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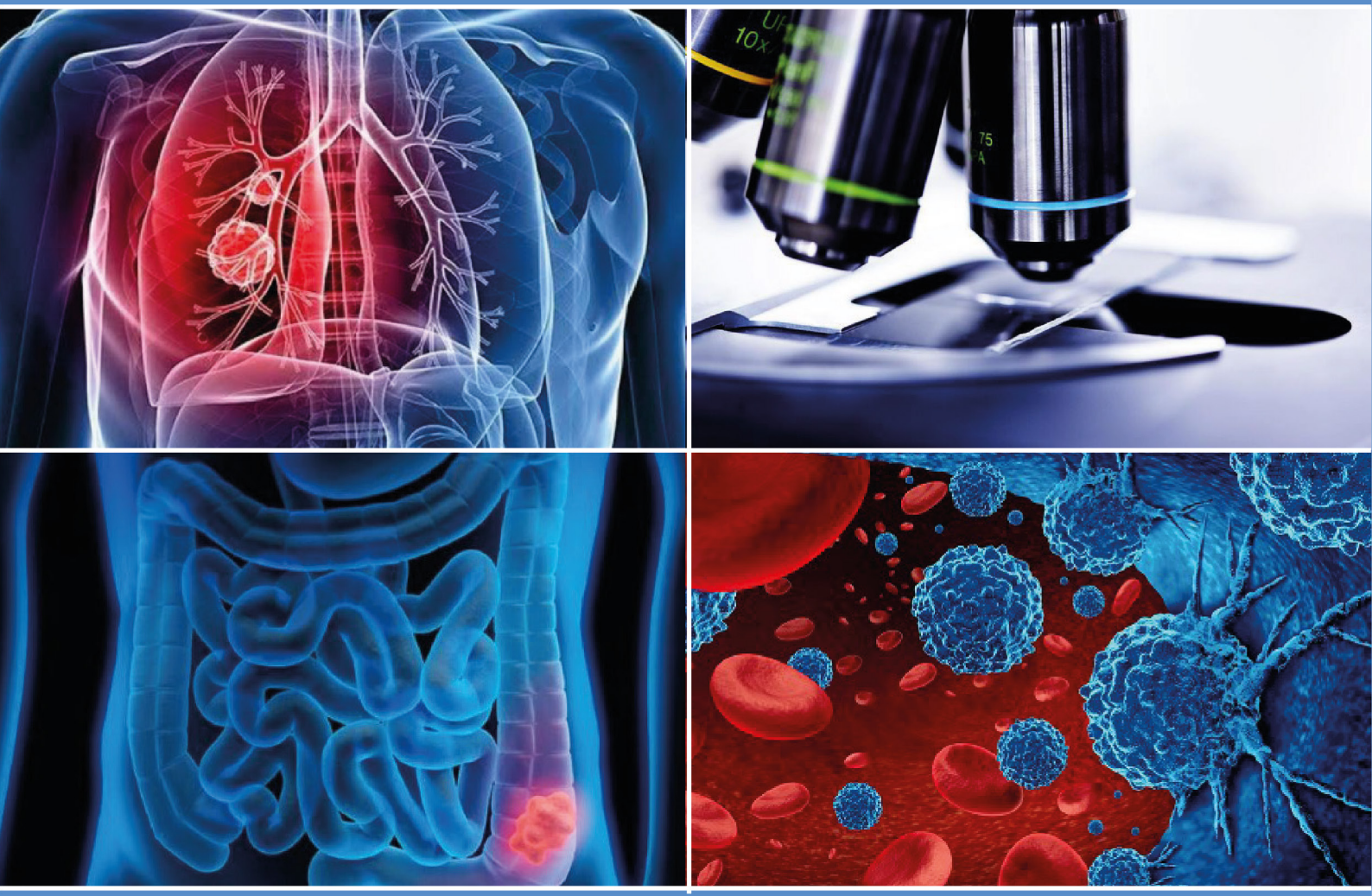

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CONTENTS

Volume: 3 Issue: 3 Year: 2025

ORIGINAL ARTICLES

REVIEW

CASE REPORT

Journal of Current Hematology & Oncology Research

Original Article

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Evaluation of treatment regimens and prognostic factors in primary central nervous system lymphomas

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ABSTRACT

Aims: The aim of this study was to determine the clinicopathological findings of patients with primary central nervous system lymphoma (PCNSL) as real-life data, examine their treatment approaches, and define the prognostic factors.

Methods: Eighty-four patients who presented with a diagnosis of PCNSL between January 2008 and July 2021 were included in this study. The treatments received by the patients and their survival outcomes were retrospectively analyzed.

Results: The median age at diagnosis was 55 (18-80 years). The median progression-free survival (PFS) was 16.8 months (12.4-21.2 months), while the median overall survival (OS) was 18 months (13.7-22.4 months) in all patients. The most commonly used chemotherapy was high-dose methotrexate based regimens, which were preferred in 68 (81%) patients. Objective response rate and disease control rate were 75% and 83.3%, respectively. Consolidation therapy was an independent prognostic factor for PFS (HR: 0.32, 95% CI, 0.18-0.55, p<0.001). There were 42 (50%) patients who had been treated by consolidation therapy. Patients who received consolidation therapy were observed to have a 67% reduction in mortality compared to those who did not (HR: 0.33, 95% CI, 0.19-0.57, p<0.001). Also, high risk in Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model was found to be associated with a 2-fold increase in mortality compared to the good risk group (HR: 2.04, 95% CI, 1.02-3.56, p=0.022). Toxicity of any grade was observed in 78 (92.9%) patients. There were 3 (3.6%) patients who died due to treatment toxicity.

Conclusion: Consolidation therapy was found to be an independent predictive factor for both OS and PFS in PCNSL. In addition, high risk class according to MSKCC prognostic model was found to be associated with increased mortality.

Keywords: Primary central nervous system lymphoma, treatment, chemotherapy, radiotherapy, prognosis

INTRODUCTION

Primary central nervous system lymphomas (PCNSL) is a type of lymphoma confined to the brain, spinal cord, cerebrospinal fluid, and vitreoretinal space, without evidence of systemic involvement.[1] It constitutes 4% to 6% of all extranodal lymphomas and makes up 4% of newly diagnosed malignant brain cancers.[2] The median age at diagnosis 65 years, even though PCNSL can be encountered at any age. Individuals who are immunocompromised, such as those with HIV/AIDS or those who have undergone organ transplants, are at a higher risk for Epstein-Barr virus-related PCNSL.[1]

The predominant histopathologic subtype of PCNSL is diffuse large B-cell lymphoma (DLBCL), occurring in over 90% of cases. The primary signs and symptoms vary based on the tumor's neuroanatomic location. Most patients present with cognitive, motor, or constitutional symptoms.[3] PCNSL most commonly occurs as a single supra-tentorial brain lesion. It is most commonly located in the frontoparietal lobe, but can also be found in the temporal lobe, the basal ganglia and the corpus callosum, in order of prevalence.[4]

Unlike other brain tumors, PCNSL are highly responsive to chemotherapy and radiotherapy, yet have a high recurrence rate. In general, the prognosis for patients with PCNSL is poor, with an approximate 5-year survival rate of 28%. Although there is still no standard treatment option for first-line treatment, high-dose methotrexate-based (HD-MTX) chemotherapy regimens are generally recommended.[5]

This study aimed to evaluate the demographic and clinical characteristics, as well as the laboratory findings of patients diagnosed with PCNSL using real-life data, analyze treatment strategies, and identify prognostic factors.

METHODS

Ethics

The study was conducted with the permission of the Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 20.04.2022, Decision No: 2022/4-28). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This research included 84 individuals diagnosed with PCNSL at three oncology centers located in Turkiye, spanning from January 2008 to July 2021. Eligible participants were adults aged 18 and above, with a confirmed diagnosis based on either histological or cytological evidence. Exclusion criteria encompassed patients who were HIV positive, had a history of immunosuppressive disorders, exhibited clinical or laboratory signs of systemic lymphoma, or had previously used steroids. The study gathered extensive laboratory, clinical, and pathological data, including performance status (assessed by the Eastern Cooperative Oncology Group, ECOG), age, gender, tumor location, various treatment strategies, progression-free survival (PFS), overall survival (OS), and any reported adverse effects. Diagnostic imaging for staging was performed using either computed tomography (CT) or positron emission tomography (PET)-CT. To predict patients outcomes, the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scoring system was applied, which evaluates two key factors: age and the Karnofsky Performance Status scale. Based on this, patients were classified into three risk categories: good risk (age <50 years), medium risk (age ≥50 years with a Karnofsky score ≥70), and high risk (age ≥50 years with a Karnofsky score <70).[6]

Treatment Protocol

The treatment protocol consisted of an initial phase of chemotherapy, followed by consolidation with either radiotherapy or stem cell transplantation. Whole brain radiotherapy (WBRT) was administered at a dose of 40 Gy, while HD-MTX was used at a dosage of ≥3 g/m^2. To evaluate safety and adverse effects, toxicity levels were measured according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Response Assessment

Post-treatment response was systematically evaluated through magnetic resonance imaging (MRI), focusing on tumor characteristics such as location, quantity, and size, as well as changes in these parameters following therapy. A complete response (CR) was classified by the full resolution of lymphoma, whereas a partial response (PR) was identified by a reduction of at least 50% in tumor size. Progressive disease (PD) was diagnosed when tumor size increased by more than 25%, or new lesions appeared, while stable disease (SD) was noted when tumor size decreased by less than 50%, but no progression was observed.[7] The objective response rate (ORR) was calculated by combining CR and PR rates, whereas the disease control rate (DCR) included CR, PR, and SD.

Statistical Analysis

Data analysis was performed using SPSS version 24.0 (IBM Corporation, Armonk, New York, USA). Chi-square tests (either Pearson's or Fisher's exact) were used to compare categorical variables. Survival data, including OS and PFS, were evaluated using the Kaplan-Meier method. OS was calculated from the diagnosis date to either death or the last known follow-up. PFS was calculated from the diagnosis date to the first occurrence of disease progression, death, or the most recent follow-up, whichever came first. The log-rank test was applied to assess survival differences. Additionally, multivariate analysis was carried out using backward stepwise selection and Cox regression to identify independent survival predictors. In the present study, a confidence interval of 95% was established, and a two-tailed significance p value of 0.05 was accepted.

RESULTS

Demographic and Clinical Data

The median age at diagnosis was 55 years (18–80), and 46 patients (54.8%) were male. ECOG PS was ≥2 in 37 (44%) patients and 29 (34.5%) patients had comorbidities. The most common comorbidity was hypertension, seen in 65.5% (19/29) of patients, followed by diabetes mellitus with 55.2% (16/29). The most frequently observed histological subtype was DLBCL, found in 75 patients (89.3%). According to the MSKCC prognostic model, 26 (31%) patients had high-risk disease (class 3). There were 17 (20.2%) patients with hemoglobin <12 g/dl and 30 (35.7%) patients had low albumin levels (≤3.5 g/dl). Forty-three (51.2%) patients had a history of surgery, and gross total resection had been performed in 26 (60.5%) of these patients. Sixty-eight (81%) patients had been treated by HD-MTX-based chemotherapy. Lumbar puncture had been done in 30 (35.7%) patients, CSF cytology was positive in 10 (33.3%) of these patients. Intrathecal treatment was administered to 10 (11.9%) patients. The other significant characteristics of the patients are outlined in **Table 1**.

The most common localization of lymphomas was frontal lobe (n=20, 23.8%). Deep localization was detected in 20 (23.8%) patients. Headache (n=53, 63.1%) and focal neurologic deficit (n=50, 59.9%) were the most common presenting symptoms. B symptoms were observed in 11 patients (13.1%). Tumor localization and symptoms have been summarized in **Table 2**.

Treatment

Radiation therapy was the initial therapy in 10 (11.9%) patients. Rituximab was used in 26 (31%) patients. Forty (47.6%) patients received HD-MTX alone, while HD-MTX+rituximab regimen, being the second most frequent treatment, was administered to 10 (11.9%) patients. The

Table 1. Baseline demographic and clinical characteristics

Characteristics	Median	Range	No	%
Age (years)	55	18-80		
Age >60 years			27/84	32.1
Male sex			46/84	54.8
Comorbidity			29/84	34.5
Histopathological subtypes				
Diffuse large B-cell lymphoma			75/84	89.3
Other B-cell lymphomas			6/84	7.1
T-cell lymphomas			1/84	1.2
Unclassified			2/84	2.4
MSKCC prognostic score				
Good risk			29/84	34.5
Intermediate risk			29/84	34.5
High risk			26/84	31.0
Treatments				
Surgery			43/84	51.2
Gross total resections			26/43	60.5
HD-MTX-based chemotherapy			68/84	81.0
Rituximab			26/84	31.0
Lumbar puncture			10/30	33.3
Intrathecal therapy			10/84	11.9
Laboratory findings				
LDH level ≥248 U/L			50/84	59.5
Lymphocyte count <1 x10^9 /L			14/84	16.7
Hemoglobin level <12 g/dl			17/84	20.2
Platelet count <150 x10^9 /L			5/84	6.0
Serum albumin level ≤3.5 g/dl			30/84	35.7
β2 microglobulin level ≥2.2 mg/L			11/57	19.3
Lymphocyte count (x10^9 /L)	1.6	0.3-8.8		
Hemoglobin level (g/dL)	13.45	8.7-17.9		
Platelet count (x10^9 /L)	254.50	121-631		
Serum albumin level (g/dl)	3.90	2.10-5.01		
β2 microglobulin level (mg/L)	1.57	0.73-5.78		

ECOG PS: Eastern Cooperative Oncology Group Performance Status, HD-MTX: High dose methotrexate, LDH: Lactate dehydrogenase, MSKCC: Memorial Sloan-Kettering Cancer Center

Table 2. Tumor location and presentation of the symptoms

	n=84 (%)
Tumor location	
Frontal	20 (23.8)
Parietal	11 (13.1)
Temporal	9 (10.7)
Occipital	4 (4.8)
Multifocal	16 (19)
Cerebellum	9 (10.7)
Basal ganglia and thalamus	6 (7.2)
Corpus callosum	4 (4.8)
Brainstem	1 (1.2)
Leptomeningeal	3 (3.6)
Ocular involvement	1 (1.2)
Deep lesions[a]	20 (23.8)
Symptoms	
B symptoms	11 (13.1)
Headache	53 (63.1)
Focal neurological deficit	50 (59.9)
Ataxia	43 (51.2)
Decreased consciousness	37 (44)
Nausea/vomiting	25 (29.8)
Seizures	24 (28.6)
Visual symptoms	20 (23.8)

[a] Deep brain involvement:corpus callosum, basal ganglia, periventricular region, brainstem, and/or cerebellum

Table 3. Treatment options and response to first-line therapy

Initial treatment regimen	n=84 (%)
WBRT	10 (11.9)
HD-MTX	40 (47.6)
HD-MTX+rituximab	10 (11.9)
HD-MTX+Ara-C+rituximab	5 (6.0)
HD-MTX+TMZ+rituximab	5 (6.0)
HD-MTX+IFOS	4 (4.8)
R-CHOP	4 (4.8)
HD-MTX+Ara-C	3 (3.6)
Ara-C	1 (1.2)
HD-MTX+Ara-C+rituximab+thiotepa	1 (1.2)
TMZ+rituximab	1 (1.2)
Consolidation treatment	**n=42 (%)**
WBRT	32 (76.2)
HD-CT with ASCT	3 (7.1)
Ara-C	2 (4.8)
HD-MTX+Ara-C	2 (4.8)
R-CHOP	2 (4.8)
HD-MTX	1 (2.4)
Best response	**n=84 (%)**
CR PR SD PD	40 (47.6) 23 (27.4) 7 (8.3) 14 (16.7)
ORR	63 (75.0)
DCR	70 (83.3)

Ara-C: Cytarabine, ASCT: Autologous stem cell transplantation, HD-MTX: High-dose methotrexate, HD-CT: High-dose chemotherapy, IFOS: Ifosfamide, R: Rituximab, TMZ: Temozolomide, WBRT: Whole brain radiotherapy, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Overall response rate (CR±PR); DCR: Disease control rate (CR±PR±SD)

median number of induction chemotherapy cycles was 4, ranging from 1 to 13. There were 42 (50%) patients who had been treated by consolidation therapy. The most common consolidation treatment was radiotherapy (in 32 (76.2%) patients). Autologous stem cell transplantation (ASCT) after high-dose chemotherapy was performed in 3 patients (7.1%). The median number of consolidation chemotherapy cycles was 3 (1-6). ORR and DCR were 75% and 83.3%, respectively. ORR was 70% in those receiving HD-MTX only and 76.9% in those receiving rituximab-based treatment. No statistically significant difference was found between the groups regarding the ORR for both treatments (p=0.601 and p=0.785, respectively). Treatment regimens and response rates had been summarized in **Table 3**.

Survival and Prognostic Factors

Progression developed in 56 (66.7%) patients, and 29 (34.5%) patients received treatment after progression. Sixty-five (77.4%) patients were deceased at the time of analysis. Median follow-up was 15.8 (2.1-178) months. The median PFS and OS were 16.8 months (12.4-21.2), and 18 months (13.7-22.4). The

2-year PFS and OS rates were 39.3% and 40.8%, respectively. At the same time the 5-year PFS and OS rates were 26% and 25%, respectively.

Univariate analyses revealed that median PFS was 24 months in patients receiving consolidation therapy while 5.7 months in patients who did not receive consolidation (p<0.001). Also, PFS was found to be significantly longer in patients who received rituximab-based treatment regimens than those who did not (24.2 vs 11.9 months, respectively, p=0.020) (**Figure 1**). Patients with high risk according to MSKCC prognostic model had lower OS than patients with low risk patients (8.5 vs. 26.4 months, respectively, p=0.013). OS was found to be shorter in patients with hemoglobin <12 g/dl and albumin levels below 3.5 g/dl compared to those with higher levels (p=0.051 and p=0.040, respectively). OS was also significantly longer in patients who received consolidation therapy with 24 months, whereas it was 8.5 months in those who did not (p<0.001). In addition, patients who received rituximab-based therapy were found have longer OS than those who did not (33.3 vs. 15.3 months, respectively, p=0.037) (**Figure 2**). **Table 4** provides a summary of the univariate analysis results for PFS and OS.

Multivariate analyses for prognostic factors revealed that consolidation therapy was an independent prognostic factor for PFS (HR: 0.32, 95% CI, 0.18-0.55, p<0.001). Patients who received consolidation therapy were observed to have a 67% reduction in mortality compared to those who did not (HR: 0.33, 95% CI, 0.19-0.57, p<0.001). Also, high risk in MSKCC prognostic model was found to be associated with a 2-fold increase in mortality compared to the good risk group (HR: 2.04, 95% CI, 1.02-3.56, p=0.022). The results of multivariate analyses for PFS and OS are summarized in **Table 5**.

Toxicity

Toxicity of any grade was observed in 78 (92.9%) patients. Dose reduction was required in 20 (23.8%) patients. A total of 52 patients (61.9%) successfully completed the prescribed treatment regimen. There were 3 (3.6%) patients who had died due to treatment toxicity. The most common grade 1 adverse event was anemia in 30 (35.7%) patients, followed by elevated transaminases in 29 (34.5%) patients. The second most common grade 1 hematological toxicity was thrombocytopenia in 27 (32.1%) patients. Mild nausea and vomiting (grade 1) were experienced by 26 patients, accounting for 31% of the total patient population. The

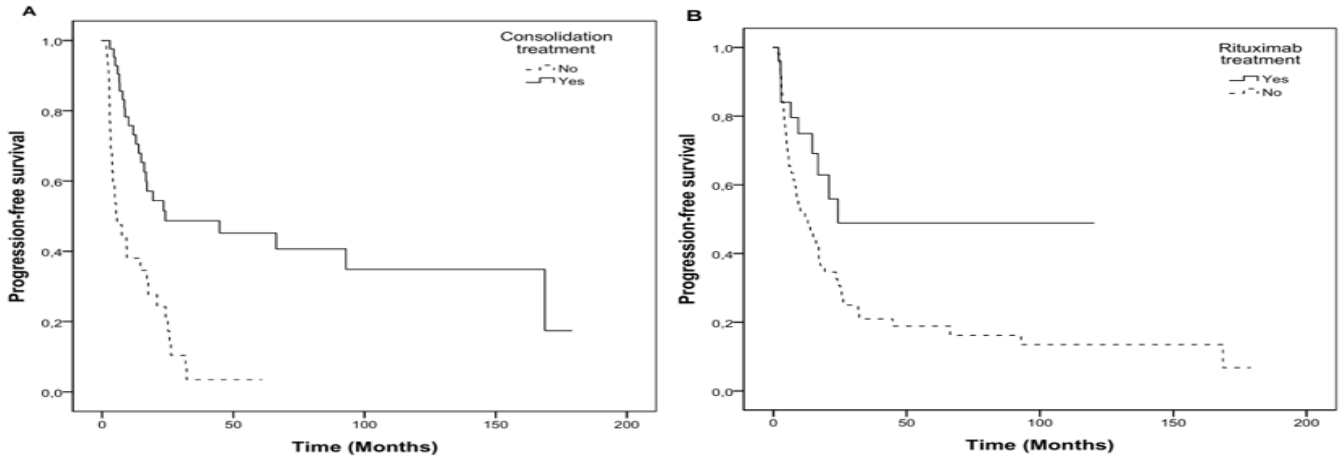

Figure 1. Kaplan–Meier curves of progression-free survival according to consolidation treatment (**A**) and rituximab treatment (**B**)

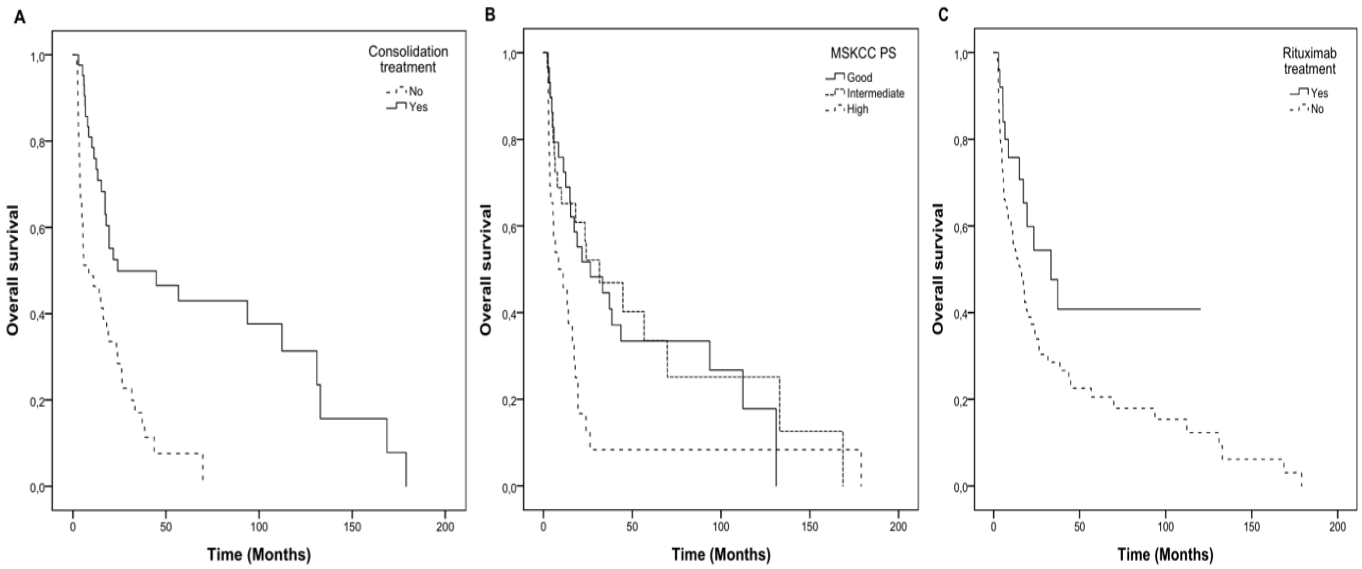

Figure 2. Kaplan–Meier curves of overall survival according to consolidation treatment (**A**), MSKCC prognostic model (**B**), and rituximab treatment (**C**)
MSKCC: Memorial Sloan-Kettering Cancer Center

Table 4. Univariate analysis of prognostic factors associated with progression-free survival and overall survival

Variables (n=84)	PFS HR (95% CI)	p value	OS HR (95% CI)	p value
Age >60 years vs ≤60 years	1.37 (0.77-2.44)	0.280	1.45 (0.85-2.46)	0.166
Gender Male vs female	1.11 (0.66-1.87)	0.689	1.42 (0.85-2.35)	0.172
ECOG PS ≥2 vs 0-1	1.21 (0.71-2.07)	0.480	1.61 (0.98-2.63)	0.060
Comorbidity Yes vs no	0.92 (0.53-1.60)	0.776	1.01 (0.60-1.70)	0.961
MSKCC prognosis score Intermediate risk vs good risk High risk vs good risk	 1.01 (0.54-1.87) 1.47 (0.75-2.87)	0.445 0.981 0.255	 0.97 (0.52-1.80) 2.14 (1.17-3.93)	0.015 0.923 0.013
LDH elevated vs normal	0.98 (0.56-1.70)	0.939	0.92 (0.54-1.55)	0.741
Lymphocyte <1x10^9/L vs ≥1 x10^9/L	1.32 (0.62-2.81)	0.467	1.64 (0.83-3.27)	0.153
Hemoglobin ≥12 g/dl vs <12 g/dl	0.57 (0.30-1.08)	0.086	0.54 (0.29-1.00)	0.051
Serum albumin level >3.5 g/dl vs ≤3.5 g/dl	0.65 (0.37-1.12)	0.123	0.58 (0.34-0.97)	0.040
β2 microglobulin ≥2.2 mg/L vs <2.2 mg/L	1.08 (0.44-2.63)	0.864	1.70 (0.76-3.77)	0.193
Surgery Subtotal resections vs gross total resections	0.66 (0.30-1.47)	0.317	0.57 (0.28-1.25)	0.171
Initial treatment others vs HD-MTX-based chemotherapy	1.6 (0.87-2.94)	0.130	1.67 (0.95-2.96)	0.077
Rituximab Yes vs no	0.45 (0.24-0.88)	0.020	0.52 (0.28-0.96)	0.037
Consolidation treatment Yes vs no	0.29 (0.17-0.52)	<0.001	0.34 (0.20-0.58)	<0.001
Deep lesions Yes vs no	0.76 (0.41-1.42)	0.392	0.69 (0.39-1.23)	0.211
B symptoms Yes vs no	1.19 (0.58-2.47)	0.621	0.82 (0.36-1.72)	0.592

CI: Confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HD-MTX: High-dose methotrexate, HR: Hazard ratio, LDH: Lactate dehydrogenase, MSKCC: Memorial Sloan-Kettering Cancer Center, OS: Overall survival, PFS: Progression-free survival

Table 5. Multivariate analysis of prognostic factors associated with progression-free survival and overall survival

	Progression-free survival		Overall survival	
Variables (n=84)	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
MSKCC prognostic score Intermediate risk vs good risk High risk vs good risk	 	 	 0.87 (0.48-1.78) 2.04 (1.02-3.56)	0.015 0.661 0.022
Hemoglobin ≥12 g/dl vs <12 g/dl	0.65 (0.31-1.35)	0.253	0.79 (0.38-1.64)	0.529
Serum albumin level >3.5 g/dl vs ≤3.5 g/dl	0.83 (0.43-1.60)	0.593	0.73 (0.39-1.35)	0.320
Initial treatment Others vs HD-MTX-based chemotherapy	0.92 (0.47-1.8)	0.817	0.91 (0.47-1.77)	0.792
Rituximab Yes vs no	0.54 (0.27-1.05)	0.069	0.59 (0.31-1.12)	0.108
Consolidation treatment Yes vs no	0.32 (0.18-0.55)	<0.001	0.33 (0.19-0.57)	<0.001

CI: Confidence interval, HD-MTX: High-dose methotrexate, HR: Hazard ratio, MSKCC: Memorial Sloan-Kettering Cancer Center

most common grade 2 toxicity was nausea in 33 (39.3%) patients, followed by anemia in 30 (35.7%) patients, and elevated transaminase levels in 16 (19%) patients. The most common grade 3 toxicity was elevated transaminase levels in 10 (11.9%) patients, followed by anemia (n=8, 9.5%) and thrombocytopenia (n=8, 9.5%). The most frequent grade 4 adverse event was neutropenia, observed in 20 patients (23.8%), while grade 4 febrile neutropenia occurred in 6 patients (7.1%). Thrombocytopenia was the second most common grade 4 toxicity, observed in 14 (16.7%) patients. Data on treatment toxicity are summarized in Table 6.

Table 6. Toxicities during treatment

Toxicity	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea	26 (31)	33 (39.3)	3 (3.6)	1 (1.2)
Vomiting	26 (31)	8 (9.5)	3 (3.6)	1 (1.2)
Diarrhea	9 (10.7)	4 (4.8)	1 (1.2)	1 (1.2)
Mucositis	15 (17.9)	5 (6.0)	5 (6.0)	4 (4.8)
Neutropenia	8 (9.5)	5 (6.0)	7 (8.3)	20 (23.8)
Thrombocytopenia	27 (32.1)	8 (9.5)	8 (9.5)	14 (16.7)
Anemia	30 (35.7)	30 (35.7)	8 (9.5)	1 (1.2)
Sensory neuropathy	8 (9.5)	2 (2.4)	1 (1.2)	0
Nephrotoxicity	11 (13.1)	4 (4.8)	6 (7.1)	0
Elevated transaminases	29 (34.5)	16 (19.0)	10 (11.9)	6 (7.1)
Hyperbilirubinaemia	9 (10.7)	3 (3.6)	2 (2.4)	1 (1.2)
Febrile neutropenia	9 (10.7)	2 (2.4)	3 (3.6)	6 (7.1)
Pneumonitis	1 (1.2)	0	1 (1.2)	0

DISCUSSION

In this study, we evaluated the clinicopathological characteristics, treatment regimens and their clinical outcomes, toxicity profile and prognostic factors in PCNSL. The median age at diagnosis was relatively younger compared to the literature and patients were mostly male. Headache and neurological deficits were the most frequently reported presenting symptoms. The most common tumor location was the cerebral hemisphere. Upfront treatment was most commonly initiated with HD-MTX-based chemotherapy regimens, cranial radiation was the most common consolidation treatment. Consolidation therapy was determined to be an independent factor influencing both

PFS and OS. In addition, high risk class according to MSKCC prognostic model was found to be associated increased mortality compared to the good prognostic class. The most common grade 1 and 2 side effects were nausea, vomiting, anemia, thrombocytopenia and elevated transaminases, while the most commonly observed grade 3 and 4 side effects, as expected were neutropenia, thrombocytopenia and elevated transaminases.

PCNSL is a type of extranodal non-Hodgkin lymphoma. Its incidence increases with age and varies according to gender.[8] A retrospective series reported that the median age at diagnosis was 58 with male predominance.[9] In our previous analysis lymphoma was found to be 10 years younger than western world.[10] In contrast to systemic lymphomas, B symptoms are less common. About 50% to 70% of patients present with focal neurological deficits. Symptoms of increased intracranial pressure are seen in one third of patients.[1,4] The lesions are often located in the cerebral hemisphere. In our study, male predominance among demographic characteristics, symptoms and lesion locations were consistent with the literature, and the patients were observed to be diagnosed at a relatively younger age with a median age of diagnosis of 55 years.

Treatment of PCNSL consists of combination induction chemotherapy regimens containing HD-MTX and consolidation treatments including radiotherapy and high-dose chemotherapy rescued by ASCT.[1,11] Limited drug penetration to central nervous system due to the blood-brain barrier (BBB), concerns about radiotherapy-induced neurotoxicity, and short duration of remission despite high response rates challenges the therapeutic decision-making process.[12] In addition, its rare incidence limits the number of randomized studies, and standard treatment is still to be determined. Therefore, issues including the role of surgery, dosing of methotrexate, optimal combinations, addition of rituximab treatment, number of consolidation chemotherapy cycles and salvage treatment approach in relapsed disease remain unclear.

In the past, the role of surgery in PCNSL was limited to biopsy, except for large masses leading to increased intracranial pressure and signs of herniation.[13] Since the disease is highly sensitive to chemotherapy and radiation therapy, surgical resection was believed to pose an unnecessary risk. Also, surgical resection was thought to be impractical since 65% of the lesions involved deep brain structures and 44% of the lesions were multifocal. In their 2012 study, Weller et al.[14] suggested a re-evaluation of the position that surgery has no prognostic role. A few subsequent studies reported that surgical resection may have certain benefits for some patients.[15,16] However, there are also contradictory studies reporting that resection has no OS or PFS benefit.[17] In our study, surgical treatment was found not to be improve PFS or OS. The cause of this condition may be due to the different and probably incomplete surgical approach. The role of surgical resection in treatment is still unclear and there is no clear consensus.

Standard chemotherapeutic agents used for the treatment of systemic lymphomas have not proven to be effective enough in PCNSL, possibly due to poor penetration from the BBB. Methotrexate penetrates the BBB at doses above 1.5 g/m^2 and reaches cytotoxic concentrations in the CSF. Different drugs have been used in combination with HD-MTX to enhance response rates and improve survival. The ORR with MTX as single agent and combination of MTX with cytarabine (ARA-C) was found to be 40% and 69%, respectively.[18] In another study, HD-MTX was compared with rituximab plus HD-MTX and the ORR was reported to be 60% and 89%, respectively. In patients receiving only HD-MTX, PFS was 4 months and OS was 16.3 months.[19] In the combination of temozolomide-MTX and rituximab, the ORR was 66% and the 2-year PFS was 57%.[20] A retrospective analysis reported that the median PFS was 17 months, and the median OS was 37 months in patients receiving HD-MTX-based therapy. Five-year PFS and OS rates were found to be 20% and 35%, respectively.[9] WBRT alone provides an impressive ORR of 90%, however, the responses are not sustained, with a survival of only 12 to 18 months.[21,22] In our study, HD-MTX-based treatment regimen was the most common treatment of choice and the ORR obtained with this regimen was calculated to be 75%. The median PFS was 16.8 months, and the median OS was 18 months across all patients. The two-year PFS rate was 39.3%, while the two-year OS rate was 40.8%. The five-year PFS rate was 26%, and the five-year OS rate was 25%. The survival data in the literature is heterogeneous and our results were consistent with the previously reported studies. Separate analysis could not be performed due to the limited number of patients initially treated WBRT and with combination regimens.

Consolidation treatment approaches can differ and are typically customized based on the patient's age, comorbidities, and response to induction therapy. WBRT is the most commonly used consolidation strategy. An appropriate alternative to WBRT is ASCT combined with high-dose chemotherapy (HDC).[23] In a phase 2 study that implemented WBRT as consolidation after HD-MTX-based induction chemotherapy, radiological response and 3-year OS were shown to be significantly improved in the consolidation arm. However, considerable increases in neurotoxicity have also been reported.[18] In a later phase 3 study, consolidating HD-MTX-based chemotherapy with WBRT improved PFS but this was not reflected in OS.[24] ASCT following more intensive high-dose myeloablative chemotherapy regimens is typically used in younger patients (<70 years) with minimal comorbidities. Recent phase 2 studies involving HDC-ASCT as consolidation therapy have shown higher ORR (>90%) and extended PFS (>74 months).[25-27] However, significant toxicity associated with this regimen should also be kept in mind when considering this treatment approach. Half of the patients in our study population received consolidation therapy, and WBRT was the most common consolidation strategy in concordance with the literature. A comparison could not be made because the number patients receiving non-WBRT treatment regimens was very limited. However, both PFS (24 vs 5.7 months, respectively) and OS (24 vs 8.5 months, respectively) were statistically significantly improved in patients who received consolidation treatment than those who did not ($p<0.001$). In our study, there were many patients who received treatment in different centers and according to previous treatment standards, so the rates of HDC-ASCT as consolidation therapy were low.

The prognostic impact of several factors in PCNSL is controversial. MSKCC prognostic model, the International Extranodal Lymphoma Study Group (IELSG) scoring system, and a new prognostic model using the absolute lymphocyte count use different variables to predict prognosis.[6,28,29] We failed to demonstrate association of PFS and OS with the variables used in IELSG scoring system including age, ECOG PS status, lesion location in deep brain, and lactate dehydrogenase level. This may be related to the small number of our patients. However, in our study, high risk class according to the MSKCC prognostic model was found to be associated with a 2-fold increase in mortality compared to the good prognostic class (p=0.022). Consolidation therapy was an independent prognostic factor for both PFS and OS (p<0.001 for both).

In a study evaluating the effectiveness of HD-MTX, the most common grade 1 adverse events were elevated transaminases (33%), nephrotoxicity (29.8%), and thrombocytopenia (20.2%), while the most common grade 2 adverse events were anemia (49%), elevated transaminases (23.3%), and nephrotoxicity (20.2%).[30] In another study investigating the contribution of adding WBRT to HD-MTX treatment, the authors reported that the most common grade 3-4 side effects were leukopenia (24%), anemia (14%), thrombocytopenia (11%), and elevated transaminases (19%).[24] Toxicity results in our study are consistent with the literature, and the most common side effects were transaminase elevations and hematological side effects. Nephrotoxicity was observed less frequently compared to the literature.

Limitations

Although our study included patients from more than one centre, the retrospective design and the small number of patients were important limitations of our study. Due to the small number of patients, we could not compare the treatment groups separately in all analyzes. Also, since CSF examination could not be performed in all patients, we were not able to evaluate its prognostic significance. We could not obtain data on other detailed pathological prognostic factors, therefore not able to include them in the analyses. The most common consolidation treatment was WBRT, but we could not thoroughly evaluate neurotoxicity due to the study's retrospective design. Despite its limitations, we think that our study will make a significant contribution to the literature by reflecting real-life data and clinical practice as well as evaluating the toxicity findings in PCNSL, which has a low incidence and on which there are limited number of phase 3 studies.

CONCLUSION

As a result, in this study in which we evaluated the clinicopathological features of patients with PCNSL, consolidation therapy was found to be an independent predictive factor for both OS and PFS. In addition, high risk class according to MSKCC prognostic model was found to be associated with increased mortality.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 20.04.2022, Decision No: 2022/4-28).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Ten-year journey with myelofibrosis: real-world data and clinical outcomes from a tertiary care center

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ABSTRACT

Aims: The aim of this study was to document the last decade of experience with primary myelofibrosis (PMF) and provide mature risk-stratified survival data and disease complication estimates.

Methods: This retrospective study included all patients diagnosed with PMF according to World Health Organization criteria between 2009 and 2019 at İstanbul Medipol University. The follow-up period extended until March 2019.

Results: A total of 74 patients (median age 60.5 years, range 30-85) were included, with 35 males (47.3%) and 39 females (52.7%). During the study period, 34 deaths (45.9%), 3 leukemic transformations (4%), and 3 thrombotic events (4.2%) were recorded, including bilateral pulmonary artery thrombosis, cephalic vein thrombosis, and left lower extremity deep vein thrombosis. The median overall survival was 6 years. There was no statistically significant difference in life expectancy between patients treated with ruxolitinib and those receiving other medications (erythropoiesis-stimulating agents, androgens, immunomodulatory agents, cytoreductive drugs such as hydroxyurea, and splenectomy) (Chi-square statistic: 3.5149, p=0.0608). One of the 11 patients treated with ruxolitinib died (9%), while the remaining 10 patients survived (91%).

Conclusion: PMF remains a serious disease with high mortality and morbidity, requiring effective treatment interventions. Despite recent advances, treatment remains unsatisfactory for most patients. Although ruxolitinib, a JAK2 inhibitor, shows promise in managing symptoms, its impact on life expectancy remains unclear, highlighting the need for novel therapeutic strategies and well-designed clinical trials.

Keywords: Myelofibrosis, ruxolitinib, thrombosis, leukemic transformation, JAK2 inhibitor

INTRODUCTION

Primary myelofibrosis (PMF) is a BCR-ABL1–negative myeloproliferative neoplasm of the bone marrow (BM), which is characterized by three situations: clonal myeloproliferation, dysregulated kinase signaling, and the release of abnormal cytokines. MF is a clonal proliferation originating from a pluripotent hematopoietic stem cell.[1] Cytokines and growth factors that are released from the BM trigger fibrosis of the marrow, changes in the stroma and colonization in the extramedullary organs such as the spleen and liver.[2]

Mutations in *Janus kinaz* 2 (JAK2), calreticulin (CALR), MPL and ASXL1, EZH2, IDH1/2, and SFSF2 can be used for molecular prognostication of primary MF (PMF).[3] The discovery of the JAK2 mutation triggered development of molecular targeted therapies for MF. The first oral agent approved for JAK1/2 inhibitor is "ruxolitinib", currently treatment of MF.[4]

Recent studies have highlighted that overall survival in patients with PMF is significantly influenced by risk stratification models such as DIPSS, mutational profiles, transfusion dependency, and the presence of constitutional symptoms. In particular, high-risk patients, as defined by DIPSS or DIPSS-Plus, demonstrate markedly reduced median survival compared to those in lower risk categories. Furthermore, molecular mutations such as JAK2, CALR, and MPL also have prognostic implications. These findings underscore the importance of integrating prognostic scoring and clinical variables in survival analysis of PMF.[15,16]

In this study, it was aimed to present the treatment results of MF patients, to compare the effect of ruxolitinib to the other treatment preferences such as erythropoiesis stimulating agents, androgens, immunomodulatory agents for anemia, cytoreductive drugs or splenectomy in terms of the life expectancy.

METHODS

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.08.2021, Decision No: E-10840098-772.02-4093).

The study included patients diagnosed with MF according to the World Health Organization Criteria between 2009-2019.[5] Clinical and laboratory data of patients, presence of transfusion dependence, driver mutation status, cytogenetic results, presence of constitutional symptoms and palpable splenomegaly, arterial or venous thrombosis before, during, and/or after the definitive diagnosis, presence of fibrotic progression or leukemic transformation, and presence of allogenic stem cell transplantion were recorded and analysed retrospectively. Dynamic international prognostic scoring system (DIPSS) was utilised as risk-stratification method by including age (>65 years), hemoglobin value (<10 g/dl), leukocyte count (>25×10^9/L), circulating blasts (≥1%), and presence of constitutional symptoms in order to classify patients into four risk groups: low, intermediate-1, intermediate-2, and high risk.[6]

Statistical Analysis

While making the statistics of the continuous structure, the mean and standard deviations, minimum and maximum values of the features; While defining categorical variables, n (%) values and 95% Confidence interval values were given. Total survival curves were estimated by the Kaplan-Meier method. Differences according to risk factors were determined by the Log-Rank test (Chi-square statistic) and the Hazard ratio was given at a 95% confidence interval. Time to the event (death) or follow-up time including time (months) were used as variables. The statistical significance level of the data was taken as $p<0.05$. In the evaluation of the data, www.e-picos.com New York software and MedCalc statistical package program were used.

RESULTS

The clinical and laboratory features at the time of diagnosis and follow-up clinical data were shown in Table 1. The median age of 74 patients included in our study was 60.5 (range: 30-85), a total of 35 patients were male (47.3%). The most common underlying disease was PMF with 57 patients (77%), followed by myelodysplastic syndrome/myeloproliferative neoplasm (MDS/MPN) (8 patients, 10.8%). During the follow-up period, a total of 34 patients died (34%). The most common complication during follow-up was thrombotic event and hemorrhage (3 patients for both, 4.2%). The number of patients with a driver mutation was 45 (40.8%), the number of JAK2 positive patients was 9 (26.5%), and the number of triple negative patients was 4 (11.8%). Overall survival was resulted as a mean of 72 months (42-109) (Figure 1).

Table 1. Descriptive statistics

Variable	All patients (n=74)
Age (y), median (range)	60.5 (30-85)
Male sex (number, [%])	35 (47.3)
Underlying diseases (no. [%])	
Polycythemia vera	3 (4.1)
Essential thrombocythemia	5 (6.8)
Chronic myeloid leukemia	1 (1.4)
Myelodysplastic syndrome	8 (10.8)
Primary myelofibrosis	57 (77)
Mortality (no. [%])	34 (45.9)
Thrombotic events (no. [%])	3 (4.2)
Transfusion events (no. [%])	20 (27)
Abnormal karyotype (no. [%])	3 (4.2)
Constitutional symptoms (no.[%])	17 (23)
Hemorrhage (no. [%])	3 (4.2)
Hematoma in spleen (no. [%])	1 (1.3)
Epistaxis (no. [%])	2 (2.7)
Allogeneic hematopoietic stem cell transplantation (no. [%])	2 (2.7)
Driver mutational (no. [%])	45 (60.8)
JAK-2 positive (no. [%])	9 (26.5)
CALR (no .[%])	1 (2.9)
JAK-2 negative (no. [%])	20 (58.8)
Triple negative (no. [%])	4 (11.8)
Overall survival (months), median (range)	72 (42-109)
Hemoglobin (g/dl), median (range)	9.75 (3.8-20)
Platelet (10^3/μL), median (range)	510.11 (4000-222.800)
Leukocyte (10^3/μL), median (range)	9.14 (1420-290000)
Spleen size (mm), median (range)	185 (84-280)
Peripheral blood blast percentage median (range)	2 (0-17)
Echocardiography control (no. [%])	21 (0.28)
Pulmonary hypertension (no. [%])	12 (0.57)

JAk-2: Janus kinaz 2, CALR: Calreticulin

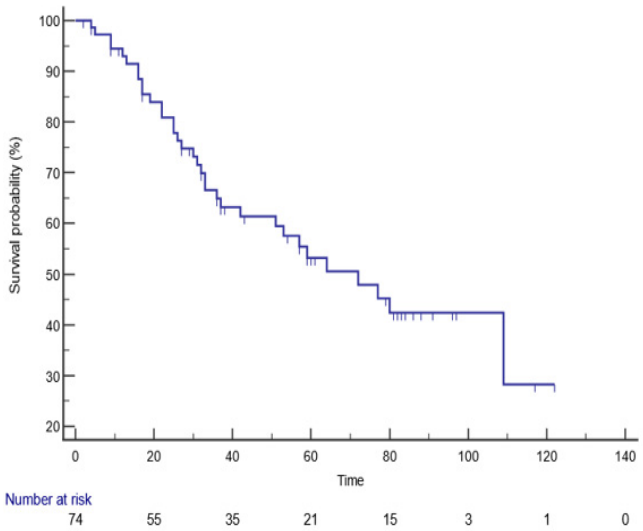

Figure 1. Overall survival of the cohort

Echocardiography control was performed in 21 patients to reveal pulmonary hypertension (PHT). It was normal in 9 patients, 12 patients had PHT (0.57%). The range of resting pulmonary artery systolic pressure was 25 to 70 mmHg above the mean right atrium by echocardiography (**Table 1**).

The DIPSS scores of the patients at the time of diagnosis were shown in **Table 2**. The most common risk score was resulted as "intermediate-2" (30 patients, 44%). The number of patients with a high risk resulted as 5 (8%).

Table 2. DIPSS scores of the cohort

DIPSS score	n	%	95% confidence interval
High	5	8	0.01-0.14
Intermediate-1	24	35	0.24-0.47
Intermediate-2	30	44	0.32-0.56
Low	9	13	0.05-0.21
Total	68	100.0	

DIPSS scores n (%) and 95% CI values in patients, DIPSS: Dynamic international prognostic scoring system, CI: Confidence interval

In the statistical analysis performed considering the overall survival of patients, there was no significant difference between the PMF and other patients (p=0.24). There was no significant difference between patients with a DIPPS score of intermediate-2/high DIPPS and low/intermediate-1 (p=0.38). Considering the treatment subtypes, there was no significant difference between the patients receiving ruxolitinib and others, but the p value was near the statistical significance limit (p=0.06) (**Table 3, Figure 2**).

DISCUSSION

The present study provides experience about PMF, mature risk-stratified survival data and associated complications. We observed several confirmatory as well as novel findings. First, PMF was validated as a disease that is more common in middle or advanced age adults, the median age of diagnosis previously reported slightly higher (67 year old), but we found it to be 60.5 year old.[7] This may reflect increased awareness of the disease and contemporary accessibility to molecular diagnostics, resulting in early diagnosis. Preponderance of PMF in females was confirmed. The driver mutational status was not available in all patients with PMF.

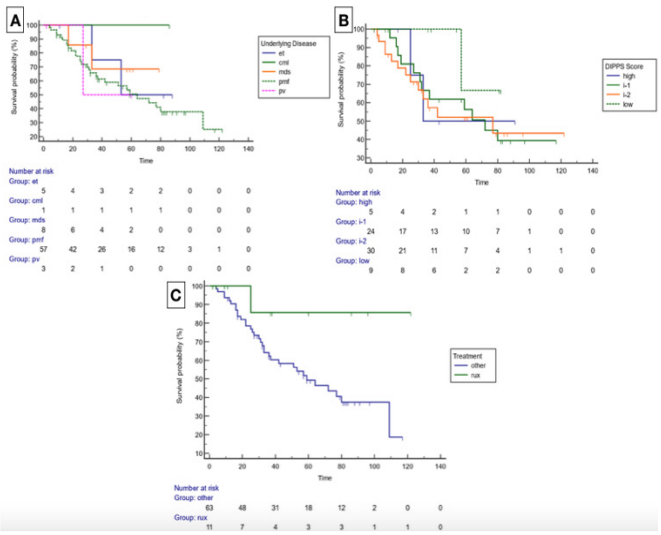

Figure 2. Overall survival curves between subgroups: A. Underlying diseases, B. Initial DIPSS scores, C. Treatment preferences (ruxolitinib and others)
DIPSS: Dynamic international prognostic scoring system

The life curves didn't differ significantly and the underlying disease type such as post chronic myeloid leukemia MF, post-essential thrombocythemia (post-ET MF) and post-polycythemia vera (post-PV MF) had no significant effect on the survival period. In the literature, survival was significantly different among the four risk categories (p<0.001).[6] Median survival was 14.6 years in low-risk, 7.4 years in intermediate-1, 4 years in intermediate-2, and 2.3 years in high risk patients. In our study, DIPSS had no effect on survival; median survival was not reached in low risk, 72 months in intermediate-1, 77 months in intermediate-2, and 33 months in high risk categories. This could be due our limited patients or availability of novel drugs.

Based on the COMFORT-1 and COMFORT-2 clinical trials, treatment discontinuation rate for ruxolitinib (JAK1 and JAK2 inhibitor) was 50% at 3 years and 75% patients did so by 5 years. Resistance and intolerance to ruxolitinib eventually develops and patients relapses. Increased splenomegaly, cytopenias, increased blood transfusion dependence and limiting thrombocytopenia are clinical feature of failure to ruxolitinib therapy.[8] It was not observed any intolerance or failure in our cohort. Neither COMFORT-1 nor COMFORT-2 trials showed benefit on survival. In COMFORT-1 trial, after median follow-up of 149 weeks, survived patients were 42 (27%) versus 54 (35%) (Hazard ratio=0.69, 95% CI=0.46–

Table 3. Comparison of survival curves (Log-rank test) and Hazard ratios with 95% confidence interval

	Non-survivors n (%)	Survivors n (%)	Mean survival (95% CI)	Hazard ratio (95% CI)	Log-rank p value
Underlying disease					
Other	5 (29.41)	12 (70.59)	67.3 (52.4-82.1)	1.63 (0.73-3.64)	0.24
PMF	29 (50.88)	28 (49.12)	67.6 (54.9-80.4)		
DIPSS score					
Low|intermediate-1	13 (39.39)	20 (60.61)	78.3 (62.8-93.8)	1.39 (0.66-2.95)	0.38
Intermediate-2 |high	15 (42.86)	20 (57.14)	71.2 (52.9-89.5)		
Treatment					
Ruxolitinib	1 (9.1)	10 (90.9)	108.1 (82.9-133.3)	2.55 (0.96-6.77)	0.06
Other	33 (52.4)	30 (47.6)	65.6 (54.3-76.8)		

CI: Confidence interval, PMF: Primary myelofibrosis, DIPSS: Dynamic international prognostic scoring system

1.03).[9] In COMFORT-2 trial, after a median follow-up of 151 weeks however, a survival advantage for ruxolitinib versus best available treatment was reported as 29 (20%) versus 22 (30%) (Hazard ratio=0.48, 95% CI=0.28–0.85).[10] Comparison of ruxolitinib to other treatment preferences (erythropoiesis-stimulating agents, androgens, or immunomodulatory agents for anemia, cytoreductive drugs such as hydroxyurea and splenectomy) has no prominent difference on life expectancy; this can be due to low number of cases in the study. From 34 patients with a mortal course, only 1 patient was treated with ruxolitinib and the other 10 patients treated with ruxolitinib were survived (90%). Therefore, further efforts like longer follow-ups or more cases are necessary to improve the results for ruxolitinib.

In the literature, JAK2 mutation was found to be negative as 60-65%, CALR mutation as 20-25%, MPL mutation as 5%, JAK2, CALR or MPL mutation ("triple negative") as 8-10%.[11,12] We were able to analysis 3 patients with abnormal karyotypes, 45 of 74 evaluated patients had a driver mutational status. Nine patients were JAK2 positive (20%), one patient was CALR positive (2%), twenty patients were JAK2 negative (44%) and four patients were triple negative (8%). Mutation rates were similar in our study compared to the literature data.

PHT is a well described complication of myeloproliferative disorders.[13] Lopez-Mattei et al.[14] reported 20 (14%) patients with echocardiographic findings consistent with PHT in a total of 143 patients diagnosed with MF. Older age, male gender, hypertension, hyperlipidemia, coronary artery disease, dyspnea, high hematocrit, high brain natriuretic peptide (BNP) and N-terminal-pro hormone BNP were found to be clinical predictors for PHT. Female gender was protective from PHT (OR=0.21, 95% CI: 0.049–0.90, p=0.035).[14] We found PHT in 12 patients in our cohort. Due to the small number of patients, it was not able to compare these parameters between the subgroups.

Limitations

The major limitations of the study were its retrospective nature and limited patients' data. It was not able to compare parameters statistically between subgroups. Ruxolitinib is a relatively new drug, there is not enough follow-up period to reveal a data.

Our study reinforces the known epidemiologic and clinical characteristics of PMF and highlights several important observations that may inform clinical practice. Notably, our cohort's median age was slightly lower than those reported in broader registries, suggesting earlier diagnosis potentially due to improved molecular diagnostics. While DIPSS risk scores are known to predict prognosis, our data did not show a statistically significant survival difference between risk groups, which may be attributable to the limited sample size or heterogeneity in treatment exposure.

Importantly, our real-world analysis found no significant difference in survival between ruxolitinib and conventional therapies, although the p-value approached significance (p=0.06). This may reflect insufficient statistical power due to the small number of ruxolitinib-treated patients. Interestingly, the absence of ruxolitinib intolerance or discontinuation in our cohort diverges from previous clinical trials, where long-term treatment discontinuation rates were substantial. This discrepancy underscores the necessity for longer follow-up and larger studies to fully assess treatment durability and tolerability.

Additionally, the observed prevalence of PHT was consistent with previous studies. However, due to limited echocardiographic screening and lack of multivariate analysis, its clinical relevance within our cohort remains uncertain.

CONCLUSION

As a result, PMF is a heterogeneous disease with significant morbidity and mortality. Our findings emphasize the need for personalized risk stratification and continued efforts to improve therapeutic outcomes. While ruxolitinib remains a valuable option for symptom management, its effect on survival remains inconclusive in our limited cohort. Prospective, multicenter studies with larger sample sizes and standardized endpoints are essential to determine optimal treatment strategies and long-term outcomes for patients with PMF.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 27.08.2021, Decision No: E-10840098-772.02-4093).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

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Prognostic factors in diffuse large B cell lymphoma: a retrospective analysis from a tertiary center

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ABSTRACT

Aims: This study aimed to evaluate the clinical characteristics and mortality risk factors of patients diagnosed with diffuse large B-cell lymphoma (DLBCL) in our center.

Methods: This cross-sectional study retrospectively analyzed the medical records of 74 DLBCL patients followed at the Hematology Clinic of Van Yüzüncü Yıl University between September 2016 and September 2021. Demographic characteristics, clinical findings, stage, treatments, and mortality-related risk factors were evaluated. Univariate and multivariable logistic regression analyses were performed to identify independent predictors of mortality.

Results: The median age of the patients was 54 years, and 59.5% were male. Of the patients, 29.7% resided in rural areas, and 66.2% were employed. The most common initial presentation was lymphadenopathy (56.8%), followed by B symptoms (43.2%). Regarding disease stage, 32.4% had stage III, 31.1% had stage IV, and 18.9% had bone marrow involvement. The mean International Prognostic Index (IPI) score was 2.07±1.67. R-CHOP was administered to 85.1% of patients, while 14.9% received R-EPOCH, and 5.4% were referred to other centers. Living in a rural area, unemployment, advanced age, presentation with B symptoms, stage IV disease, bone marrow involvement, triple hit lymphoma and higher IPI scores were significantly more common in 25 patients who died (33.8%) compared to 49 patients who survived (66.2%) ($p<0.05$). In multivariable logistic regression analysis, rural residency (OR: 93.706, 95% CI: 1.789–4908.115, $p=0.025$) and higher IPI scores (OR: 18.595, 95% CI: 2.761–125.236, $p=0.003$) were identified as independent risk factors for mortality in DLBCL patients.

Conclusion: This study demonstrated that rural residency and higher IPI scores are independent risk factors for mortality in DLBCL patients. Future multicenter prospective cohort studies with larger sample sizes and broader clinical parameters are needed to better define the risk factors associated with mortality in DLBCL.

Keywords: Lymphoma, large B-cell, diffuse, mortality, prognosis, rural population

INTRODUCTION

Large B-cell lymphomas represent a diverse array of disorders, comprising approximately 30–50% of all cases of non-Hodgkin lymphoma. Among these, DLBCL stands as the most prevalent variant, accounting for over 80% of reported instances.[1] Patients often present with progressive lymphadenopathy or extralymphatic manifestation, and the diagnosis is predominantly confirmed via excisional biopsy. DLBCL is further categorized into molecular subtypes, specifically the germinal center B-cell-like (GCB, 60%) and activated B-cell-like (ABC, 25–30%) classifications. The ABC subtype is linked to a less favorable prognosis and is more frequently encountered in older individuals and those exhibiting extranodal involvement.[1]

For the purposes of staging and evaluating therapeutic response in DLBCL, the Ann Arbor and Lugano classification systems are employed.[2-4] Positron emission tomography-computed tomography (PET-CT) is integral in assessing the overall tumor burden at the time of diagnosis and in monitoring treatment efficacy.[3] The conventional therapeutic strategy consists of immunochemotherapy regimens incorporating rituximab, with the R-CHOP regimen being

the most widely adopted. Nevertheless, patients who exhibit primary or secondary resistance to treatment commonly face a grim prognosis.

The IPI is extensively utilized for prognostic assessment, and in recent years, innovative risk stratification frameworks that integrate biological and genetic markers have been established.[5-8] The etiology of DLBCL is complex and multifactorial, influenced by genetic susceptibility, viral pathogens, and environmental risk factors. Treatment modalities are tailored based on the patient's age, functional status, and the biological subtype of the malignancy.

This study seeks to explore the influence of both traditional prognostic indicators and social determinants, such as living in rural areas, on the prognosis of patients diagnosed with DLBCL, thus examining the correlation between living conditions and disease advancement.

METHODS

The research was sanctioned by the Van Yüzüncü Yıl University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 10.12.2021, Decision No: 2021/13-19). Informed consent was obtained from all participants before the interventions. All procedures adhered to ethical standards and conformed to the principles set forth in the Declaration of Helsinki.

The sociodemographic attributes of the patients (age, gender, residence, occupation), characteristics pertinent to the disease (symptoms at presentation, stage at diagnosis, etiology, presence of genetic markers), IPI score, treatments administered, and clinical outcomes (mortality) were systematically assessed. The Ann Arbor classification was utilized for staging, whereas the IPI was applied for prognostic evaluation.[9,10]

Statistical Analysis

The data analysis was conducted using SPSS version 21.0. Categorical variables were reported as frequencies and percentages, while continuous numerical variables were represented as mean±standard deviation, or median (minimum–maximum) values. The Pearson's Chi-square test facilitated the comparison of categorical variables across groups. The normality of continuous numerical variables was evaluated through the Shapiro-Wilk test. Given that the normal distribution criterion was not satisfied, the Mann-Whitney U test was employed for comparisons between two independent cohorts. To ascertain independent risk factors for mortality, a multivariable logistic regression analysis (enter method) was executed, incorporating parameters that demonstrated statistical significance ($p<0.05$) in univariate assessments. The outcomes were summarized using odds ratios (OR) with 95% confidence intervals (CI). A bar graph was utilized to illustrate the distribution of categorical variables among groups. Statistical significance was established with a p-value <0.05.

RESULTS

In this investigation, a cohort of 74 individuals diagnosed with DLBCL was scrutinized, with a male representation of 59.5% (n: 44) and a mean age of 53.99±16.81 years. Notably, 29.7% of the participants were from rural locales, while 66.2% engaged in occupations yielding income. The predominant clinical manifestations included lymphadenopathy (56.8%) and B symptoms (43.2%). Within the patient population, 32.4% were categorized as stage III, 31.1% as stage IV, and 18.9% exhibited bone marrow infiltration. The average IPI score was recorded at 2.07±1.67. Genetic examinations disclosed double-hit mutations in 47.3% of the subjects and triple-hit mutations in 52.7% (Table 1). Pertaining to therapeutic interventions, 85.1% of the participants underwent R-CHOP treatment, in contrast to 14.9% who received R-EPOCH. During follow-up, it was observed that 33.8% of the individuals died and 66.2% survived. When the risk factors associated with mortality were evaluated, it was found that the patients who died were living in rural areas (60.0%-14.3%, $p<0.001$), unemployed (52.0%-24.5%, $p=0.018$), older age (mean 64.52±15.82%-48.61±14.73%, $p<0.001$), stage IV malignancy (64.0%-14.3%, $p<0.001$), showing bone marrow involvement (40.0% vs. 8.2%, $p=0.001$), having triple hit mutations (76.0% vs. 40.8%, $p=0.004$) and showing high IPI scores (28.0%, all patients with a score of 5 died) ($p<0.001$) (Table 2).

Table 1. Distribution of clinical characteristics of patients

Variables	n (%)
Gender	
Male	44 (59.5%)
Female	30 (40.5%)
Presenting complaint	
Lymphadenopathy	42 (56.8%)
B symptoms	32 (43.2%)
Stage (Ann Arbor)	
I	6 (8.1%)
II	21 (28.4%)
III	24 (32.4%)
IV	23 (31.1%)
Bone marrow involvement	
Absent	60 (81.1%)
Present	14 (18.9%)
Origin	
Germinal center	28 (37.8%)
Non-germinal center	46 (62.2%)
Genetic marker	
Double hit	35 (47.3%)
Triple hit	39 (52.7%)
IPI score	
0	18 (24.3%)
1	13 (17.6%)
2	15 (20.3%)
3	9 (12.2%)
4	12 (16.2%)
5	7 (9.5%)

IPI: International Prognostic Index

Through multivariable logistic regression analysis, residency in rural areas (OR: 93.706; 95% CI: 1.789–4908.115; $p=0.025$) and elevated IPI scores (OR: 18.595; 95% CI:

Table 2. Comparison of patients' clinical characteristics with mortality status

Variables	Exitus (n=25)	Alive (n=49)	p value
Initial complaint			
Lymphadenopathy	9 (36.0%)	33 (67.3%)	0.010
B symptoms	16 (64.0%)	16 (32.7%)	
Stage (Ann Arbor)			
I	0 (0.0%)	6 (12.2%)	<0.001
II	2 (8.0%)	19 (38.8%)	
III	7 (28.0%)	17 (34.7%)	
IV	16 (64.0%)	7 (14.3%)	
Bone marrow involvement			
No	15 (60.0%)	45 (91.8%)	0.001
Yes	10 (40.0%)	4 (8.2%)	
Origin			
Germinal center	6 (24.0%)	22 (44.9%)	0.080
Non-germinal center	19 (76.0%)	27 (55.1%)	
Genetic marker			
Double hit	6 (24.0%)	29 (59.2%)	0.004
Triple hit	19 (76.0%)	20 (40.8%)	
IPI score			
0	0 (0.0%)	18 (36.7%)	<0.001
1	0 (0.0%)	13 (26.5%)	
2	2 (8.0%)	13 (26.5%)	
3	6 (24.0%)	3 (6.1%)	
4	10 (40.0%)	2 (4.1%)	
5	7 (28.0%)	0 (0.0%)	

IPI: International Prognostic Index

2.761–125.236; p=0.003) were identified as independent risk factors contributing to mortality. The treatment modalities employed (R-CHOP and R-EPOCH) along with bone marrow transplantation did not exhibit a statistically significant effect on mortality (p>0.05). All independent risk factors that have an effect on mortality and risk factors that have no effect on mortality are listed in **Table 3**.

Table 3. Independent risk factors for mortality (multivariable logistic regression analysis, enter method)

Variables	OR [95% CI]	p value
Age	0.907 [0.803-1.024]	0.115
Residence (rural)	93.706 [1.789-4908.115]	0.025
Employment status	0.079 [0.004-1.614]	0.099
Chief complaint	2.704 [0.168-43.639]	0.483
Stage (Ann Arbor)	0.568 [0.095-3.389]	0.535
Bone marrow involvement	3.319 [0.095-115.819]	0.508
HIT	0.697 [0.068-7.166]	0.761
IPI score	18.595 [2.761-125.236]	0.003
Constant	3.369	0.787

OR: Odds ratios, CI: Confidence interval, IPI: International Prognostic Index Dependent variable: Mortality status; Nagelkerke R^2: 0.848

DISCUSSION

DLBCL is the most common subtype of non-Hodgkin lymphoma, and its prognosis varies depending on clinical and biological factors. Response rates to the standard R-CHOP regimen range between 50% and 80%, while 20% to 50% of patients experience resistance or relapse.[11] Therefore, early prognostic assessment of the disease is of great importance.

In this study, the mortality rate among DLBCL cases was determined to be 33.8%, which is consistent with previously reported mortality data. Based on disease extent, five-year survival rates have been reported to range between 57% and 74%.[12] The relatively short follow-up period in our study made it challenging to determine a definitive survival rate. Regarding the epidemiological characteristics of the disease, 59.5% of the patients were male. Previous studies have also reported that DLBCL is more frequently observed in males.[13,14] However, no significant association between gender and mortality was identified in our study.

The mean age at diagnosis was calculated as 54 years, which is relatively lower compared to previous studies.[15] Although the patients who died were older, age was not found to be an independent risk factor for mortality. An increase in IPI score was determined to significantly elevate the risk of mortality, independent of other variables (OR: 18.595; 95% CI: 2.761–125.236, p=0.003). Consistent with previous studies, higher IPI scores were confirmed to be associated with lower survival rates.[16]

Regarding the clinical presentation of the disease, the most common presenting symptoms were lymphadenopathy (56.8%) and B symptoms (43.2%). Although B symptoms are more common in dying patients, they have not been identified as an independent risk factor for mortality. Stage IV disease and bone marrow involvement were observed more frequently in patients who died; however, similar to the findings in other studies, these parameters were not independent risk factors for mortality.[17]

In our study, compared to those residing in urban areas, individuals living in rural regions exhibited a significantly higher risk of mortality (OR: 93.706 [95% CI: 1.789–4908.115], p=0.025). Previous studies have investigated the impact of residential areas on DLBCL outcomes. Tao et al.[18] conducted a study evaluating the effect of socioeconomic status on mortality in DLBCL patients and reported that individuals living in neighborhoods with lower socioeconomic levels had significantly poorer survival outcomes following a DLBCL diagnosis. The study highlighted that one of the most critical indicators of this association was whether patients resided in urban or rural areas, emphasizing that those living in rural regions were often surrounded by communities with similarly lower socioeconomic status.[18]

Similarly, Loberiza et al.[19] found that compared to lymphoma patients residing in rural areas, those living in urban regions had a significantly lower risk of mortality. Conversely, Lee et al.[20] reported that DLBCL patients in rural areas exhibited survival rates comparable to those in major urban centers and central regions, whereas patients residing in small to medium-sized urban areas had poorer outcomes.

Several studies have attempted to explain the potential causes of this phenomenon, suggesting that cancer patients in urban areas have better access to healthcare services compared

to those in rural regions. This improved access is believed to positively influence survival duration and survival probability.[21-24] In our study, we also hypothesize that the increased mortality rate among patients living in rural areas may be associated with poorer access to healthcare services and lower health awareness within this population.

Limitations

The major limitations of this study include the short follow-up period, single-center nature, and lack of direct measurement of socioeconomic status and access to healthcare. Additionally, additional factors such as treatment response and toxicity were not assessed in detail.

CONCLUSION

In this study, clinical and epidemiological factors associated with mortality in DLBCL patients were evaluated. High IPI score and residence in rural areas were identified as independent prognostic risk factors. Mortality rates were consistent with previously reported data in the literature, with factors such as advanced disease stage, bone marrow involvement, and triple-hit mutation being significantly associated with mortality. However, gender, treatment regimen, and bone marrow transplantation did not demonstrate a significant impact on overall survival. This study demonstrates the need for multicenter studies that include treatment-related variables in order to better evaluate treatment responses and prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The research was sanctioned by the Van Yüzüncü Yıl University Hospital Scientific Researches Evaluation and Ethics Committee (Date: 10.12.2021, Decision No: 2021/13-19).

Informed Consent

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

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The role of ELABELA in targeted treatment of acute myeloid leukemia

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ABSTRACT

Acute myeloid leukemia is a clonal stem cell disease. Various molecular targets are being sought in this disease which has a low chance of cure. However, it is desired that targeted treatments should have few side effects. We tried to understand whether the embryogenic peptide ELABELA, which has been closely associated with many pathways involved in cancer mechanism, is a peptide worth investigating in targeted treatment of acute myeloid leukaemia.

Keywords: ELABELA, acute myeloid leukemia, cellular pathways, targeted therapy, new peptide

INTRODUCTION AND OVERVIEW OF ACUTE MYELOID LEUKEMIA (AML)

Acute myeloid leukemia (AML) is a genetically, epigenetically and clinically heterogeneous disease characterized by the accumulation and expansion of immature myeloid cells in the bone marrow (BM) and peripheral blood (PB), resulting in failure of normal hematopoiesis.[1]

Morphological heterogeneity of AML arises from the diversity of genotypes seen.[2]

As in other cancers, various intracellular and extracellular signaling pathways, proteins, peptides, receptors etc. in these pathways play a role in the pathogenesis of AML. Although blocking and inhibition of some molecules involved in these complex pathways have led to important developments in cancer treatment, the results are still unsatisfactory.[3-5]

CANCER STEM CELLS (CSCS) AND THEIR ROLE IN AML

Cancer stem cells (CSCs) are responsible for cancer recurrence, metastasis and resistance to treatment, especially in leukemias. The activities of CSCs are controlled by many intracellular and extracellular factors and these factors can be used as drug targets for cancer therapy. CSCs have been initially identified in leukemia. CSCs can generate tumors through self-renewal and differentiation into multiple cellular subtypes.[6-11]

ELABELA: A NOVEL PEPTIDE IN EMBRYOGENESIS AND CANCER

During embryogenesis, apela (ELABELA/ELA/Toddler) and apelin receptor (AR) mRNA expression is increased, leading to apela-AR signaling that facilitates the migration of progenitor cells to the anterior lateral plate mesoderm via Nodal/TNFβ-dependent signaling for proper cardiovascular development in zebrafish.[12-14] However, following this, apela levels rapidly decrease and apelin mRNA levels increase.[15] CSCs and normal stem cells share some of the same regulatory signaling pathways such as Wnt/β-catenin, Sonic Hedgehog (Hh), and Notch pathways involved in the self-renewal process.[16-18] Targeting these common pathways may result in complications such as profound cytopenia and BM failure. Therefore, finding targets that have lost their functions after the embryonic period, but reappear or persist in possible CSCs will be advantageous in destroying the cancer stem cell, and even if this does not happen, it will be advantageous in protecting against the side effects of treatment. One of these targets may be Apela peptide, which has lost its function after the embryonic period but is abundantly expressed in embryonic stem cells[12-14] and has been shown to be expressed in some cancer cells in recent studies.[19-21]

Apela binds to an unknown receptor different from apelin in ESCs, inhibits apoptosis of stem cells and stimulates self-renewal. Apela may have varying effects on ESCs derived from different species. Human and murine pluripotent ESCs respond differently to exogenous apela treatment. In human ESCs, it inhibits apoptosis.[22] In mice, apela can cause apoptosis in a non-peptidic manner.[23]

In this paper, we examine whether ELABELA, a peptide that has an important role in signaling pathways involved in AML mechanism and especially in ESC, is worth investigating in targeted treatment.

Wnt signaling is required for the sustainability of leukemic stem cells. Several molecules involved in or modulating Wnt signaling have a prognostic value in AML. These include: β-catenin, LEF-1, phosphorylated-GSK3β, PSMD2, PPARD, XPNPEP, sFRP2, RUNX1, AXIN2, PCDH17, CXXC5, LLGL1, and PTK7.[2]

From a successful treatment perspective, the cancer stem cell model implies that the LSC population must be eliminated to eradicate the disease and achieve long-term remissions.[24]

Notch-, Wnt- and Hedgehog signaling pathways are particularly important for LSC biology.[25]

Numerous lines of evidence suggest that abnormal WNT signaling may also impair cancer immune surveillance, thereby stimulating immune escape and resistance to various immunotherapies, including immune checkpoint blockers.[26,27]

Both p53 and the Wnt signaling pathway play important roles in regulating the differentiation of mouse embryonic stem cells (mESCs). Lee et al.[27] identified the Wnt signaling pathway as one of the main targets of p53 in mESCs.

Glycogen synthase kinase-3 (GSK-3) and protein phosphatase 2A (PP2A) are two important signaling molecules involved in AML pathogenesis and MYC stability. GSK-3β is involved in the regulation of cell metabolism, cell differentiation, apoptosis, autophagy and tumorigenesis of leukemia. PP2A is a serine/threonine phosphatase that suppresses tumor growth and regulates kinase-directed intracellular signaling pathways.[29]

Takam Kamga et al.[29] have shown that pharmacological interference via small molecule inhibitors of Wnt and/or GSK-3 signaling reduces AML cell survival by sensitizing leukemia cells to chemotherapeutic agents both in vitro and in vivo.

The G protein-coupled chemokine receptor CXCR4 is specifically associated with cancer metastasis and HIV-1 infection.[31] The chemokine receptor, CXC receptor 4 (CXCR4), with its ligand chemokine ligand 12 (CXCL12), plays a key role in the survival and migration of normal and malignant stem cells into the BM. High CXCR4 expression in AML and ALL blasts has been shown to be an indicator of poor prognosis for these diseases. Several small molecule inhibitors, short peptides, antibodies and antibody drug conjugates have been developed to more effectively target and kill malignant cells expressing CXCR4. Apelin and apela are two peptide ligands for a class A G-protein coupled receptor (GPCR) called the AR (AR/APJ/APLNR). They function by binding to this receptor, and this is known as the Apelinergic system (Apelin/APJ system). Binding of both endogenous peptides to the AR produces similar physiological effects. The AR transmembrane (TM) domain is highly homologous to the chemokine receptors CXCR4 and CCR5.[15,32]

Apelin peptides (apelin and ELABELA) and the GPCR of the same origin, known as the apelin receptor (Aplnr), play key roles in apoptosis, cell proliferation, angiogenesis, metabolic disorders and various cancers.[33,34] The CXCR4 receptor interacts with CXCL12 (SDF-1) generated by BM endothelial and stromal cells, including CXCL12-bol reticular (CAR) cells. Therefore, CXCR4 may be an attractive molecular target for the treatment of these malignancies. Studies have shown that increased CXCR4 expression is correlated with poor results in patients with AML and B-cell ALL. This is potentially due to the role of CXCR4 in retaining leukemic cells within the BM and their role in activating pathways that support the survival, growth and chemotherapy resistance of these malignant cells. In AML cases, leukemic blasts with high CXCR4 expression have been associated with higher relapse rates and lower overall survival. Patients with FMS-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD) or nucleophosmin mutation have significantly higher CXCR4 expression than their wild-type counterparts. The CXCR4 receptor plays a crucial role in leukemia maintenance through several mechanisms, including survival signaling and retention of leukemia cells in the protective BM niche.[35-44] LSCs are tumor-initiating cells that are resistant to standard chemotherapy and promote the persistence and relapse of AML.[45]

CXCL12 antagonists are designed to disrupt the CXCR4/CXCL12 axis and sensitize malignant cells to chemotherapy.[35] Of the CXCL12 antagonists, successful treatment has only been achieved with CX-01.[46]

In apoptosis, the B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax) protein releases cytochrome c from mitochondria, activating a cascade of reactions that assists the successive activation of caspases and ultimately leads to cell death. Bcl-2 is believed to inhibit Bax's release of cytochrome c, thereby restricting the downstream activation of the apoptotic machinery. Both Bax and Bcl-2 are cytoplasmic proteins.[47] BCL2 is thought to mediate resistance to standard treatment in patients with unfavorable risk AML.[48]

Mutation of the tumor suppressor gene TP53 is associated with poor prognosis in AML. The TP53 gene is largely a stress response protein with functions ranging from apoptosis to cell cycle control. The fate of the p53 protein in the cell is mainly determined by the rate of degradation rather than the rate of generation. p53 is mainly degraded by the interaction of p53 with MDM2 (double minute 2 protein). This coupling of p53/MDM2 can be disrupted when stress or DNA damage is detected, resulting in the stabilization of p53. Overexpression of MDM2 leads to deactivation of p53.[49,50] MDM2 and MDM4 are negative regulators of TP53 activity targeting degradation via ubiquitination. In AML, MDM2 is frequently overexpressed, so cells can have low functional TP53 activity without TP53 deletion/mutation. Nutlin-3a is a small molecular inhibitor of MDM2/p53 interaction, thus this therapeutic provides increased p53 levels secondary to reduced p53 degradation and consequently up-regulates

apoptosis.[50,51] It has been suggested that Venetoclax plus idasanutlin may be an effective treatment for relapsed/refractory AML.[52]

Apelin and apela are two peptide ligands for a class A GPCR called the AR. They function by binding to this receptor, and this is known as the apelinergic system (apelin/APJ system). Coupling of both endogenous peptides to the AR produces similar physiological effects. It is well known that the apelin/APJ system can regulate apoptosis in various cell types, subsequently mediating the occurrence and development of associated diseases. Recent evidence suggests that the Apelin/APJ system affects apoptosis in various diseases through different signaling pathways in different disease pathways. Pretreatment of cardiomyocytes with a pelin-13 effectively prevents apoptosis induced by glucose deprivation (GD) and can significantly increase Akt and mTOR phosphorylation by positive regulation of Bcl-2 protein and negative regulation of Bax and cleaved caspase-3. The apelin/APJ system also increases the expression of Bcl-2 and decreases the expression of Bax protein.[53-57] Inhibition of the apela or apelinergic system will show the effect of both venotoclax and idasanutline together.

Apela functions as an endogenous ligand for the GPCR, APLNR, and Apela and APLNR have been shown to direct angioblast migration to control vascular patterning in zebrafish embryos.[14,58,59]

MOLECULAR MECHANISMS LINKING ELABELA TO AML

Apela is predicted to bind to a different receptor than apela.[15] Apela is highly expressed in human blastocysts before implantation and contributes to human embryonic stem cell (hESC) pluripotency through an alternative receptor. In a study in human pluripotent embryonic stem cells (ESCs), apela inhibited cell apoptosis and stimulated self-renewal. However, these undifferentiated stem cells did not express AR. Only after differentiation, about three days later, AR expression was detected.[22] This is highly suggestive of the existence of an additional, as yet unknown receptor for apela and indicates that apela is involved in pluripotent stem cells prior to and independent of AR formation. In this case, targeting apela in the treatment of AML, or at least in the preparatory regimen for hematopoietic stem cell transplantation, will perhaps enable cancer stem cell targeting.

The non-coding region of Apela has been shown to be involved in the regulation of p53-mediated DNA damage-induced apoptosis in mouse embryonic stem cells (mESCs). Apela negatively regulates the interaction between heterogeneous nuclear ribonucleoprotein L (hnRNPL) and p53.[23] Seo et al.[59] showed that DNA damage-induced hnRNP L positively regulates p53 expression. Li et al.[22] have shown that Apela negatively regulates the interaction between hnRNPL and p53, resulting in an antiapoptotic effect. Yi et al.[19] showed that apela expression was high in ovarian cancer cells. Disruption of apela expression in these cell lines suppressed cell growth, cell migration and cell cycle progression. They showed that apela demonstrated this effect independently of APLNR and affected cell growth and cell cycle progression in a p53-dependent way. Loss of apela in high p53-expressing cells caused a decrease in cell number due to cell death, which was caused by p53-induced cell apoptosis.

Mouse double minute2 (MDM2) is a critical negative regulator of the tumour suppressor p53, which plays a key role in controlling its transcriptional activity, protein stability and nuclear localization. MDM2 expression is upregulated in many cancers, resulting in loss of p53-dependent activities such as apoptosis and cell cycle arrest.[61]

The PI3K/Akt signaling pathway has been shown to play a critical role in tumorigenesis of hematopoietic cells. Activation of the PI3K/Akt pathway occurs even in the early stages of tumors and is correlated with poor prognosis and therapeutic resistance in various human cancers.[22,62]

Mammalian target of rapamycin (mTOR) is an evolutionarily conserved kinase in eukaryotes that plays a critical role in sensing and responding to factors such as nutrient availability, energy sufficiency, stress, hormones and mitogens. mTOR forms two complexes, referred to as mTOR complex 1 (mTORC1) and mTORC2. mTORC1 also regulates mitochondrial biogenesis and autophagy.[63-66] Hoshii et al.[66] in their study revealed that mTORC1 is required for leukemia initiation.

The phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR pathway are two pathways that are crucial for many aspects of cell growth and survival in cancer as well as physiological.[68]

GSK3β functions as a link between the PI3K/mTOR and WNT/β-catenin pathways through AMP-activated protein kinase (AMPK).[69,70]

AMPK activation leads to inhibition of mTORC1 by two independent mechanisms: activation of the negative mTORC1 regulator tuberous sclerosis complex 2 (TSC2) and inhibition of the mTORC1 sub-unit RAPTOR.[71-73] c-Myc is an essential transcription factor that plays a convincing role in leukemogenesis. In vitro and in vivo studies have suggested that higher expression of c-Myc is correlated with the progression of AML.[74] Two key regulators of c-Myc are glycogen synthase kinase 3beta (GSK-3β) and PP2A.[29] GSK-3β is involved in the regulation of cell metabolism, cell differentiation, apoptosis, and autophagy and leukemia tumorigenesis.[75] GSK-3β is also involved in leukemia survival, chemotherapy resistance and body protection.[76] GSK-3β is a vital tumor suppressor.[77] In its tumor suppressor function, GSK-3β regulates Wnt signaling to passivate inhibitory phosphorylation of β-catenin and prevents cell cycle progression.[78] Soulet et al.[78] demonstrated the effects of ELA on autophagy and mTORC1. They showed that ELA is also involved in the regulation of the expression of mTORC1 network proteins and autophagy. They identified ELA as an important positive regulator of mTORC1.

Apela stimulates hESC cell cycle progression and protein translational by activating PI3K/AKT/mTORC1 signaling and blocks stress-induced apoptosis. These pathways are the main signals reported to correlate with apoptosis. MDM2 also inhibits p53 through this pathway. It is predicted that the apelinergic system may inhibit apoptosis through these

common pathways (53- 57). hnRNPC is a negative regulator of p53. It was also shown that the 1-41 p53 region, the region where p53 binds to MDM2, interacts with hnRNPC. These results showed that hnRNPC may be synergistic with MDM2 in regulating p53 stability. Doxorubicin competes with p53 for binding to the RNA recognition motif of hnRNPC, thereby increasing p53 stability and inducing p53-dependent apoptosis.[80] Chemokines are produced by cancer-associated fibroblasts, a component of stromal cells, and affect the metastatic potential and region-specific spread of cancer cells. Stromal-derived factor-1 (SDF-1/CXCL12) belongs to the CXC chemokine family. The effects of CXCL12 in many cancers have been described, including its role in promoting local invasion and distant lung cancer metastasis.[81-83] Wang et al.[83] in their study showed that CXCL12 blocks apoptosis in human adenocarcinoma cell line via CXCR4. They observed that the expression levels of Bcl-2 and bcl-xl in the adenocarcinoma cell line were increased by treatment with CXCL12 and decreased by CXCR4 antagonist and JAK2 inhibitor. Apela, which has been shown to be antiapoptotic, has also been shown to interfere with the chemokine CXCR4a signaling pathway.[22]

In summary, apela and apelinergic system has been shown to inhibit apoptosis in many steps (via bcl-2, bcl-xl, mdm2, hnRPLN, p53, PI3K/Akt/mTORC1, chemokines). Based on these results, we can say that apela and the apelinergic system occupy a central position in leukaemia.

AKT, ERK and mTOR kinases form a complex pathway that regulates various cellular functions, most prominently cell growth, migration and survival.[79]

AML LSCs (leukemia stem cells) maintain naturally high mitophage activity through AMP-activated protein kinase (AMPK) activation to maintain a low physiological state of reactive oxygen species (ROS), which is critically required for the preservation of their self-renewal potential.[85]

Autophagy is frequently activated in cancer and is largely associated with metabolic reprogramming and oncogenesis. Autophagy (i.e. lipophagy) has been shown to participate in lipid catabolism to supports OxPHOS, i.e. to maintain energy metabolism by delivering free fatty acids (FFAs) to mitochondria via degradation of lipid droplets (LD) in AML cells but not in normal hematopoietic cells. Autophagy supports OXPHOS, whereas inhibition of OXPHOS reduces autophagic flow.[86]

Autophagy is thought to inhibit cancer development. Conversely, once cancer has formed, increased autophagic flow often provides tumor cell survival and growth.[87-89] In other words, autophagy has different effects on cancer formation and progression. Therefore, both inhibition and activation of autophagy can be used in treatment.[87,88]

mTORC1 stimulates biosynthetic pathways, including the synthesis of proteins, lipids and nucleotides, and promotes cell growth by inhibiting cellular catabolism through suppression of the autophagic pathway. However, inhibition of autophagy initiates cancer formation. So mTORC1 probably contributes to the development of AML. Altman et al.[90] have demonstrated the antileukemic effects of blocking mTORC1 and mTORC2 in cell culture studies. However, mTORC1 negatively regulates and inhibits autophagy. Inhibition of autophagy in AML is among the treatment targets.[90-92]

Soulet et al.[78] showed that ELA plays a role in the regulation of the expression of mTORC1 network proteins. They showed that ELA activates mTORC1 and this activation inhibits autophagy. They also showed that the effect of ELA on autophagy is abolished in the absence of mTORC1 expression. ELA has been shown to be an important positive regulator of mTORC1. This correlation may suggest that mTORC1 and ELA may be jointly responsible for the initiation of AML.

BCL-2 inhibitors (venetoclax) inhibit oxidative phosphorylation (OXPHOS) in leukemic stem cells (LSC) and lead to cell death. Inhibition of OXPHOS reduces autophagic flow.[86]

ELABELA AND POTENTIAL THERAPEUTIC TARGETING IN AML

Targeting apela, which seems to be almost central to the cancer pathways involved in AML, is promising. However, cell culture studies will be very valuable to see the real effect of apela and will reveal more real results. Although blocking/inhibiting Apela seems logical according to the pathways it is involved in and the results of the studies, it is also possible to encounter a different result in cell culture studies. For example, Soulet et al.[78] reported that sunitinib and ELA showed synergistic effects in suppressing tumor growth and angiogenesis in mice. In the same study, they found that APELA expression was upregulated in colon, lung, stomach and thymoma cancers, but did not change in other cancer tissues analyzed except kidney cancer tissues, while APLN and APLNR expression was upregulated in clear cell renal carcinoma (ccRCC) and downregulated in papillary renal cell carcinoma (RCC). In other words, the expression of apela and APLNR differs in different cancer types; therefore, inhibition or induction of APLNR is likely to show different effects in different cancer types. Sunitinib (SU11248) is a small molecule FLT3 inhibitor with selectivity for PDGFR, VEGFR1, VEGFR2, KIT, and FLT3. It has both direct anti-tumor and antiangiogenic properties. The use of sunitinib is currently approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumor and AML.[93] Cell culture studies will be valuable to understand whether this synergistic effect is observed in AML.

CONCLUSION

As a result, many molecules and cancer pathways involved in AML formation have a close connection with Apela. Therefore, Apela seems to be a peptide worth investigating in AML treatment. Cell culture studies and later phase studies will provide valuable information to the literature.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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A rare case report: cytarabine-induced skin rash

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ABSTRACT

Cytarabine, a commonly used antimetabolite in hematologic malignancies, has various side effects, including dermatological toxicity. A 61-year-old male with relapsed diffuse large B-cell lymphoma (DLBCL) was started on the MATRIX regimen, including high-dose cytarabine. On the third day of treatment, he developed a palmar rash, which later progressed to petechiae and purpura on the trunk, back, and lower extremities. No systemic corticosteroid treatment was administered, and the rash gradually resolved by the 13th day. This case highlights a rare dermatological reaction to cytarabine. Although cutaneous toxicity of cytarabine is uncommon, clinicians should be aware of its potential manifestations and manage patients symptomatically to avoid unnecessary interventions while ensuring treatment continuation.

Keywords: Chemotherapy, cytarabine, palmar-plantar erythema, generalized exanthematous pustulosis

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy, with B-cell lymphomas constituting the majority of cases. Diffuse large B-cell lymphoma (DLBCL) is the most frequently observed histological subtype, accounting for approximately 30% of newly diagnosed cases annually.[1] In Turkiye, based on 2014 data, the incidence of DLBCL is 6 per 100.000 people.[2] It is slightly more common in males than in females (male/female ratio=1.5).[3]

The first-line treatment for DLBCL patients is the CHOP protocol, which is combined with the Anti-CD20 monoclonal antibody rituximab and administered every 21 days as the standard regimen.

For relapsed or refractory DLBCL patients, autologous stem cell transplantation (ASCT) is the only option to achieve long-term remission. However, factors such as the patient's age, treatment-related morbidities, and low performance status may prevent the application of ASCT in all cases. For patients who do not respond to first-line treatment, salvage regimens such as R-ICE, R-DHAP, or MATRIX protocols may be used. Clinical studies have reported no significant difference in relapse rates among these regimens. Therefore, salvage therapy should be selected based on individual patient evaluations to determine the most appropriate protocol.

Cytarabine treatment can lead to cardiovascular, dermatological, gastrointestinal, hepatic, and immunological side effects. A review of the literature indicates that cytarabine can cause severe dermatological toxicity.[4,5] Dermatologic reactions include acute generalized exanthematous pustulosis, alopecia, dermal ulcers, efflorescence, pruritus, skin rashes and urticaria. However, rashes affecting the palmar surface due to cytarabine treatment are quite rare. This report presents a case of a patient who developed a drug eruption starting with a palmar rash following cytarabine treatment during the MATRIX regimen, administered after a CNS relapse in a patient previously treated with R-CHOP.[6]

CASE

A 61-year-old male patient presented with dyspeptic complaints and was diagnosed with DLBCL following a gastric biopsy. He underwent six cycles of the R-CHOP chemotherapy protocol. After treatment, he was considered to be in remission and placed under follow-up. Notably, the patient had developed erythema during the R-CHOP regimen, which resolved without sequelae.

During remission follow-up, the patient presented to the emergency department with altered consciousness, vision loss, and speech impairment. Imaging revealed a 22×20 mm mass measuring in the left temporal lobe. A total excision of the mass was performed by neurosurgery. Upon pathological examination revealing DLBCL infiltration of the mass, the patient was referred to us with a diagnosis of central nervous system (CNS) lymphoma relapse. The patient, who

had previously received 6 cycles of R-CHOP chemotherapy, was subsequently initiated on the MATRIX chemotherapy regimen. This protocol included methotrexate 850 mg/day on the first day, followed by cytarabine 3400 mg twice daily on the second and third days.

On the third day of treatment, shortly after the completion of intravenous cytarabine infusion, the patient developed lesions on the palms and perioral area (**Figure 1**). At the same time, he experienced subfebrile fever. However, no symptoms suggestive of Cytarabine syndrome such as myalgia, bone pain, chest discomfort, conjunctival irritation, or severe fatigue were observed during the clinical course. On the 7th day of treatment, the lesions spread, becoming more prominent as petechiae and purpura, with greater intensity on the palms and less intensity on the trunk, back, and lower extremities. These lesions were non-pruritic and painless (**Figure 2, 3**).

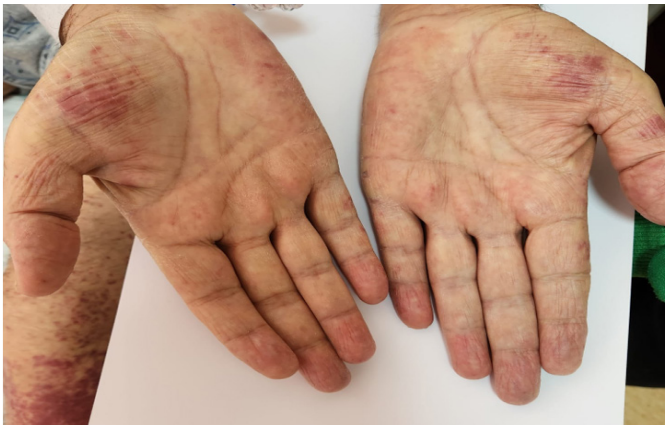

Figure 1. Lesions that developed on the palms after the completion of the intravenous cytarabine dose on the 3rd day of treatment

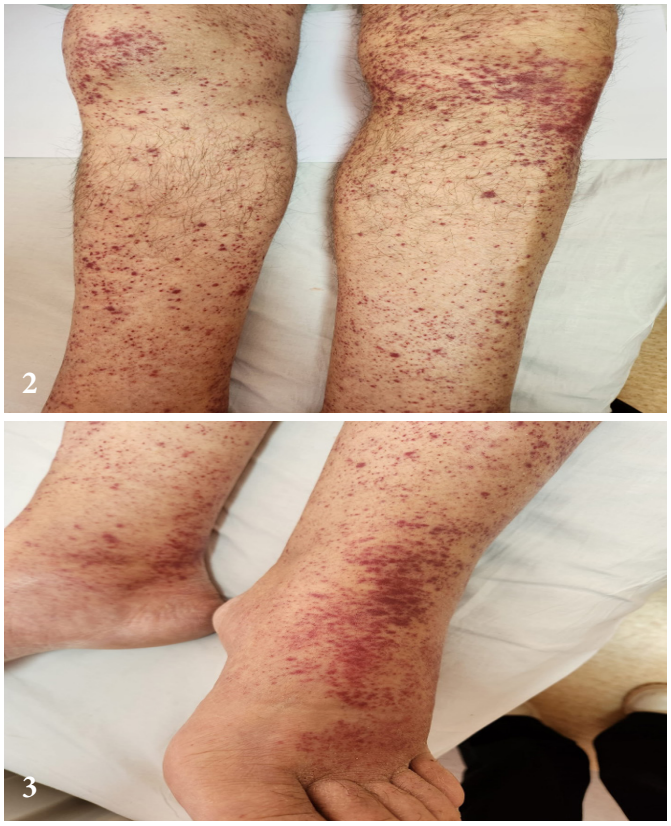

Figure 2 and 3. Non-pruritic and painless petechiae and purpura that developed on the trunk, back, and lower extremities on the 7th day of treatment

Upon the development of cutaneous lesions, a dermatology consultation was requested. Antinuclear antibody (ANA) and extractable nuclear antigen (ENA) antibody tests were performed to rule out leukocytoclastic vasculitis. As the test results were negative, a subsequent rheumatology consultation was obtained, and the preliminary diagnosis of vasculitis was excluded. Dermatology recommended topical treatment with a carbamide-containing emollient for hydration and a methylprednisolone aceponate-containing pomade for the affected areas. During this period, neither oral nor intravenous steroid treatment was administered. The lesions responded well for optimal clinical management to treatment, with the petechiae and purpura beginning to fade by the fourth day after onset (day 13 of treatment) (**Figure 4**).

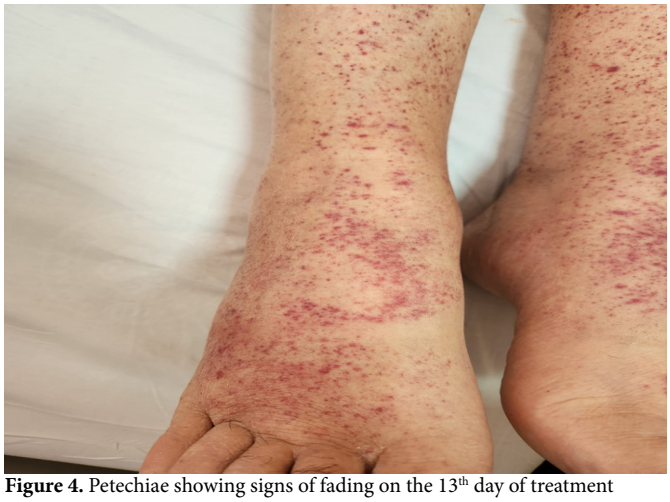

Figure 4. Petechiae showing signs of fading on the 13th day of treatment

Resolution of the lesions following topical treatment and completion of the chemotherapy regimen supported the diagnosis of a drug-induced skin eruption.

The patient provided written informed consent for the publication of this case report and accompanying images.

DISCUSSION

DLBCL is one of the most common subtypes of hematologic malignancies and requires a multidisciplinary approach due to its aggressive course. In this case, we discuss the development of a cutaneous reaction following cytarabine-containing MATRIX chemotherapy in a patient presenting with CNS relapse of DLBCL.

Cytarabine is a widely used antimetabolite in the treatment of hematologic malignancies, acting by inhibiting DNA synthesis during the S phase of cell division. However, dermatologic side effects of this drug are rarely reported. In the literature, the most frequently reported dermatologic reactions associated with cytarabine include a broad spectrum of manifestations such as palmar-plantar erythrodysesthesia, morbilliform rashes, and acute generalized exanthematous pustulosis.[1,7] While skin rashes are common in cytarabine treatment, palmar erythema and similar skin eruptions are rare. A few cases in the literature have reported similar symptoms. Specifically, the development of palmar rashes or petechiae/purpura is rare but has been documented. In our case, the appearance of petechiae and purpura starting in the

palmar-plantar region and spreading to the trunk and lower extremities after intravenous cytarabine administration exemplifies the drug's toxic effects on the skin.

Cytarabine-induced cutaneous toxicities generally follow a benign course and tend to resolve spontaneously. Literature reports indicate that symptoms generally emerge within 2–8 days after treatment initiation and regress within 1–2 weeks.[1,7] Similarly, in our case, the rash began on the third day of treatment and showed signs of fading by the 13th day. The fact that the patient's symptoms improved with only topical treatment, without the need for systemic corticosteroid therapy, supports the notion that cytarabine-induced skin lesions are usually asymptomatic and benign.

Previous studies have identified a correlation between cytarabine dosage and dermatologic reactions. Particularly in patients receiving high-dose cytarabine, more severe skin toxicities have been reported; however, these findings have been observed to decrease with repeated doses.[7] Additionally, the causes of skin manifestations are multifactorial and may not be solely attributed to cytarabine, as other agents used in combination therapy can contribute to their occurrence. For example, a 2017 study by Karol et al.[8] reported that the combination of cytarabine and methotrexate could exacerbate skin reactions.

Vasculitis-like findings during cytarabine treatment are rare, and the exact pathogenesis of such reactions remains unclear.[1] In our case, vasculitis was considered a possible diagnosis following dermatology consultation. However, the absence of positive rheumatologic markers and other systemic symptoms suggested that the rash was specifically related to cytarabine.

CONCLUSION

As a result, although cutaneous reactions associated with cytarabine therapy generally follow a benign course, careful evaluation of such adverse effects is essential for optimal clinical management. Avoiding unnecessary tests and providing appropriate symptomatic treatment may allow continuation of therapy without negatively impacting the patient's prognosis.

This case underscores the importance of recognizing drug-induced cutaneous reactions that may develop during chemotherapy. Clinicians should be aware that drug-induced skin eruptions may occur during cytarabine-based chemotherapy and collaborate with dermatology specialists to ensure timely and appropriate management.

ETHICAL DECLARATIONS

Informed Consent
The patient signed and free and informed consent form.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

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

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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