

Clinical features and possible prognostic factors in patients with Marginal Zone Lymphoma: Retrospective analysis from two centers

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Abstract

Objectives

Marginal zone lymphoma accounts 5%-17% of all non-Hodgkin lymphomas and has an indolent clinical course. The parameters that predict prognosis and the need for treatment are still unclear. The aim of the current study was to examine the impact of parameters on the course of disease and the need for treatment in marginal zone lymphoma.

Methods

A retrospective study was conducted with marginal zone lymphoma patients in the two centres between 2010 and 2018. The demographic and disease characteristics, and also hematological and biochemical parameters at the time of diagnosis were examined. The effect of the parameters on overall survival and need for treatment were analyzed.

Results

During the follow-up, 25 patients required treatment and 15 patients were followed up without treatment. Overall survival was significantly higher in patients with nodal marginal zone lymphoma than in extranodal and splenic marginal zone lymphoma patients. Overall survival of patients who required treatment was 92.9 months while untreated patients was 58.4 months and there was no significant difference among the groups. The platelet count of untreated patients at the time of diagnosis were significantly higher than patients who received treatment. No significant relationship was found between any parameter and overall survival.

Conclusions

We demonstrated platelet count at the time of diagnosis as a predictive factor for future treatment need. It is an objective and simple blood test that may be helpful to predict the course of the disease although further studies are warranted.

Introduction

Marginal zone lymphoma (MZL) is characterized by the proliferation of B cells in postgerminal centers found in mucosa-associated lymphoid tissue (MALT), lymph nodes, and the spleen [1]. MZL has indolent clinical course commonly and present with limited stage of disease [2]. Median age of MZL is about 60 years and there is slight female predominance. MZL accounts 5–17% of all non-Hodgkin lymphomas (NHL) [3].

MZL includes three subtypes: extranodal (EMZL), splenic (SMZL) and nodal MZL (NMZL) depending on site of involvement [4]. Although many morphologic and immunophenotypic features of these subtypes are similar with their indolent course, there are also differences in frequency, pathogenesis, clinical presentation and treatment [5]. According to the 2016 Revised WHO Classification, extranodal MZL is the most frequent subtype while nodal MZL is the least common form [6].

EMZL involves the organs with low lymphoid tissue like stomach, lungs, salivary glands that have accumulated B cells in response to chronic infections or autoimmunity. The most common site is stomach. Bone marrow (BM) and peripheral lymph node involvement is rare. Patients with SMZL, present with splenomegaly, abdominal lymphadenopathy (LAP) and cytopenia due to BM involvement. Patients with NMZL have lymphnode-based disease and spleen or extranodal sites have not been affected [7]. NMZL has worse prognosis than EMZL and SMZL [8]. Treatment options depends on disease subtypes, localization of involvement and symptoms [9]. Some patients can be followed with watch-and-wait principle where as some require treatment during follow-up period. Recurrence usually occurs within 5 years after treatment [10].

As it is a rare disease group, the prognostic factors of MZL have been studied in small cohorts [11]. Although studies have determined factors such as age, serum lactate dehydrogenase (LDH), B symptoms, and beta 2 microglobulin to be associated with prognosis or OS of the disease, the results are heterogeneous [9]. Parameters predicting the need for treatment are still unclear. Therefore, in the current study, the impact of parameters on the course of disease and need for treatment was analysed in patients with MZL.

Material And Methods

A retrospective study was conducted with MZL patients in the Hematology Departments of two centres (Diskapi Yildirim Beyazit Training and Research Hospital and Gulhane Training and Research Hospital) between 2010 and 2018. Patients were classified in 3 groups: nodal, extranodal and splenic MZL.

Demographic data, date of diagnosis, chemotherapy regimen, treatment response and follow-up periods were recorded for all patients. Hematological parameters including hemoglobin (Hb) level, hematocrit (Hct) level, platelet count, white blood cell count (WBC), neutrophil count, lymphocyte count, monocyte count, plateletcrit, platelet distribution width, mean platelet volume (mpv), albumin, LDH levels, ferritin and B12 vitamin levels were examined at the time of diagnosis. Response rates, OS and time to treatment duration (TTD) were calculated and the effect of parameters on OS and TTD were analyzed.

Statistical analysis

SPSS Statistics 20 software (IBM, Armonk, NY, USA) was used for statistical analysis. Descriptive data were given as a percentage. The Independent Samplest-test (t-table value) was used to compare two independent groups with normal distribution and the Mann-Whitney U-test (Z-table value) was used for

data not showing normal distribution. χ^2 -cross tables were used to detect the relationship between qualitative variables. Only significant statistical variables in univariate analysis were included in the multivariate Cox regression model. Two-sided p -values < 0.05 were considered statistically significant. Receiver operating characteristic curve (ROC) and area under the curve (AUC) analysis were used to determine the cut-off value of ferritin to assess its relationship with survival. Survival was estimated from Kaplan-Meier curves. OS was calculated from the time of diagnosis to death or until the final visit. Comparisons between patient groups were made using the log-rank test.

Ethical approval and informed consent

All procedures performed in this study were conducted in accordance with the ethical standards of the institutional and / or national research committee and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Patient records from Ankara Diskapi Yildirim Beyazit and Gulhane Training and Research Hospitals confirmed that all patients gave informed consent before hospitalization and prior to chemotherapy and for other relevant diagnostic / therapeutic procedures.

Results

Evaluation was made of 40 MZL patients, comprising 25 (62.5%) females and 15 (37.5%) males with a mean age of 64.13 ± 10.39 years. The demographic and clinical characteristics of the patients are shown in Table 1. The total follow-up period was mean 19.6 months (range, 0.1–92.9 months).

Table 1
The clinical and demographic characteristics of patients

	All patients (n = 40)
Median age, year (range)	64.13 (35–81)
Gender n (%)	15 (37.5%)
Male	25 (62.5%)
Female	
Number of comorbidity [Median (Min-Max)]	0.5 [0.0–4.0]
IPI score [Median (Min-Max)]	2.0 [1.0–5.0]
Hb (gr/dL) [mean ± SD]	11.73 ± 2.81
Plt (x10⁶/L) [mean ± SD]	194000 ± 13200
Wbc (x10⁶/L) [mean ± SD]	10280 ± 9360
LDH (U/L) [mean ± SD]	294.4 ± 149.6
Final status	32 (80.0%)
Alive	8 (20.0%)
Exitus	
Follow up period (month) [Medyan (Min-Max)]	19.6 [0.1–92.9]
IPI: International Prognostic Index, Hb: Hemoglobin, Plt: Platelet, WBC: White blood cell count, LDH: Lactate dehydrogenase	

During the follow-up period, 25 patients required treatment and 15 patients were followed up without treatment. The median TTD was 29.9 months (range,13.7–30.9 months). In the comparison of treated and untreated patients, there was a significant difference in respect of platelet count. The initial platelet count of patients who received treatment was significantly lower than untreated patients ($p = 0.040$). Table 2 shows the comparisons of these two groups. Logistic regression analysis was performed and platelet count was found to be an independent risk factor for treatment need (OR: 0.93, 95% CI: 0.87–0.99, $p = 0.029$) (Table 3). According to receiver operating characteristics (ROC), the platelet cut-off value was determined as $148500 \times 10^6/L$ with 80.0% sensitivity and 52% specificity (AUC = 0.703; $p < 0.05$).

Table 2
The comparison of patients with and without treatment

(N = 40)	Patients with treatment (n = 25)	Patients without treatment (n = 15)	p
Age year [mean ± SD]	62,68 ± 10,81	66,53 ± 9,52	p = 0,262
Gender n (%)	11 (%44,0)	4 (%26,7)	p = 0,448
Male	14 (%56,0)	11 (%73,3)	
Female			
Number of comorbidity, n [Median (Min-Max)]	1,0 [0,0–4,0]	0,0 [0,0–3,0]	p = 0,174
Stage (%)	5 (%20,0)	6 (%40,0)	p = 0,352
1 or 2	3 (%12,0)	2 (%13,3)	
3	17 (%68,0)	7 (%46,7)	
4			
IPI score (%)	5 (%20,0)	5 (%33,3)	p = 0,502
< 2	19 (%76,0)	10 (%66,7)	
2–4	1 (%4,0)	-	
> 4			
Hb (gr/dL) [mean ± SD]	11,0 [7, 3–17, 6]	13 [7, 6–14, 8]	p = 0,102
Plt (x10 ⁶ /L) [mean ± SD]	155840,00 ± 90097,48	258466,67 ± 165829,03	p = 0,040
Wbc (x10 ⁶ /L) [mean ± SD]	4700,0 [1900,0-37800,0]	9900,0 [1670,0-30600,0]	p = 0,175
Neut (x10 ⁶ /L) [mean ± SD]	2480,0 [1100,0-21600,0]	5090,0 [770,0-11000,0]	p = 0,094
LLR	2,5 [1, 3–12, 4]	2,7 [1,4–41,3]	p = 0,967
Lenf (x10 ⁶ /L) [mean ± SD]	2000,0 [300,0-28900,0]	2800,0 [200,0-19200,0]	p = 0,567
LDH (U/L) [mean ± SD]	281,5 [122,0-739,0]	218,0 [158,0-574,0]	p = 0,161

IPI: International Prognostic Index, Hb: Hemoglobin, Plt: Platelet, WBC: White blood cell count, LDH: Lactate dehydrogenase, LLR: Leukocyte/lymphocyte ratio,

(N = 40)	Patients with treatment (n = 25)	Patients without treatment (n = 15)	p
Albumin (mg/dl) [mean ± SD]	4,1 [2, 4–4, 9]	4,2 [3, 4–4, 6]	p = 0,084
Ferritin (ng/mL) [mean ± SD]	87,0 [7,0-1500,0]	62,5 [12,0-290,0]	p = 0,146
Vitamin B12 (ng/mL) [mean ± SD]	205,0 [85,0-546,0]	254,5 [116,0-756,0]	p = 0,299
IPI: International Prognostic Index, Hb: Hemoglobin, Plt: Platelet, WBC: White blood cell count, LDH: Lactate dehydrogenase, LLR: Leukocyte/lymphocyte ratio,			

Table 3
Logistic regression model according to treatment requirement

Variable	B	Standart error	Wald	Sd	p	OR	95% CI OR	
							Lower	Lower
Plt(x10.000)	-0,069	0,032	4,777	1	0,029	0,933	0,877	0,993
Constant	1,897	0,731	6,738	1	0,009	6,664		
*Ref.kategory	CCR = 72,5%		$\chi^2_{(8)} = 9,474, p = 0,304$					

According to the survival analysis, the median OS of all MZL patients was 58.4 months (range, 53.5–95.9 months). A statistically significant difference was found in terms of OS according to diagnostic subtypes (p = 0.009). OS was significantly higher in patients with nodal MZL than in extranodal and splenic MZL patients (Table 4). There was no significant effect on OS of age, gender, IPI score, hemogram parameters including hemoglobin, platelet count, WBC, neutrophil count, lymphocyte count, and monocyte count. The OS of patients who received treatment was mean 92.9 months and for untreated patients it was 58.4 months, with no significant difference determined between the groups (p < 0.05)

Table 4
Comparison of some characteristics according to diagnosis subtype

Variable (N = 40)	Diagnostic subtypes			p
	Nodal (n = 15) ⁽¹⁾	Extranodal (n = 9) ⁽²⁾	Splenic (n = 16) ⁽³⁾	
OS (month) [Median (Min-Max)]	32,2 [5,0–65,5]	15,5 [0,2–23,3]	15,8 [20, 1]	0,009 [1–2, 3]
Need to treatment	4 (%26,7)	4 (%44,4)	7 (%43,8)	0,548
Yes	11 (%73,3)	5 (%55,6)	9 (%56,2)	
No				

Discussion

Factors that may affect the need for treatment, prognosis and survival of MZL patients have been investigated for many years [1, 9].

Since MZL has indolent low grade lymphoma like follicular lymphoma, the need for treatment can be determined according to the Groupe pour l'Etude de Lymphome Folliculaire (GELF) criteria. GELF recommends treatment for patients with involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm, any nodal or extranodal tumor mass with a diameter of ≥ 7 cm, B symptoms, splenomegaly, pleural effusions or peritoneal ascites, or cytopenia [12],[13]. Therefore, some MZL patients require treatment where as others are followed up without treatment. The parameters, especially at the time of diagnosis, which can predict the need for treatment during follow-up are still unclear. Mayer et al determined that age, serum LDH, a high IPI score and transformation into aggressive lymphoma are independent risk factors for reduced OS in MZL [14]. In the current study, it was demonstrated that an initial lower platelet count is a predictive parameter for the need for treatment. However, no significant relationship was found between platelet count and OS.

Previous studies have reported that platelet count was prognostic for some hematological malignancies, such as splenic marginal zone lymphoma and acute lymphoblastic leukemia [15, 16]. Bone marrow infiltration, the side-effects of drugs, splenic sequestration, or infections may be the cause of thrombocytopenia in lymphoma [17]. A previous study showed that thrombocytopenia was an independently poor prognostic factor of OS and progression-free survival in patients with diffuse large B-cell lymphoma [18].

Another current study reported that SMZL patients with anemia, hypoalbuminemia, International Prognostic Index (IPI) scores of 2 to 3, higher LDH levels, age > 60 years and platelet counts $< 100000/L$, had required treatment [19]. In the current study, there was no correlation between Hb, IPI, LDH levels, and the age of receiving treatment.

From a scan of literature, it can be seen that the survival rate of extranodal MZL is higher. A previous study determined that prognosis was significantly better for patients with extranodal MZL [8]. Mazloom et al reported that splenic MZL patients had the best prognosis in a study of 275 MZL patients [20]. Unlike these findings in literature, the results of the current study determined the OS of nodal MZL to be higher than that of extranodal and splenic MZL.

Limitations of this study were the retrospective design and low number of patients. In addition, the prognostic impact of molecular/genetic characteristics and pathological features was not evaluated due to unavailable data. Therefore, larger prospective studies are needed to confirm the prognostic factors.

In conclusion, platelet count was identified as a risk factor for the need for treatment. Platelet count at diagnosis is an objective and simple blood test that may be helpful to predict the course of the disease, although further studies are warranted.

Declarations

Conflict of interest: The Authors declare that there is no conflict of interest.

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Ethics approval: Approval for this study was given by the Local Ethics Committee. (approval number :87/11, 08.05.2020)

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