specifically inhibit the function of EGFR, a type of receptor tyrosine kinase that regulates pathways responsible for cell growth and survival. *EGFR* gene mutations, particularly exon 19 deletions and the L858R point mutation in exon 21, are detectable in around 10-20% of individuals diagnosed with NSCLC [3-5].

The treatment of *EGFR*-mutant lung cancer poses a significant challenge because of the emergence of TKI resistance. These

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targeted therapies initially demonstrate promising responses and improved progression-free survival in patients with *EGFR*-mutant NSCLC. However, acquired resistance gradually diminishes their long-term efficacy [4-6].

One of the major mechanisms responsible for acquired resistance to EGFR-TKIs is the secondary T790M mutation in exon 20 of the *EGFR* gene [7]. This alteration is located in the highly conserved ATP-binding pocket of the *EGFR* kinase domain, leading to steric hindrance and reduced binding affinity of first- and second-generation TKIs. To address sensitizing *EGFR* mutations as well as the T790M resistance mutation, third-generation EGFR-TKIs such as osimertinib have been developed. Osimertinib, in particular, has demonstrated substantial clinical effectiveness in individuals with T790M-mutant NSCLC. It has exhibited superior response rates and extended periods of progression-free survival compared to first- and second-generation TKIs [6].

Various methods have been used to identify the T790M mutation, including tissue-based biopsies, liquid biopsies, and the analysis of cell-free DNA. Ideally, the detection of this mutation should be performed on tumor tissue obtained through re-biopsy. However, patients experiencing disease progression may develop lesions in locations that are difficult to access. Furthermore, the poor performance status of patients can also present challenges in re-biopsy procedures [8].

In cases in which accessing tumor tissue via re-biopsy is not feasible, an alternative approach involves liquid biopsy. This innovative technique allows the analysis of cell-free tumor DNA (cfDNA) present in the plasma and other body fluids of patients. By genotyping cfDNA, liquid biopsy offers a noninvasive means to gain valuable insights into the molecular profile of the tumor, enabling clinicians to detect genetic mutations and guide treatment decisions effectively [8-10].

Droplet digital PCR (ddPCR) represents a significant advancement in molecular diagnostics, offering unprecedented precision and sensitivity for quantifying nucleic acids. By partitioning a sample into thousands of discrete reactions within water-in-oil droplets, ddPCR provides a digital, absolute quantification approach that overcomes the limitations of traditional real-time PCR. ddPCR has garnered noteworthy attention for its potential to revolutionize the precise detection of the T790M mutation. By offering unparalleled sensitivity, quantification precision, and the ability to discern rare mutational events, ddPCR is a promising tool in the realm of liquid biopsy-based diagnostics for patients with NSCLC [11,12].

In this article, we present our experience with T790M mutation analysis in patients with NSCLC using the ddPCR method with liquid biopsy.

Methods

Study Group

In this retrospective study, data obtained from liquid biopsy samples from 183 patients diagnosed with NSCLC who were referred from various centers with suspicion of progression while under first- or second-generation EGFR-TKI treatment were analyzed. The patients in this study cohort were examined in our clinic center during the period from October 2022 to September 2024.

The research received ethical approval from the Etlik City Hospital Ethics Committee (document number: AEŞH-BADEK-2024-843, date: 25.09.2024). All patients met the genetic testing standards established by the National Comprehensive Cancer Network.

cfDNA Isolation and T790M Mutation Analysis

To extract cfDNA from plasma, approximately 10 mL of blood samples were collected in cell-free DNA BCT® (Streck) tubes. The cfDNA obtained from these samples was evaluated for the presence of the *EGFR* T790M mutation using the Bio-Rad QX100 ddPCR system. Two replicates were performed for each sample. PCR was conducted using the appropriate protocol on the Bio-Rad T100® instrument. Subsequent to PCR, reading and analysis were performed using the QX100 Droplet Reader® device.

Statistical Analysis

Mutant cfDNA molecules are reported as the number of copies per milliliter (mL) of plasma. The mutant allelic frequency was determined as the ratio of mutant to wild-type droplets. Descriptive statistics were used to summarize the demographic and genetic characteristics of the patients. Mean age, standard deviation, and median values were calculated for the overall group as well as for subgroups (e.g., patients with and without the T790M mutation, male and female patients). The distribution of T790M and other *EGFR* mutations is presented as percentages.

Results

Patients diagnosed with NSCLC and who had acquired resistance to *EGFR*-TKIs who were referred to us between October 2022 and September 2024 were included in our study. The mean age of the patients was 64.7 years. The T790M positivity rate was 29 out of 183 (15.85%). The patients exhibited variable levels of T790M positivity, including low-positive cases, which were detected in some patients (Figure 1). It has been observed that the average age of female patients is slightly higher compared with that of males, with the average age of males with the detected mutation being 62.77, whereas it is 66.63 in females (Figure 2). Of the patients, 92 out of 183 (50.2%) were male, and 91 out of 183 (49.8%) were female. The T790M mutation was detected in 14/92 male patients (15.2%) and 15/91 female patients (16.48%) (Figure 3). In the T790M-positive group, the average age of female patients was slightly higher than that of males, with the average age of males with the detected mutation being 60.42 years, whereas that of females is 65.6 (Figure 4).

Other EGFR mutations were detected in 85 of 183 patients (46.45%), with 37 out of 85 (43.5%) being male and 48 of 85 (56.5%) being female. The mean age of the patients was 65.06

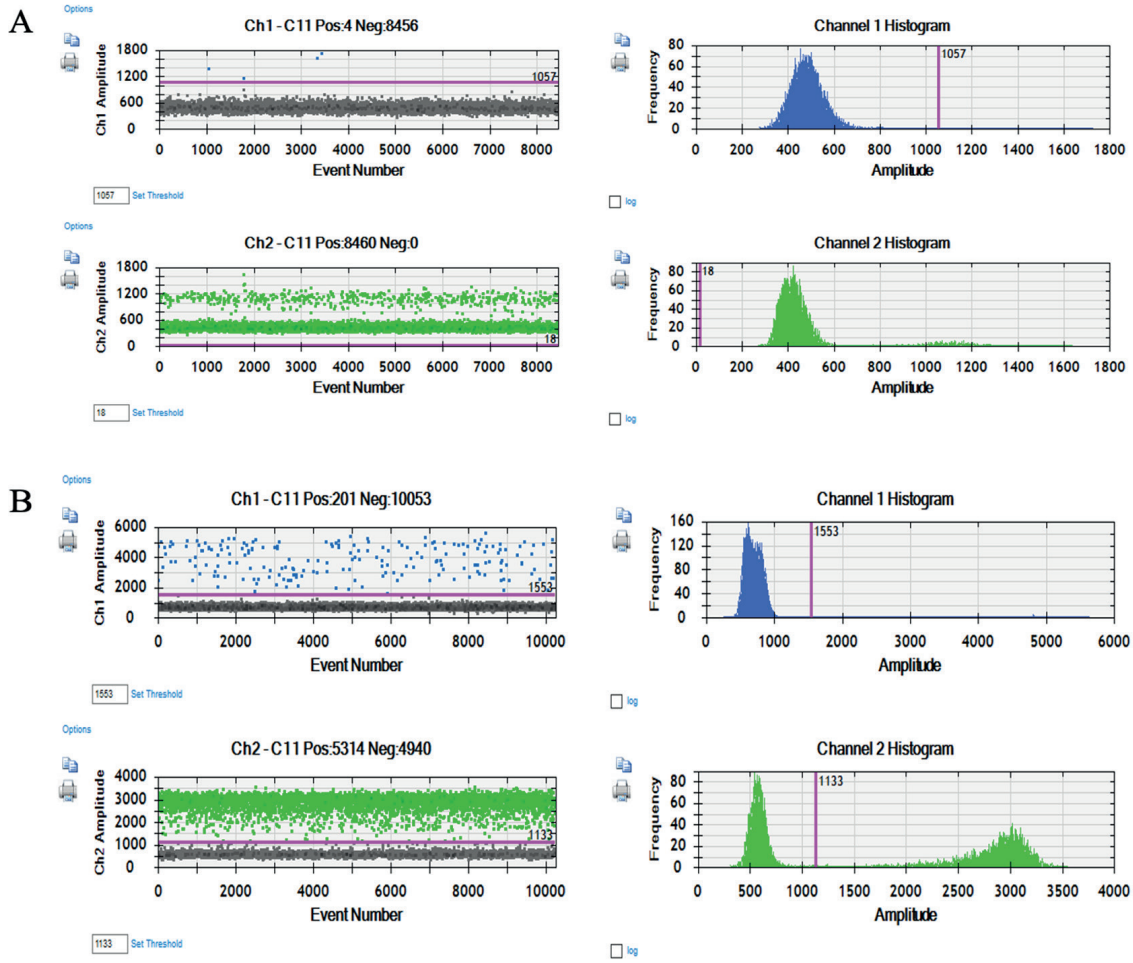

Figure 1. A) Data image of low positive sample (<5%). B) Data image of significant positive sample (>5%)

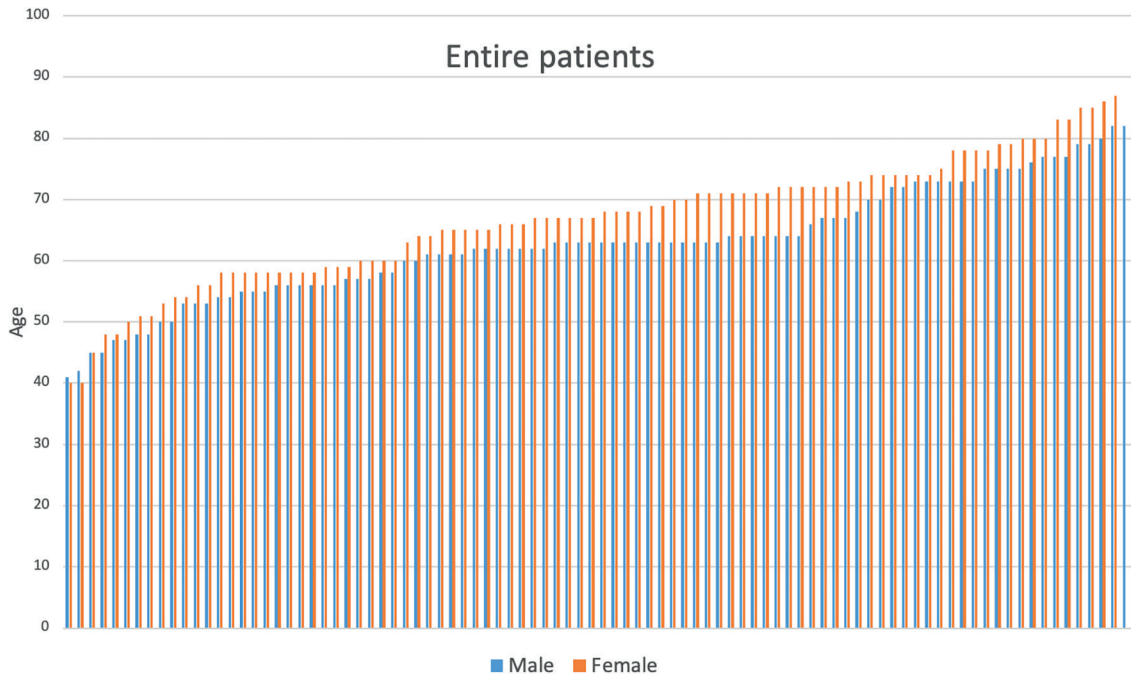

Figure 2. Patients' characteristics in terms of age. The age distribution of the entire patient group, arranged from youngest to oldest

years. In total, 17 out of 85 patients (18.75%) - 9 males and 8 females - had concomitant T790M mutations as well (Table 1).

Discussion

The use of EGFR-TKIs significantly affects progression-free survival in individuals diagnosed with *EGFR*-mutated NSCLC. Personalized targeted therapies are gaining popularity in cancer treatment, offering increased clinical efficacy and reduced toxicity. This approach is becoming increasingly important, emphasizing the need to tailor treatments to individual patients to achieve better results. Therefore, a precise exploration of the molecular foundations of cancers is becoming increasingly important.

The T790M mutation can develop during or after EGFR-TKI therapy, leading to disease progression. This mutation results in resistance to first- and second-generation EGFR-TKIs. Therefore, the detection of the T790M mutation plays a critical role in the development of treatment strategies. A third-generation EGFR-TKI is an effective treatment option for patients with the T790M mutation. Third-generation EGFR-TKIs prolong progression-free survival and improve overall survival rates in patients with the T790M mutation.

The ddPCR method is a more sensitive technique than various analysis methods such as Sanger sequencing, pyrosequencing, next-generation sequencing (NGS), quantitative PCR, and amplification-refractory mutation system PCR (ARMS-

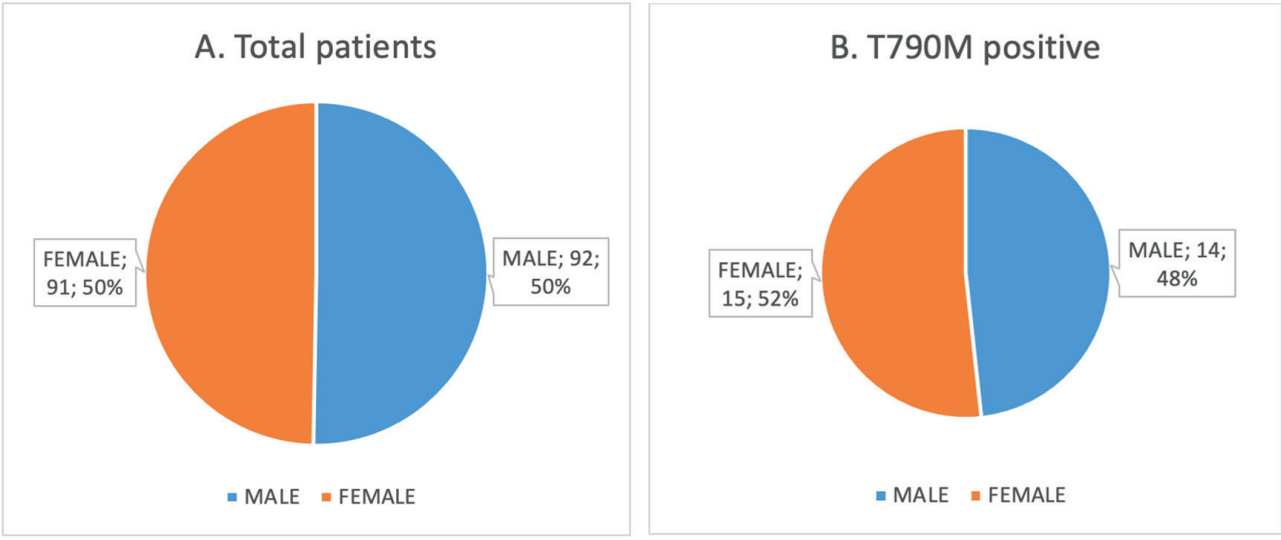

Figure 3. A) Distribution of total patients in terms of gender. B) Distribution of T790M positive group in terms of gender

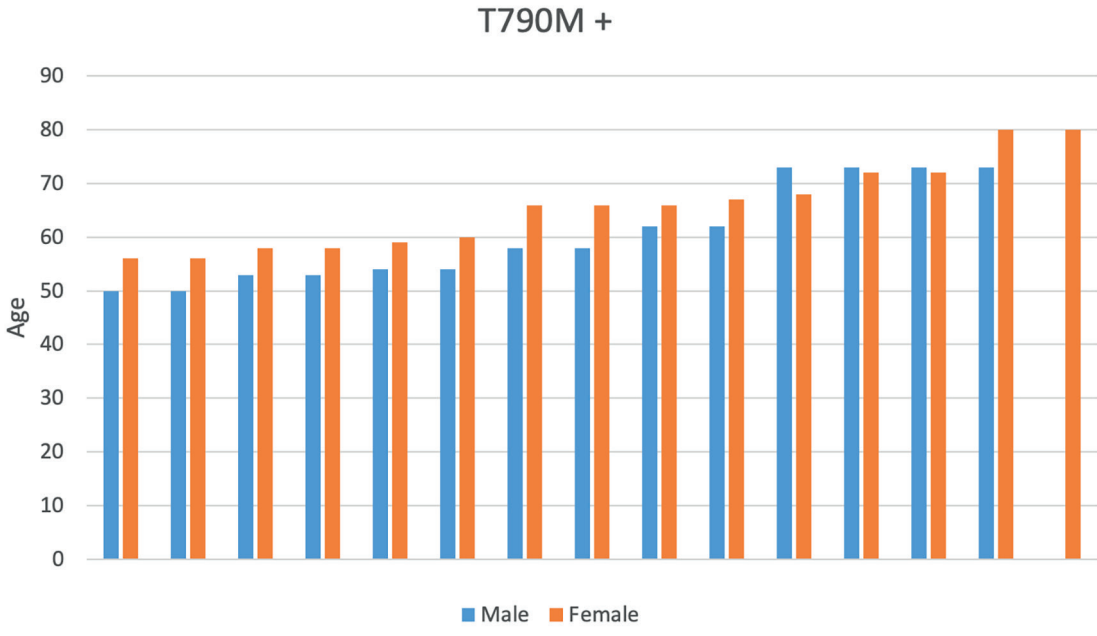

Figure 4. Patients' characteristics in terms of age. Age distrubiton of the T790M positive patients, arranged from youngest to oldest

Table 1. Results of the overall patients

Patient	Age (year)	Gender	*EGFR* T790M*	Other *EGFR* variants
1	67	Female	N	-
2	73	Male	N	L858R
3	50	Female	N	del exon 19
4	59	Female	+	del exon 19
5	48	Female	N	-
6	64	Male	N	-
7	75	Male	N	del exon 19
8	48	Female	N	-
9	45	Female	N	del exon 19
10	80	Male	N	del exon 19
11	66	Male	N	del exon 19
12	58	Female	N	L858R
13	56	Male	N	del exon 19
14	54	Female	N	del exon 19
15	63	Male	N	-
16	62	Male	N	-
17	63	Male	N	del exon 19
18	57	Male	N	-
19	75	Male	N	-
20	58	Female	N	L858R
21	58	Female	N	-
22	63	Male	N	-
23	66	Female	+	-
24	74	Female	N	del exon 19
25	77	Male	N	-
26	60	Female	N	-
27	60	Female	+	-
28	73	Male	+	del exon 21, L858R
29	57	Male	N	-
30	71	Female	N	del exon 21, L858R
31	68	Male	N	del exon 19
32	70	Female	N	del exon 21, L858R
33	64	Male	N	-
34	56	Male	N	-
35	67	Male	N	-
36	62	Male	N	-
37	79	Female	N	-
38	53	Male	N	del exon 21, L858R
39	63	Male	N	-
40	67	Female	N	del exon 19
41	61	Male	N	-
42	64	Female	N	ins exon 20
43	73	Male	N	del exon 21, L858R

Table 1. Continued

Patient	Age (year)	Gender	*EGFR* T790M*	Other *EGFR* variants
44	71	Female	N	-
45	42	Male	N	del exon 19
46	79	Male	N	-
47	45	Male	N	del exon 19
48	75	Male	N	-
49	78	Female	N	G719X
50	64	Male	N	-
51	61	Male	N	del exon 21, L858R
52	80	Female	N	del exon 21, L861Q
53	51	Female	N	-
54	68	Female	+	del exon 19
55	63	Male	N	del exon 19
56	87	Female	N	-
57	55	Male	N	-
58	69	Female	N	del exon 19
59	65	Female	N	G719X
60	65	Female	N	-
61	56	Female	+	del exon 19
62	40	Female	N	del exon 19
63	65	Female	N	-
64	66	Female	+	del exon 19
65	60	Male	N	-
66	80	Female	+	-
67	64	Male	N	-
68	58	Female	N	-
69	63	Male	N	del exon 19
70	73	Male	+	del exon 21, L858R
71	62	Male	+	del exon 19
72	72	Female	+	-
73	63	Male	N	-
74	82	Male	N	-
75	73	Female	N	-
76	68	Female	N	-
77	47	Male	N	-
78	56	Male	N	-
79	60	Female	N	-
80	72	Female	N	-
81	63	Male	N	del exon 19
82	71	Female	N	-
83	77	Male	N	del exon 19
84	53	Male	+	del exon 18
85	62	Male	N	-
86	85	Female	N	-

Table 1. Continued

Patient	Age (year)	Gender	*EGFR* T790M*	Other *EGFR* variants
87	58	Female	N	-
88	48	Male	N	-
89	58	Male	+	-
90	78	Female	N	G719X
91	50	Male	+	del exon 19
92	74	Female	N	del exon 19
93	64	Male	N	-
94	70	Female	N	-
95	58	Female	+	-
96	56	Male	N	-
97	72	Male	N	-
98	71	Female	N	del exon 19
99	74	Female	N	-
100	63	Male	N	del exon 19
101	83	Female	N	del exon 21
102	67	Female	N	del exon 19
103	74	Female	N	-
104	61	Male	N	-
105	53	Female	N	inframe exon 19
106	59	Female	N	-
107	67	Male	N	-
108	70	Male	N	del exon 19
109	54	Male	+	-
110	67	Female	N	-
111	55	Male	N	-
112	63	Female	N	ins exon 20
113	73	Male	+	L858R
114	41	Male	N	del exon 19
115	79	Male	N	N
116	71	Female	N	del exon 19
117	45	Male	N	Q746_A750del
118	75	Male	N	Q746_A750del
119	78	Female	N	G719X
120	63	Male	N	NA
121	61	Male	N	L858R
122	79	Female	N	L861Q
123	51	Female	N	L747_Q749del, L747_A750delinsP, T790M
124	63	Male	N	del exon 19
125	86	Female	N	NA
126	55	Male	N	NA
127	69	Female	N	del exon 19
128	65	Female	N	G719X

Table 1. Continued

Patient	Age (year)	Gender	*EGFR* T790M*	Other *EGFR* variants
129	64	Female	N	E746_A750del, T790M
130	56	Female	+	NA
131	40	Female	N	del exon 19
132	65	Female	N	NA
133	66	Female	+	del exon 19
134	60	Male	N	NA
135	80	Female	+	del exon 19, p.L747_P753delinsS
136	63	Male	N	NA
137	58	Female	N	NA
138	63	Male	N	del exon 19
139	73	Male	+	L858R
140	62	Male	+	del exon 19
141	72	Female	+	del exon 19
142	63	Male	N	NA
143	82	Male	N	NA
144	73	Female	N	NA
145	68	Female	N	L861Q
146	47	Male	N	NA
147	56	Male	N	NA
148	60	Female	N	NA
149	72	Female	N	NA
150	63	Male	N	del exon 19
151	71	Female	N	V786M
152	77	Male	N	del exon 19
153	53	Male	+	del exon 18
154	62	Male	N	NA
155	85	Female	N	L858R
156	58	Female	N	NA
157	48	Male	N	NA
158	58	Male	+	NA
159	78	Female	N	G719X
160	50	Male	+	N
161	74	Female	N	NA
162	64	Male	N	NA
163	71	Female	N	NA
164	58	Female	+	del exon 19
165	57	Male	N	N
166	72	Male	N	N
167	72	Female	N	Q746_S752delinsV
168	74	Female	N	N
169	64	Male	N	N
170	83	Female	N	NA

Table 1. Continued

Patient	Age (year)	Gender	*EGFR* T790M*	Other *EGFR* variants
171	67	Female	N	L747_T751del
172	75	Female	N	del exon 19
173	62	Male	N	del exon 19
174	54	Female	N	Q746_S752delinsV
175	59	Female	N	NA
176	67	Male	N	N
177	70	Male	N	del exon 19
178	54	Male	+	NA
179	68	Female	N	del exon 19
180	56	Male	N	N
181	76	Male	N	NA
182	67	Female	+	NA
183	72	Female	N	Q746_S752delinsV

**EGFR* (NM_005228.5), +: Positive results, N: Normal results, NA: Not available, *EGFR*: Epidermal growth factor receptor

PCR) [13-15]. Additionally, ddPCR can be performed using minimal biopsy material or liquid biopsy, making it possible to analyze the T790M mutation in samples such as blood plasma without requiring invasive procedures. The gene can precisely differentiate between mutant and wild-type DNA molecules, providing reliable analysis even in heterogeneous tumors. The method is superior in terms of both accuracy and reproducibility of results and is a critical feature for long-term monitoring of treatment response.

Compared with qPCR, ddPCR has a lower error margin and can detect lower allele frequencies. It also achieves higher success rates in challenging samples that may be at the detection limits of qPCR. In addition, ddPCR is ideal for analyzing cell-free DNA in plasma or other fluids, which is a crucial advantage in cases in which tissue biopsy is not possible or is associated with high risk. Additionally, ddPCR can be used to monitor the dynamics of the T790M mutation during and after treatment. For instance, it is an effective tool for tracking the response to third-generation EGFR-TKI therapy and the development of resistance.

The ability to assess liquid biopsies using this highly sensitive method is particularly important for individuals with NSCLC given that the characteristics and location of the tumor frequently limit the possibility of re-biopsy. Detection and determination of the treatment approach for the *EGFR* T790M variant, one of the most important mutations responsible for acquired treatment resistance, are of significant importance for these patients. Therefore, this method presents an effective option for addressing these challenges and making treatment decisions. Furthermore, its affordability, ease of interpretation, and relatively short turnaround time are also among the advantages of this method. While NGS can simultaneously identify various mutations, including copy number variations and rearrangements, which adds to its significance, it still carries a comparably higher cost and lower sensitivity and demands a more intensive workload during the analysis phase. Sequencing-based techniques such as Sanger are capable of detecting potential *EGFR* mutations outside of hotspot regions; however, their sensitivity is limited compared with that of ddPCR [16,17].

In this study, liquid biopsies obtained from 183 patients diagnosed with NSCLC who were referred to our clinic with suspicion of developing resistance to first- or second-generation TKI treatment were evaluated for the development of the T790M mutation using the ddPCR method. The positivity rate we observed was 15.85%, which appears to be slightly lower than the reported rates ranging from 25% to 50% in the literature [12,18,19]. We consider that one of the reasons behind the slightly diminished positivity rate, in accordance with the literature, could stem from patients suspected of manifesting disease progression against first- and second-generation TKIs not entirely meeting the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria.

Biopsies with low tumor cell density, heterogeneous structures, or insufficient tissue material can complicate the detection of the T790M mutation. Although liquid biopsies may better reflect tumor heterogeneity, the sensitivity of ddPCR can decrease in patients with low tumor burden due to reduced levels of circulating tumor DNA (ctDNA). In addition, a sufficient number of droplets must be generated to detect low-frequency mutations. In post-treatment biopsies, DNA may be damaged or the number of mutations may decrease. These factors may be among the reasons for the low mutation detection rates observed in our patient cohort.

Referral of patients with NSCLC receiving TKI treatment evaluated according to RECIST 1.1 criteria to the medical genetics clinic and collaborative efforts between the departments of medical oncology and medical genetics could potentially be beneficial in diagnosing the development of resistance to these agents and consequently in diagnosing disease progression associated with it [20].

Personalized targeted therapies, which are gaining popularity each day, provide significant advantages for patients, including increased clinical efficiency and reduced toxicity, and can only be achieved through detailed molecular profiling. Future studies aimed at showcasing the strong potential of advancing molecular diagnostic tools like ddPCR hold promising prospects, particularly for individuals with NSCLC and various other cancer types. Because of its ability to detect mutations even at low allele frequencies, ddPCR is particularly effective for the early diagnosis of resistance mutations like T790M. The method enables the analysis of ctDNA from blood plasma or other fluids without the need for invasive biopsies. This approach is particularly applicable to patients in whom tissue biopsy is not feasible or poses significant risks. In minimal residual disease monitoring, ddPCR can detect low levels of remaining cancer cells after treatment, allowing for the prediction of recurrence risk. Through our own study, we aimed to contribute by sharing the experience of our center in this field.

Study Limitations

The study included not only patients who developed resistance to first- and second-generation TKIs but also those suspected of showing disease progression even if they did not fully meet the RECIST 1.1 criteria. The quantity and quality of ctDNA vary among different patients and at different disease stages. The sensitivity of the ddPCR method largely depends on the amount of DNA used, which can lead to false-negative results. Therefore, enrichment or pre-amplification may be required before ddPCR testing of low-concentration samples.

Conclusion

Despite the inclusion of patients who do not fully meet the criteria for first- or second-generation TKIs treatment, a significant rate of T790M positivity was detected. This highlights the importance of liquid biopsy with ddPCR in patients with potential tyrosine kinase resistance.

Ethics

Ethics Committee Approval: The research received ethical approval from the Etlik City Hospital Ethics Committee (document number: AEŞH-BADEK-2024-843, date: 25.09.2024).

Informed Consent: Retrospective study.

Acknowledgment

We would like to thank the patients for allowing us to conduct the study using their data.

Footnotes

Authorship Contributions

Design: A.B., Data Collection or Processing: A.B., E.E.A., Analysis or Interpretation: A.B., E.E.A., Writing: A.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Article

Evaluation of Factors Associated with Oncological Emergencies in Hematological and Solid Malignancies

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ABSTRACT

Aim: The number of patients with cancer admitted to emergency service (ES) is increasing daily, and oncologic emergencies (OEs) are a significant cause of mortality among these patients. In this study, we aimed to examine the reasons for ES visits of patients with cancer and to determine the frequency of OEs and related factors.

Methods: Patients aged 18 years and older with malignant neoplasms admitted to our hospital's ES between 2017 and 2020 were retrospectively analyzed. Demographic and clinical characteristics, laboratory parameters, and diagnoses were obtained from the hospital's electronic database and patient files. In terms of diagnoses, they were classified as oncologic and other emergency diagnoses (OED), and statistical analyses were performed.

Results: The study was completed in 1.593 patients. The median age was 59. The prevalence rates of hematologic and solid malignancies were 6.5% and 93.5%, respectively. Leukemia and gastrointestinal system malignancies were the most common hematological and solid malignancies. In total, 90.8% of the patients had metastases. Forty-eight point seven percent of the patients were diagnosed as OEs. Forty-nine point five percent of the patients were discharged from the ES, 48.2% were hospitalized, and 0.6% died at the ES. In total, 11.8% died in the ES or after hospitalization. The mortality rate in the OE group was 22.2%. OEs were more common in patients with hematological malignancies, with a 67.3% ratio ($p<0.001$). Among solid malignancies, OEs were more frequent in gynecological, lung and central nervous system malignancies ($p<0.001$). No significant difference was found between the OE and OED groups in terms of the presence of metastasis ($p=0.108$); therefore, when evaluated with the type of organ metastasis, OEs were more common in lung, brain, liver, and bone metastases ($p<0.001$). Admission to ES by ambulance, presence of comorbid diseases, higher Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS), potassium, calcium, total bilirubin, C-reactive protein (CRP), and lactate values were associated with an increased risk of OE, whereas female gender, solid malignancy, and higher hemoglobin and blood urea nitrogen values were associated with a decreased risk of OE. A higher ECOG PS score [odds ratio (OR)=3.806, $p<0.001$], presence of brain metastasis (OR=3.225, $p<0.01$), higher CRP (OR=1.010, $p<0.001$) and lactate (OR=1.227, $p<0.01$) were found to be associated with mortality in patients with OE.

Conclusion: Classifying cancer patients admitted to the ES as OEs and non-OEs may reduce the workload of ES, enable physicians to recognize OEs earlier, make rapid and accurate decisions appropriate to the situation, and provide emergency intervention for oncologic complications.

Keywords: Neoplasms, medical oncology, emergencies

Introduction

Cancer is a significant health problem in Turkey and worldwide. One of every six deaths in the world and one of every five deaths in Turkey are due to cancer [1,2]. Advances in medical research, treatment methods, and technology have increased life expectancy and extended the follow-up period for patients with cancer [2]. Oncologic emergencies (OEs) are clinical manifestations of metabolic, neurologic, cardiovascular, hematologic, and/or infectious origin that develop directly or indirectly due to cancer or that require emergency treatment [3]. Complaints may vary from person to person due to disease

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stage, age, diagnosis, metastasis, comorbidity, and other factors [3,4]. According to the mechanism of occurrence, they may be metabolic (tumor lysis syndrome, malignant hypercalcemia, hyponatremia and inappropriate anti-diuretic hormone syndrome), mechanical/obstructive (superior vena cava syndrome, cardiac tamponade, hyperviscosity syndrome, malignant pleural effusion/ascites, medulla spinalis compression..), treatment-related (extravascular escape of chemotherapeutics, cytokine release syndrome, anaphylaxis, and capillary leak syndrome, etc.), and blood-related (bone marrow suppression, anemia, febrile neutropenia, etc.) [4]. These events can occur at any stage of the disease, from the onset to the end stage. Failure to diagnose and treat patients with these conditions leads to high morbidity and mortality rates [4]. Patients with cancer are frequently admitted to the emergency service (ES) due to local and systemic diseases caused by cancer, treatment-related complications, end-of-life symptoms, and OEs [3]. OEs are the most important clinical conditions, accounting for 30-50% of oncology patients presenting to the ES [5]. With the increasing prevalence of cancer, ES visits among patients with cancer are increasing [5]. The follow-up and treatment of cancer requires multidisciplinary teamwork. Emergency physicians are an important part of this team. What is expected from emergency physicians on the team is to determine whether there is an OE during the emergency admission of patients with cancer. Therefore, detailed anamnesis of patients with cancer should be performed, system examinations should be performed, and diagnostic tests for complaints and examination findings should be requested within a short period. Emergency interventions should also be initiated in the presence of OE. Failure to correctly diagnose a patient and treatment delays may result in a poor prognosis for the patient [5]. The current study aimed to determine the frequency of OEs and demographic, clinical, and laboratory factors associated with diagnosis and mortality in patients with cancer admitted to our oncology branch hospital.

Methods

This retrospective study was conducted at the ES of University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital after Ethics Committee Approval (no. 2023-09/78, date: 19.10.2023). We retrospectively analyzed 5,000 patients aged 18 years and older who presented to the ES between 2017 and 2020 and were diagnosed with malignant neoplasm according to International Classification of Diseases-9. Oncology patients who were being treated in another center, palliative care patients who were not receiving active treatment, follow-up patients who were cured, newly diagnosed patients in the investigation process, and patients referred to our hospital for hospitalization from another center were excluded from the study. The study was completed in 1,593 patients. Demographic characteristics, mode of presentation (outpatient or ambulance service), presenting complaint, cancer diagnoses, oncologic treatments [surgery/chemotherapy/radiotherapy (RT)], laboratory parameters (hemogram, biochemistry, blood gas, coagulation..) Glasgow coma scale and Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS), diagnoses [OE-other emergency diagnoses (OEDs)], and outcomes (hospitalization/discharge/death) were obtained from the hospital electronic database and patient files. Patients were divided into two groups: OE and OEDs according to the diagnoses received at discharge, hospitalization, and referral, and demographic, clinical characteristics, and outcomes were compared between the groups.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences 25.0 (IBM Co®. USA). The Kolmogorov-Smirnov test was used to detect the normal distribution. Categorical data are expressed as numbers and percentages (%). Numerical variables without normal distribution are presented as median and interquartile range (25^{th}-75^{th} percentile). Categorical data were compared using the chi-square test according to the percentage of the expected count. Yate's correction or likelihood ratio was performed. Numerical data with or without normal distribution were compared using the independent samples t-test and Mann-Whitney U test, respectively. Binary logistic regression analysis was performed to identify variables associated with OE diagnosis and mortality in patients with OE.

Results

This study included 1.593 patients diagnosed with malignancy. The average age of the patients was 59 years. 53.2% were women and 46.8% were men. 57.1% of the patients were outpatients, and 42.9% came to the ES by ambulance. 93.5% of the patients had solid organ malignancy, and 6.5% had hematologic malignancy. The most common hematologic malignancy was leukemia, with a rate of 3.3%. The most common solid malignancies were gastrointestinal cancer 32.6%, breast cancer 27.0%, lung cancer 17.3%, genitourinary cancer 8.5% and gynecologic cancer 7.6%. 90.8% of patients had metastases. The most common organ metastases were lung, bone, liver, and brain. In total, 64.5% of the patients had undergone surgery for cancer. 73.2% had received chemotherapy, and 29.7% had received RT in the previous month. Furthermore, 56.7% of the patients had at least one comorbid disease. Hypertension (39.9%), diabetes mellitus (18.8%), coronary artery disease (12.8%), and chronic obstructive pulmonary disease 8.1% were the most common comorbidities. The median ECOG PS score was 1.0. After emergency admission, 43.3% of the patients were discharged, 48.2% were hospitalized, and 0.6% died in the ES. Additionally, 10% of the patients died after transfer to another clinic or intensive care unit (ICU). The mortality rate both in the ES and after hospitalization was higher in the OE group ($p<0.001$). Demographic and clinical characteristics of patients with cancer admitted to the ES are presented in Table 1. The most common reasons for admission to ES were pain (abdominal pain, chest pain, muscle and joint pain, surgical site pain, pain due to mass pressure, headache) at 72.6%, fatigue at 66.5%,

fever at 29.4%, nausea-vomiting at 27.8%, shortness of breath at 25.0%, neurologic symptoms (seizure, confusion, dizziness, loss of strength, etc.) at 18.2%, cardiac complaints (palpitations, syncope, etc.) at 9.6%, and genitourinary symptoms (dysuria, hematuria, anuria, vaginal bleeding, etc.) at 9.3%, respectively.

47.8% of the patients included in the study had OE diagnoses, and 52.2% had OED diagnoses. According to the mechanism of occurrence, the most common OEs were mechanical (47.3%), blood-related (45.6%), metabolic (11.0%), and treatment-related (2.6%). Sixty-two of the patients had two different OE diagnoses, and only 0.4% had three different OEs. Among all OE diagnoses, febrile neutropenia and sepsis were the most common (22.9%). The most common OEDs were chemotherapy side effects (nausea-vomiting, diarrhea, dehydration) at 32.6%, pain (bone-joint pain, abdominal pain, chest pain, headache, etc.) at 18.8%, and infectious diseases (upper respiratory infections, cellulitis, etc.) with 17.5%. OE and OED diagnoses are presented in Table 2.

In our study, the mean age in the OE group was 58.63±12.97 and higher than that in the OED group, with a mean age of 57.18±12.87 ($p<0.031$), and the male/female ratio was higher for the OE group ($p<0.01$). OEs were more common in hematological malignancies, with a 67.3% ratio ($p<0.001$). Among solid malignancies, OEs were more frequent in lung cancer and central nervous system malignancies ($p<0.001$). OEs were more common in patients with metastasis; also, when evaluated with the type of organ metastasis, OEs were more common in lung, brain, liver, and bone metastases ($p<0.001$). The most common symptoms in the OE group were weakness (66.5%), abdominal pain (29.8%), fever at 29.4%, nausea or vomiting (27.8%), musculoskeletal pain (25.0%), and dyspnea (25.0%). The OE group's hospitalization and mortality ratios

Table 1. The demographic and clinical features of patients with cancer admitted to the emergency service

	n/% (n=1593)	Median (IQR) or mean±SD
Age (years)		59.0 (50.0-67.0)
Sex Female Male	 847 (53.2) 746 (46.8)	
The type of malignancy Solid Hematological	 1489 (93.5) 104 (6.5)	
Disease status Locally advanced stage Metastatic disease Recurrence/metastasis Advanced-stage metastatic Refractory/recurrence	 561 (35.1) 554 (34.8) 327 (20.5) 113 (7.1) 38 (2.4)	
Metastasis (local or distant)	1447 (90.8)	
Metastasis location Another organ/location Lung Bone Liver Brain	 1403 (88.1) 486 (30.5) 423 (25.6) 401 (25.2) 119 (7.5)	
History of cancer surgery Yes No	 1028 (64.5) 565 (35.5)	
Chemotherapy in the previous month	1200 (73.2)	
Radiotherapy in the previous month	473 (29.7)	
Patients with comorbidities	904 (56.7)	
ECOG PS		1.0 (1.0)
The type of admission Outpatient Ambulance	 910 (57.1) 683 (42.9)	
Outcomes of emergency services Discharged Hospitalized Transferred to another center Death at the ES Refuse of treatment	 789 (49.5) 768 (48.2) 24 (1.5) 10 (0.6) 2 (0.1)	

IQR: Interquartile range, SD: Standard deviation, ECOG PS: Eastern Cooperative Oncology Group Performance Status Scale, ES: Emergency service

Table 2. Emergency diagnosis for patients with cancer admitted to the emergency service

Oncologic emergencies (n=761)	(n/%)	Other emergency diagnosis (n=832)	(n/%)
Metabolic causes	83 (11.0)		
TLS	43 (5.7)	Chemotherapy side effects	271 (32.6)
Syndrome involving inappropriate ADH	22 (2.9)	Pain	156 (18.8)
Maling hypercalcemia	18 (2.4)	Infectious diseases	146 (17.5)
Mechanic causes	361 (47.4)		
Malignant pleural effusion	128 (16.8)	Pathology of the respiratory system	58 (7.1)
Intestinal and biliary obstruction	91 (12.0)		
Increased ICP	83 (10.9)	Surgical complications	47 (5.6)
Cardiac tamponade	18 (2.4)		
Pathological fracture	14 (1.8)	Radiotherapy-associated side effects	42 (5.0)
VCSS	12 (1.6)		
Spinal cord compression	11 (1.4)	Acute renal failure	39 (4.7)
Hyper viscosity	4 (0.5)		
Treatment-related causes	20 (2.6)	Pathology of the gastrointestinal tract	31 (3.7)
Hemorrhagic cystitis	9 (1.2)		
Anaphylaxis/capillary leakage syndrome	9 (1.2)	Malnutrition/electrolyte imbalance	15 (1.8)
Chemotherapeutic extravasation	2 (0.2)		
Blood disorders	347 (45.6)	Central nervous system pathology	11 (1.3)
Febrile neutropenia and sepsis/septic shock	174 (22.9)		
Anemia/leucopenia/thrombocytopenia	85 (11.2)	Pathology of the cardiovascular system	10 (1.2)
Acute bleeding/coagulopathy	45 (5.9)		
Arterial or venous embolism	41 (5.4)	General symptom	4 (0.5)
GVHD	2 (0.3)		
Multiple oncologic emergency diagnoses	50 (6.6)	Cardiopulmonary arrest	2 (0.2)

Total number of diagnoses: ADH: Anti-diuretic hormone, ICP: Intracranial pressure, VCSS: Vena cava superior syndrome, GVHD: Graft-versus-host disease, TLS: Tumor lysis syndrome

were significantly higher (p<0.001). The median ECOG score was 2.0 in the OE group, 1.0 in the OED group, and significantly higher in the OE group (p<0.001). The demographic and clinical findings were compared among the groups assigned according to the presence of OE (Table 3). In our study, two groups were compared in terms of laboratory parameters. White blood cells (WBC), neutrophil count, hemoglobin (HGB), platelet count, calcium, total protein, and albumin levels were significantly lower in the OE group (p<0.05). Blood urea nitrogen (BUN), uric acid, phosphorus, aspartate aminotransferase (AST), amylase, total and direct bilirubin, C-reactive protein (CRP), D-dimer, international normalization ratio (INR) and lactate levels were higher in the OED group (p<0.05). The frequency of pyuria was higher in the OED group than in the OE group (p<0.001). Abnormal electrocardiogram findings were detected in 20% of the patients. Abnormal ECG findings were more common in the OE group (p<0.001). The laboratory values of the OE and OED groups are presented in Table 4.

The binary logistic regression analysis found that admission to ES by ambulance, presence of comorbid diseases, higher ECOG PS, higher potassium, calcium, total bilirubin, CRP, and lactate values were associated with an increased risk of OE, whereas female gender, solid malignancy, and higher HGB and BUN values were associated with a decreased risk of OE (Table 5). The analysis did not include D-dimer, phosphorus, and INR because of the relatively low number of measurements. When regression analysis was performed for mortality in the OE group by adding ALT and creatinine to the variables in Table 5, a higher ECOG PS score [odds ratio (OR)=3.806, p<0.001], presence of brain metastases (OR=3.225, p<0.01), higher CRP (OR=1.010, p<0.001) and lactate (OR=1.227, p<0.01) were found to be associated with mortality in patients with OE.

Discussion

Patients with cancer present to the ES with a variety of clinical presentations related to the underlying disease or as a result of treatment complications. ES visits of patients with cancer may be associated with life-threatening OEs with a high mortality rate. Early diagnosis and appropriate treatment can effectively restore quality of life [6].

Data from the Ministry of Health and several studies have found a high rate of male sex among patients with cancer [7-11]. Therefore, female patients were predominant in our study, similar to the results of Bozdemir et al. [12] and Swenson et al. [13]. Our median age was 59 years, which is similar to that of similar studies in the literature [7,10,11]. Comorbidities are more common in patients with cancer than in the general population; one study reported that more than half of patients with cancer aged >75 years had at least three comorbidities [14]. The most common comorbidities were hypertension, diabetes, and heart disease. Comorbid conditions in patients with cancer lead to more ES visits and may lead to increased mortality [14]. In terms of cancer type, the most common solid organ cancers in our study were gastrointestinal, breast, and lung cancers. Similar to studies by Bozdemir et al. [12], Alıcı et al. [15], Kocak et al. [16]. The presence of metastases

Table 3. Comparison of demographic and clinical features between the oncological emergency and non-oncological emergency patient groups

	Oncological emergency (n=761)	Other emergency diagnosis (n=832)	p
Age (mean±SD)	58.63±12.97	57.18±12.87	0.031
Sex (n/%) Female Male	 377 (44.5) 384 (51.5)	 470 (55.5) 362 (48.5)	 **<0.01**
Malignancy type (n/%) Hematological Solid	 70 (67.3) 691 (46.4)	 34 (32.7) 798 (53.6)	 **<0.001**
Hematological (n/%) Leukemia Lymphoma Others	 41 (77.4) 22 (56.4) 7 (53.8)	 12 (22.6) 17 (43.6) 6 (46.2)	 **<0.001**
Organ/system tumors (n/%) Breast Gastrointestinal system Lung Urogenital system Ear-nose-throat-larynx Gynecological Cranial Bone and soft tissue Others	 130 (32.3) 215 (44.3) 160 (62.2) 56 (44.1) 14 (43.8) 72 (63.7) 25 (89.3) 9 (40.9) 10 (45.5)	 272 (67.7) 270 (55.7) 97 (37.8) 71 (55.9) 18 (56.2) 41 (36.3) 3 (10.7) 13 (59.1) 12 (54.5)	 **<0.001**
Location of metastasis (n/%) Another organ/location Lung Bone Liver Brain	682 (89.6) 658 (86.5) 318 (41.8) 240 (31.5) 229 (30.1) 87 (11.4)	765 (91.9) 744 (89.4) 168 (20.2) 183 (22.0) 172 (20.7) 32 (3.8)	0.108 0.144 **<0.001** **<0.001** **<0.001** **<0.001**
Chemotherapy in the previous month (n/%)	560 (46.7)	640 (53.3)	0.130
Radiotherapy performed in the previous month (n/%)	242 (51.2)	231 (48.8)	0.879
Patients with comorbidity (n/%)	436 (48.2)	468 (51.8)	0.686
Duration of cancer diagnosis (years)	5.0 (4.0-6.0)	5.0 (4.0-5.0)	0.076
ECOG PS (median, IQR)	2.0 (1.0-2.0)	1.0 (0.0-1.0)	**<0.001**
Outcome of ES Hospitalized Discharged Transferred to another center Death Refuse of treatment Total mortality	 606 (79.6) 28 (16.8) 19 (2.5) 6 (0.8) 2 (0.3) 169 (22.2)	 162 (19.5) 661 (79.4) 5 (0.6) 4 (0.5) 20 (2.4)	 **<0.001** **<0.001**

IQR: Interquartile range, SD: Standard deviation, ECOG PS: Eastern Cooperative Oncology Group Performance Status Scale, ES: Emergency service

is one of the most important factors in the management of patients with cancer because it causes various complications, decreases survival, and leads to frequent ED visits [7]. In our study, 90.8% of patients had metastatic disease. In similar studies from our country, the metastasis ratio was 54-72.9% [7,8,12]. The presence of metastases may be an important indicator of emergency physicians to more accurately evaluate the management of patients with cancer. In our study, 73.2% of patients had received chemotherapy and 29.7% had received RT in the previous month. A study conducted in Australia showed that 70% of visits to the ES by patients with cancer occurred within 4 weeks after chemotherapy, and 88% of such visits resulted in hospitalization [17]. Fatigue, pain, fever, and dyspnea were the most common reasons for ES visits. In similar studies conducted in our country, dyspnea was the most common cause of presentation [17-19]. Pain, gastrointestinal symptoms, and general condition deterioration have been listed as the most common reasons for admission to ES in different studies [7,9,13]. OE and OED frequencies were 47.8% and 52.2%. In the OE group, the mean age was

Table 4. Comparison of laboratory results between patients with and without oncological emergency

Laboratory parameters	Oncological emergency (n=761)	Other emergency diagnosis (n=832)	p
WBC (mm^3)	7700.00 (2700.00-13300.00)	8100.00 (5550.00-11450.00)	**<0.01**
Neutrophil count (mm^3)	5500.0 (1400.00-9900.00)	5700.00 (3500.00-8900.00)	**<0.001**
HGB (mg/dL)	10.4 (8.8-12.0)	11.3 (10.1-12.6)	**<0.001**
Platelet count (mm^3)	191.000 (95000-311000)	243000 (174000-318500)	**<0.001**
Glucose (mg/dL)	116.0 (100.0-150.0)	117.00 (101.00-148.00)	0.144
BUN (mg/dL)	19.0 (12.4-32.0)	18.0 (12.9-26.0)	**<0.001**
Creatinine (mg/dL)	0.7 (0.5-1.2)	0.8 (0.6-1.2)	0.266
Uric acid (mg/dL)	5.4 (4.0-6.9)	5.1 (4.1-6.1)	**<0.001**
Na (mg/dL)	136.0 (132.0-139.0)	136.0 (134.0-139.0)	0.051
K (mg/dL)	4.1 (3.7-4.7)	4.2 (3.7-4.6)	0.152
Ca (mg/dL)	8.3 (7.5-8.9)	8.6 (8.0-9.2)	**<0.001**
P (mg/dL)	4.1 (3.1-5.8)	3.3 (3.9-5.0)	0.028
Total protein (mg/dL)	5.4 (4.9-6.1)	6.0 (5.1-6.5)	**<0.001**
Albumin (mg/dL)	3.1 (2.4-3.5)	3.4 (3.0-3.9)	**<0.001**
ALT (U/L)	19.0 (12.0-39.0)	19.0 (12.0-30.0)	0.052
AST (U/L)	26.0 (18.0-50.0)	23.4 (17.0-37.0)	**<0.001**
Amylase (U/L)	47.0 (32.0-85.0)	45.0 (31.5-68.0)	**<0.01**
Total bilirubin (mg/dL)	0.8 (0.5-1.2)	0.6 (0.4-1.0)	**<0.001**
Direct bilirubin (mg/dL)	0.2 (0.1-0.5)	0.1 (0.1-0.3)	**<0.001**
CRP (mg/dL)	68.0 (14.0-140.0)	8.0 (0.0-62.0)	**<0.001**
D-Dimer (ng/mL)	2850.00 (1550.00-5400.00)	1260.00 (630.00-3452.25)	**<0.001**
INR	1.2 (1.1-1.5)	1.1 (0.9-1.1)	**<0.001**
Troponin (ng/mL)	0.11 (0.10-0.23)	0.10 (0.08-0.16)	**<0.001**
pH	7.36 (7.33-7.43)	7.36 (7.35-7.39)	0.403
Lactate	2.1 (1.3-3.4)	1.2 (0.9-2.1)	**<0.001**
Urinary analysis Normal Pyuria Hematuria	 583 (76.6) 44 (5.8) 17 (2.2)	 557 (66.9) 94 (11.3) 2 (0.2)	 **<0.001**
Electrocardiography Normal sinus rhythm Abnormal findings	480 (63.1) 232 (30.4)	627 (75.4) 45 (5.4)	 **<0.001**

WBC: White blood cell, HGB: Hemoglobin, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, INR: International normalization ratio

58.63±12.97 years, and male gender was more prevalent, which is consistent with the literature [7-9]. The frequency of comorbid disease was similar between the OE and OED groups. However, the incidence of diabetes mellitus was higher in the OE group. Regarding cancer type, OEs had a higher proportion of hematologic malignancies than solid malignancies. Among solid malignancies, the frequency of OE was higher in patients with central nervous system tumors, gynecological and lung cancers. We could not find any studies that would compare our data. OEs were detected at a higher rate in cancer patients with organ metastasis. Among the presenting complaints, only fever, dyspnea, and abdominal pain were associated with an increased risk of OEs. The most common OE diagnoses in our study were febrile neutropenia, malignant pleural effusion/ascites, intestinal/biliary obstruction, anemia, leukopenia, thrombocytopenia, increased ICP, and TLS. In a study by Eşdur [20], febrile neutropenia was the most common OE (31.3%), followed by brain metastasis/increased intracranial pressure (24.5%), biliary obstruction (8%), GI obstruction (4.9%) and TLS at 3.7% [19]. Febrile neutropenia is one of the most common fatal complications of ESs, and its early diagnosis and management are crucial [20,21]. In our study, chemotherapy-related side effects, pain, and infectious diseases were the most common diagnoses in the OED group. It has been shown in the literature that chemotherapy-induced symptoms cause frequent ES visits, and ES visits may be reduced if patients are encouraged to self-manage similar symptoms through education [21].

The median ECOG score was significantly higher in the OE group. Since the performance score mainly depends on the patient's

Table 5. The clinical and laboratory parameters associated with oncological emergency

	B	S.E.	p	OR	95% CI for OR	
					Lower	Upper
Age	0.000	0.006	0.979	1.000	0.989	1.011
Female/male	0.372	0.137	**<0.01**	0.689	0.527	0.901
Outpatient/ambulance	0.433	0.148	**<0.01**	1.541	1.154	2.059
Duration of cancer diagnosis	0.020	0.033	0.547	0.980	0.919	1.046
Comorbidity	0.333	0.150	**0.026**	1.395	1.041	1.870
Hematological/solid malignancy	1.173	0.358	**<0.001**	0.310	0.153	0.624
Metastasis	0.025	0.312	0.935	0.975	0.529	1.798
Lung metastasis	0.587	0.156	**<0.001**	0.556	0.410	0.754
Brain metastasis	0.066	0.277	0.811	0.936	0.544	1.610
Liver metastasis	0.159	0.166	0.339	1.172	0.846	1.622
Bone metastasis	0.108	0.160	0.499	1.114	0.815	1.523
Chemotherapy in the previous month	0.038	0.156	0.805	0.962	0.709	1.305
RT in the previous month	0.144	0.148	0.330	1.155	0.864	1.543
GCS	-0.054	0.147	0.713	0.947	0.710	1.264
PS	0.695	0.092	**<0.001**	2.004	1.672	2.402
WBC (mm^3)	0.000	0.000	0.642	1.000	1.000	1.000
Neutrophil count (mm^3)	-0.055	0.016	<0.01	0.946	0.916	0.977
HGB (mg/dL)	-0.140	0.031	**<0.001**	0.870	0.819	0.923
Platelet count (mm^3)	-0.001	0.000	0.015	0.999	0.998	1.000
Glucose (mg/dL)	0.001	0.001	0.446	1.001	0.999	1.002
BUN (mg/dL)	-0.016	0.005	<0.01	0.984	0.975	0.993
Uric acid (mg/dL)	0.001	0.018	0.938	1.001	0.968	1.036
Na (mg/dL)	0.000	0.001	0.793	1.000	0.998	1.003
K (mg/dL)	0.268	0.093	**<0.01**	1.307	1.089	1.569
Ca (mg/dL)	0.124	0.050	**0.014**	1.133	1.026	1.250
Total protein (mg/dL)	0.013	0.022	0.568	1.013	0.970	1.057
Albumin (mg/dL)	-0.029	0.038	0.436	0.971	0.902	1.046
AST (IU/L)	0.000	0.001	0.965	1.000	0.998	1.002
GGT (IU/L)	0.001	0.001	0.172	1.001	1.000	1.002
Amylase (U/L)	0.001	0.001	0.346	1.001	0.999	1.003
Total bilirubin (mg/dL)	0.374	0.183	**0.040**	1.454	1.016	2.080
Direct bilirubin (mg/dL)	-0.449	0.296	0.129	0.638	0.358	1.140
CRP (mg/dL)	0.004	0.001	**<0.001**	1.004	1.002	1.007
Troponin 1 (ng/mL)	-0.020	0.023	0.373	0.980	0.937	1.025
Lactate	0.262	0.052	**<0.001**	1.300	1.174	1.438
Constant	1.901	2.503	0.448	6.692		

Nagelkerke R2: 0.426, RT: Radiotherapy, GCS: Glasgow coma scale, ECOG PS: Eastern Cooperative Oncology Group Performance Score, CRP: C-reactive protein, BUN: Blood urea nitrogen, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, HGB: Hemoglobin, WBC: White blood cells, CI: Confidence interval, OR: Odds ratio

daily activities, predicting the outcome in an emergency setting can be simple and practical. For patients with cancer, a higher ECOG PS is associated with a worse prognosis [8,22,23]. Laboratory findings are important for cancer diagnosis and treatment follow-up. In our study, we obtained laboratory findings from 88.9% of the patients. WBC, HGB, platelet count, neutrophil count, calcium, total protein, and albumin levels were lower in the OE group than in the OED group. BUN, uric acid, phosphorus, AST, amylase, total and direct bilirubin, CRP, D-dimer, INR, and lactate levels were higher in the OE group than in the OED group. The mortality rate in our study was 22.2% in the OE group and 11.9% for all patients at ES or hospitalization, consistent with previous studies that included patients with cancer who visited ES [8,13].

Although there are few studies on biochemical data in the literature, BUN, creatinine, CRP, and potassium levels were significantly higher in patients who died or were hospitalized in the ICU [24]. In Turkish cancer statistics, low HGB, platelet, and albumin levels were associated with a significant increase in the frequency of ICU admission and mortality [25]. In this study, a higher ECOG PS, brain metastasis, CRP, and lactate levels were associated with mortality in patients with OE.

The admission to ES by ambulance, presence of comorbid diseases, higher ECOG PS, potassium, calcium, total bilirubin, CRP, and lactate values were associated with an increased risk of OE, whereas female gender, solid malignancy, and higher HGB and BUN values were associated with a decreased risk of OE in this study. We could not find any study that evaluated risk factors for OE diagnosis.

Unfortunately, ES admissions in our country have exceeded the world averages. In the case of overcrowding caused by an increasing number of patients, it is crucial to identify cancer patients and their diagnoses, especially OEs. Emergency physicians should know all the clinical and pathological conditions of patients with cancer, especially to predict, recognize, and treat potential complications early. Although considerable information on managing treatment-related complications has been published, few studies have evaluated the management of disease-related signs and symptoms requiring ES presentation [5,7-9]. Therefore, it is vital to know the reasons for the presentation of oncology patients admitted to the ES and to examine the problems encountered in the clinic for early diagnosis and treatment. Close collaboration between the oncology team and emergency physicians is required to manage the emergency medical conditions of patients with cancer to develop a common management algorithm. With the help of algorithms, early recognition of OEs, prognosis prediction, and effective treatment can be achieved. Algorithms can be a potentially valuable guiding tool for busy emergency physicians who do not have oncologist support and do not encounter many patients with cancer, and they can improve the care of these patients.

Study Limitations

The first limitation of this study was that it was a retrospective, single-center study. Patients in the terminal stages of cancer and those who have already been cured were not included in the study. The high number of patients, including patients with different cancer types, and the fact that ES physicians diagnosed with OE may be considered strong aspects of the study.

Conclusion

The results of these and similar studies may help increase the awareness of emergency physicians, who are increasingly encountering patients with cancer, about OEs and provide more information and guidance in diagnosing and identifying risk factors.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (no. 2023-09/78, date: 19.10.2023).

Informed Consent: Retrospective study.

Footnotes

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Case Report

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Is Bone Marrow Metastasis in Gastric Cancer Adequate for Best Supportive Care Decisions? Or is There Still a Chance?

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ABSTRACT

Gastric carcinoma is one of the most common types of cancer worldwide. Although intra-abdominal metastasis is common, bone marrow metastasis (BMM) is quite rare, and patients with this condition may present with cytopenia. We present the case of a patient with gastric carcinoma and BMM who experienced bone marrow suppression and bicytopenia (anemia and thrombocytopenia) regressing after two cycles of chemotherapy. A 58-year-old male patient with advanced-stage gastric adenocarcinoma presented with bicytopenia. BMM was confirmed by bone marrow aspiration biopsy. Bone marrow suppression regressed after initiation of chemotherapy. BMMs are rare in gastric carcinoma, and there is no standard treatment for these malignancies. Our case report is remarkable as it demonstrates a rare case of bone marrow suppression following chemotherapy in a patient and suggests the potential efficacy of 5-FU and platinum-based chemotherapy.

Keywords: Gastric cancer, bone marrow, metastasis, chemotherapy

Introduction

Gastric carcinoma is the 5th most common type of cancer worldwide and is generally more prevalent in Asian countries than in others [1]. Patients are typically symptomatic upon diagnosis, with the most common symptoms being dysphagia, weight loss, and persistent abdominal pain. Most patients are diagnosed at an advanced stage, which often precludes curative treatment. In advanced-stage disease, the liver, peritoneum, and intra-abdominal lymph nodes are the most common sites of distant metastasis. Ovarian and central nervous system metastases are less frequent, whereas bone and bone marrow metastases (BMMs) occur in less than 10% of patients [2]. Concurrent occurrence of BMM and disseminated intravascular coagulation (DIC) in gastric carcinoma is extremely rare, and treatment response is generally limited [3]. In this case report, we describe an advanced-stage gastric carcinoma patient who developed bicytopenia and DIC secondary to BMM. The patient's bone marrow suppression, bicytopenia, and DIC improved significantly after two cycles of chemotherapy.

Case Report

A 58-year-old male patient with diabetes mellitus and coronary artery disease presented with a weight loss of 20 kg in 6 months. Esophagogastroduodenoscopy revealed multiple ulcerated lesions at the lesser curvature of the stomach, and a biopsy confirmed gastric adenocarcinoma with a signet ring cell component (c-erbB2 negative). Thoracoabdominal computed tomography (CT) imaging showed multiple intra-abdominal and mediastinal lymph nodes. Positron emission tomography (PET)/CT examination detected widespread metastatic foci in the bones, multiple metastatic lymph nodes in the mediastinum, and a malignant mass at the lesser curvature along with multiple intra-abdominal metastatic lymph nodes. Blood tests revealed bicytopenia with normal anemia markers and no atypia on peripheral blood smear examination. Bone marrow aspiration biopsy confirmed gastric adenocarcinoma metastasis. Due to increased D-dimer and decreased fibrinogen levels, the patient was evaluated at the hematology clinic. Oxygen therapy was not

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required, and pulmonary thromboembolism was ruled out on imaging. Platelet, fresh frozen plasma, and erythrocyte suspensions were administered based on a preliminary diagnosis of DIC. The patient's condition was attributed to BMM of gastric adenocarcinoma, and chemotherapy was initiated with a 50% reduction in the mFOLFOX6 dose. The following chemotherapy, the patient's bicytopenia and DIC improved, with blood test results showing recovery and resolution of bone marrow suppression. The patient's general condition improved after chemotherapy, and he is currently monitored during the third month of treatment. Blood values before chemotherapy, on the 15th day after each chemotherapy cycle, and two months after starting chemotherapy are summarized in Table 1.

Discussion

Although BMM is common in solid organ tumors, it is rarely detected in metastatic gastric carcinoma. It is mostly observed in poorly differentiated subtypes in relatively young patients, and there is no standard treatment method [4]. Similar to this information, our patient was a young 58-year-old, and in the pathological examination, it was reported that the tumor had a signet ring cell component. Signet ring cell subtype shows poor differentiation. In a series examining the frequency of BMM in patients with gastric carcinoma, the incidence of BMM was found to be 1% [5]. In a study examining 2150 patients with metastatic gastric carcinoma, the frequency of BMM was reported to be only 0.9% [6]. The most useful imaging modality for detecting BMMs is PET/CT, and in our patient, widespread increased metabolic activity was detected in bone using PET/CT [7]. Although cytopenia alone may be seen in patients with BMMs, patients may present with cytopenia and DIC, as in our case [3]. The causes of anemia and bicytopenia in patients with gastric carcinoma who have undergone surgery or whose gastric mucosal integrity is impaired may be iron and vitamin B12 deficiency. In our patient, anemia markers were observed and were within the normal range. Gastric carcinoma presenting with DIC generally has a poor prognosis and is known to be resistant to chemotherapy; however, it has been reported in some case series that they benefit from 5-FU-based chemotherapy [8-10]. In a study, it was reported that the response rate to 5-FU, platinum, and taxane-based chemotherapy in patients with gastric cancer and BMMs was approximately 30%, and the average survival was approximately 1 year [11]. Our patient was treated with the mFOLFOX6 protocol, which contains 5-FU and a platinum-based chemotherapy agent, and it was observed that the suppression of bone marrow regressed with treatment from the first cycle. In parallel with the response we received with chemotherapy, a study reported that the prognosis was better in gastric carcinoma patients with BMMs in those who received palliative chemotherapy than in those who did not receive chemotherapy, and overall survival was found to be longer in the group receiving chemotherapy [12]. In another study, the average survival in patients with bone marrow metastatic gastric carcinoma receiving chemotherapy was reported to be 3 months, whereas it was reported to be two months in patients monitored with best supportive care [8]. This information in the literature supports the limited response to treatment in bone marrow metastatic gastric carcinoma, and although benefit is extremely rare in these patients, more courageous use of chemotherapy may be required.

Conclusion

BMMs are rare in gastric carcinoma, and no standard treatment method has been established for these patients. Treatments that have shown limited benefits may be withheld due to cytopenia resulting from bone marrow involvement. Our case report is noteworthy because it represents a rare case of bone marrow suppression and DIC responding positively to chemotherapy in a patient with bone marrow metastatic gastric carcinoma. This highlights the potential for the more robust use of 5-FU and platinum-based chemotherapy regimens in such cases.

Table 1. The patient's blood values before chemotherapy, on the 15th day after the first and second cycles of chemotherapy, and two months after initiation of chemotherapy

Test	Before chemotherapy	15th day after the first cycle of chemotherapy	15th day after the second cycle of chemotherapy	Two months after initiating chemotherapy
Hemoglobin (gr/dL)	6.1	7.9	8.5	8.4
Total bilirubin level (mg/dL)	2.43	1.9	1.09	0.99
Direct bilirubin administration (mg/dL)	0.7	0.6	0.37	0.25
Platelet (x10^3 cell)	26	79	106	140
INR	2	1.6	1.54	1.35
LDH (U/L)	934	693	383	266
D-dimer (µg/L)	35,200	22,650	10,800	
Fibrinogen (mg/dL)	99.4	99.7	116	116

LDH: Lactate dehydrogenase, INR: International normalization ratio

Ethics

Informed Consent: It was not necessary.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., Concept: F.Y., Design: N.A., Data Collection or Processing: B.K., Analysis or Interpretation: F.Y., Literature Search: E.A., Writing: B.K.

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Letter to the Editor

Squamous Cell Lung Cancer Presenting with Initial Rare Paraneoplastic Hematological Findings

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Keywords: Lung cancer, paraneoplastic hematological findings, squamous cell carcinoma

Dear Editor,

Hematologic paraneoplastic syndrome, known as paraneoplastic leukemoid reaction (PLR), has been associated with several solid tumors and is classified in the literature as having more than 50,000 leukocytes/mm^3 [1]. Although rare, solid tumors presenting with eosinophilia and thrombocytosis have been reported in the literature [2,3]. We report a 71-year-old male patient who was a former smoker (41 pack-years) diagnosed with stage IV lung cancer. He was admitted to the endocrinology outpatient clinic with fatigue and dry mouth. The patient was referred to the hematology outpatient clinic due to leukocytosis (27.950 mm^3), eosinophilia (4.320 mm^3), thrombocytosis (742.000 mm^3), and anemia (11 g/dL) in laboratory tests. Due to the patient's clinical and laboratory findings, bone marrow aspiration and biopsy were performed. Bone marrow aspiration revealed bone marrow metastasis and hypereosinophilia (Figure 1). Because of the presence of metastases in bone marrow aspiration, the patient underwent computed tomography (CT) of the neck, chest, abdomen, and pelvis with intravenous contrast solution. In the thorax CT of the patient, there was a pleural effusion measuring 23 mm was noted in the thickest part of the right hemithorax. A mass atelectasis complex was observed in the lower lobe of the right lung with a size of 95x60 mm and an invasive appearance in the posterior mediastinum. The right lower lobe bronchus was completely obliterated (Figure 2). Sampling with thoracentesis and bronchoscopic biopsy performed on the patient. He was diagnosed with non-small-cell carcinoma and squamous cell carcinoma lung cancer (Figure 3). PLR is an explanation for hyperleukocytosis in solid tumors. However, this is still an exclusion criteria for diagnostic paraneoplastic hematological syndromes, which are usually asymptomatic and often present either at diagnosis or during disease progression, typically in advanced disease [4]. It is a possible indicator of disease progression and response to therapy because it is known to be linked to poor prognosis and clinical outcomes [4]. As a result, it should be kept in mind that patients presenting with leukocytosis, thrombocytosis, and eosinophilia may have paraneoplastic findings due to not only hematological malignancies but also solid tumors.

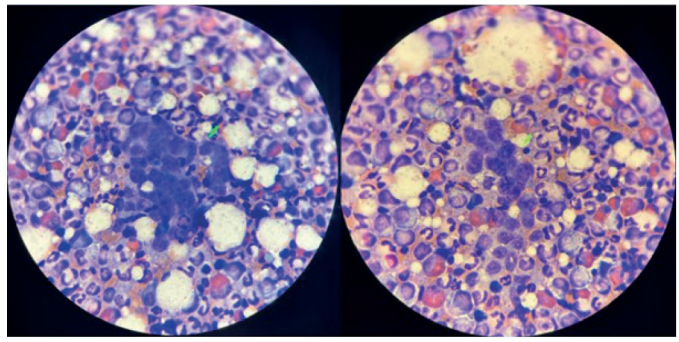

Figure 1. Squamous carcinoma cells clustered together with hematopoietic precursor cells, bone marrow aspiration

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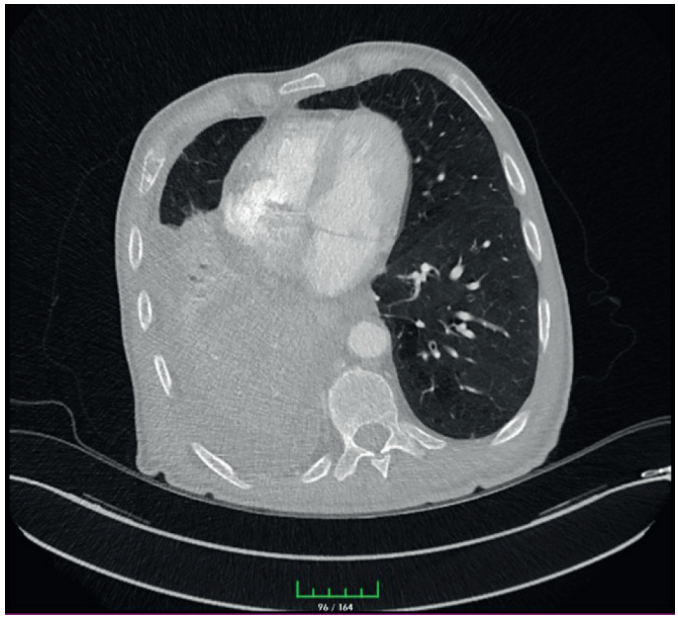

Figure 2. A mass atelectasis complex in the lower lobe of the right lung with a size of 95x60 mm

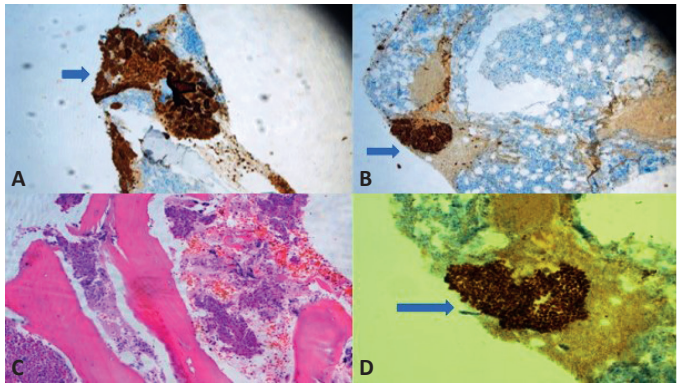

Figure 3. A, B) Tumor infiltration, immunohistochemical staining of pan-cytokeratin 10x10, C) Tumor infiltration on the upper side of the hematoxylin-eosin stained slide 10x10, D) P40 immunohistochemical staining 20x10

Ethics

Informed Consent: Informed consent was obtained from all patients included in the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: C.U., Concept: R.Ç., Design: R.Ç., Data Collection or Processing: C.U., Analysis or Interpretation: R.Ç., Literature Search: R.Ç., Writing: R.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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2024 Referee Index

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