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Research Article

Prognostic Value of Absolute Monocyte Count in Patients with Mantle Cell Lymphoma

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Abstract

Objectives: Mantle cell lymphoma (MCL) is one of the lymphoma subtypes that accounts for approximately 6% of Non-Hodgkin's lymphomas. In this study, we aimed to investigate the relationship between AMC at diagnosis and overall and disease-free survival in addition to other prognostic factors of the MCL patients.

Methods: Clinical, laboratory, and demographic data of 23 MCL patients were analyzed retrospectively who underwent treatment in the Department of Haematology at Istanbul University Faculty of Medicine between January 2006 and September 2014. Relationship with AMC at diagnosis and overall, disease-free survival was assessed and compared with other prognostic factors.

Results: The mean age of patients was 61.56±10.99. The median overall and disease-free survival were 61±2.1 and 44±4.3 months, respectively. There was no statistically significant relationship between AMC at diagnosis and overall (0.75) or disease-free (p=0.06) survival. The overall and disease-free survival was not statistically significant between the patient groups with absolute monocyte count >0.5x10^9/l and ≤0.5x10^9/l. However, we found a moderate correlation between LDH and absolute monocyte count at diagnosis (r=0.499; p=0.015).

Conclusion: The correlation between LDH levels and absolute monocyte count at diagnosis suggests a relation between these two parameters and prognosis.

Keywords: Absolute monocyte count, disease-free survival, mantle Cell Lymphoma, overall survival, prognostic factor

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Mantle cell lymphoma (MCL) is a mature B-cell Non-Hodgkin lymphoma (NHL). Although it has been classified as centrocytic lymphoma and lymphocytic lymphoma at the intermediate level of differentiation in different classification systems, it is classified as aggressive by the Revised Europe-America (REAL) and the World Health Organization (WHO) classifications. It has been defined as B cell lymphoma.[1,2] In MCL, t (11,14) (q13; q32) and associated cyclin D1 expression are seen. While it constitutes 4% of all lymphomas in America, this rate is 7-9% in Europe, and its annual incidence is 2-3/100000.[3] The median age of onset is 60-65, and the majority of cases are at an advanced stage at the time of diagnosis. It constitutes the worst subgroup among all NHL in terms of overall survival (OS), and it is important to distinguish it from other indolent lymphomas because it is aggressive.

Average survival is reported to be three years in many studies, but this period can be extended to 5 years with new chemoimmunotherapy protocols and autologous transplantation.[4] These intensive and aggressive treatment

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regimens are known to be applied to young and high-performing status patients. Interestingly, an indolent clinical course is observed in a small group of patients.[5] It is difficult to talk about a standard treatment approach in light of current data; therefore, when planning treatment, it is essential to determine the prognosis in different patient groups and choose the appropriate treatment approach.[6] Many prognostic factors that can predict the course of the disease and scoring systems derived from these factors have been studied and published. These studies specifically aimed to determine which patients would have a more aggressive disease course. Current prognostic factors include the clinical features of the patients and the biological characteristics of the tumor cells. In contrast, due to insufficient data, no single factor can fully explain the biological and clinical discrepancy in patients. B-cell neoplasms depend on microenvironmental signals for their survival and proliferation and govern the composition and function of the microenvironment itself. Recent studies have proven that monocytes and macrophages suppress anti-tumor immunity and support tumor angiogenesis through microenvironmental regulation.[7] The relationship between absolute monocyte count (AMC) and short survival in Hodgkin lymphoma (HL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) has been shown in some previous studies.[8,9] The prognostic value of absolute monocyte count in MCL and its use as a simple scoring tool has been successfully proven in a few recent studies.[10] The aim of our research was to evaluate the patients with Mantle Cell Lymphoma diagnosis retrospectively followed at the Hematology outpatient clinic of Istanbul University Istanbul Faculty of Medicine between January 2006 and September 2014, and to investigate the prognostic value of AMC at the time of diagnosis by examining the clinical and demographic characteristics of all patients.

Methods

This study was conducted by retrospectively examining patient files. The study group consisted of a total of 23 cases who were diagnosed with Mantle Cell Lymphoma and followed up in the Department of Hematology, Department of Internal Medicine, Istanbul Faculty of Medicine, between January 2006 and September 2014. Our study was approved by the Istanbul University Ethics Committee at the board meeting dated 05/06/2015 and numbered 11. The files were extracted from the Hematology archive, and the information of a total of 30 patients diagnosed with MCL was examined retrospectively. However, seven of these patients were excluded from the study because the absolute monocyte count at admission could not be reached, they were lost to follow-up, or their treatment was unfinished for any reason. Age, gender, treatments they have received so far, and follow-up periods (in months) were recorded from the files of the cases. The performance status of the patients at the time of admission was evaluated according to the Eastern Cooperative Oncology Group (ECOG) classification in the physical examination section of the files. Using the ECOG scale, patients were grouped as 0, 1, and 2, 3, 4 according to their performance status.[11] From the file review, the stage of the patients at the time of admission was determined as I, II, III, and IV according to the Ann Arbor staging system. Stages I-II were classified as early stages, and stages III-IV were classified as advanced stages. At diagnosis, fever over 38°C, night sweats, and weight loss of ≥10% of body weight in the last six months were noted as B symptoms. Additionally, the laboratory findings of the patients (Hemoglobin (Hb), platelet count, LDH, leukocyte, and absolute monocyte count) were recorded. Absolute monocyte count was grouped as $> 0.5 \times 10^9$/l and $\leq 0.5 \times 10^9$/l. Prognostic findings were evaluated and recorded with the MIPI scoring system. MIPI score was grouped as low, medium, and high. The final status of the patients was determined as complete response (CR), partial response (PR), no response (stable disease), progression, relapse, exitus, and out of follow-up. Response evaluation was made according to the response criteria developed in the USA in 1999.[12] The living conditions of the patients were learned from the information in the file. Overall survival was calculated in months as the time from diagnosis to death or last follow-up. Disease-free survival was defined as the time from the date of initial diagnosis of the patients to the first date of disease recurrence or last follow-up date or death in those with CR, and the time from the first date of disease progression, last follow-up date or death in those with PR and unresponsive disease. Information about the survival status of all patients included in the study was obtained and included in the survival analysis. The effects of disease stage, performance status, LDH levels, absolute monocyte count, and MIPI scores on overall survival and disease-free survival were investigated.

Statistical analysis was performed with the Statistical Package for Social Sciences version 17.0 (SPSS-17.0, for Windows Vista) package program with a 95% confidence interval. Spearman rank test was used to evaluate the variables affecting treatment response. Kaplan Meier statistical analysis was used for survival analysis, log-rank analysis was used to evaluate variables affecting survival, and chi-square statistical analysis was used to compare qualitative variables. A value of $p<0.05$ was considered statistically significant. COX regression analysis was used to evaluate to what extent the variables that had an impact on survival contributed to the Kaplan-Meier test.

Results

A total of 23 MCL patients who were followed up at Istanbul University Istanbul Faculty of Medicine Department of Internal Medicine Hematology Polyclinic between January 2006 and September 2014 were included in the study, and the characteristics of the patients are given in Table 1. Of the 23 patients included in the study, 19 patients (82.6%) were male, and four patients (17.4%) were female. The average age of all patients was 61.56±10.99 (39-78 years), the average age of women was 64.7±3.3, and the average age of men was 60.8±2.6. When examined according to the AnnArbor staging system at the time of diagnosis, it was determined that there were no early Stage (Stage I and II) patients, five patients (21.7%) were Stage III, and 18 patients (78.2%) were Stage IV. Eight (34.7%) of the patients had B symptoms at diagnosis. There were no B symptoms in 15 patients (65.2%). ECOG performance status at diagnosis: It was 0 in 1 patient (4.3%), 1 in 13 patients (56.5%), 2 in 8 patients (34.7%), and 3 in 1 patient (4.3%). No patients had a performance score of 4 at the time of diagnosis. According to the MIPI score at the time of diagnosis, six patients (26%) were in the low-risk group, three patients (13%) were in the medium-risk group, and 14 patients (60.8%) were in the high-risk group. At admission, serum LDH levels were found to be above the upper limit of normal in 21 patients (91.3%). When the treatment received by all patients during the follow-up period was examined retrospectively, it was found that seven patients (30.4%) received one-step treatment, nine patients (39.1%) received two-step treatment, five patients (21.7%) received three-step treatments, one patient (4.3%) received four-step treatment, and one (4.3%) patients received five-step treatment. During the follow-up, it was determined that seven patients (30.4%) had undergone autologous bone marrow transplantation. The treatment protocols that the patients generally received during the follow-up period were: five patients (22%) received R-CHOP, nine patients (39%) received CHOP, three patients received (13%) BoRiD, two patients (8.6%) received BR, five patients (22%) received FCR, two patients (8.6%) received COP, two patients (8.6%) received BEAM, two patients (8.6%) received oral cyclophosphamide, 3 patients (13%) received BVR, two patients (8.6%) received lenalidomide, one patient (4.3%) received ibrutinib. All patients participating in the study were included in the survival analysis. Twelve patients (52.1%) died during follow-up. The mean overall survival time was 61±2.1 months. The 5-year overall survival rate was 34.7%. The overall survival rate and disease-free survival rate are given in Figures 1 and 2, respectively. No effect of absolute monocyte count on overall survival was detected (p=0.75). The 5-year survival percentage of patients with performance status 0 and 1, according to ECOG, was 57%, and the 5-year survival percentage of patients with performance status 2-4, according to ECOG, was 0%. The relationship with overall survival was examined in two groups as ECOG performance

Table 1. Clinical features of the MCL patients at the time of diagnosis

Feature	n (%)
Mean age (min/max)	62 (39–78)
Gender	
Male	19 (83)
Female	4 (17)
Mean absolute leukocyte (min/max)	7.3 (1.3-52) x 10^9/l
Mean absolute monocyte (min/max)	0.8 (0.2–9.1) x 10^9/l
ECOG PS	
0, 1	16 (70)
2, 3 ,4	7 (30)
Presence of B symptoms	8 (35)
Ann Arbor Classification	
I-II	0 (0)
III-IV	23 (100)
Serum LDH	
Greater than the upper limit	21 (91)
Lower than the upper limit	2 (9)
MIPI	
Low	6 (26)
Intermediate	3 (13)
High	14 (61)

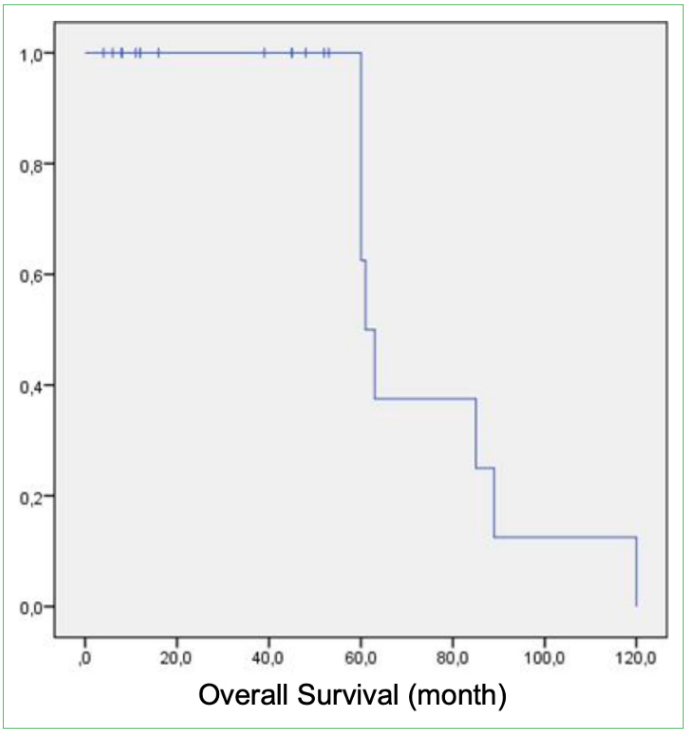

Figure 1. Overall survival rate.

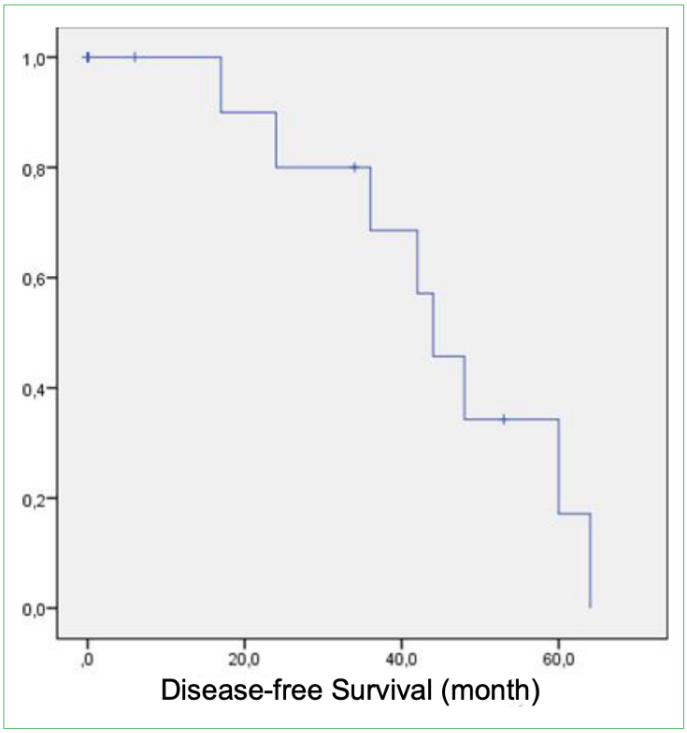

Figure 2. Disease-free survival rate.

status 0.1 and 2.3. There was no statistically significant relationship between performance status and overall survival (p=0.30). The 5-year survival percentage of patients with LDH levels below the upper limit of normal and patients with LDH levels above the upper limit of normal was determined as 50% and 33%, respectively. This relationship between LDH level and overall survival was not found to be statistically significant (p=0.16). There was no significant difference in overall survival between low-intermediate (p=0.29) and intermediate-high risk groups (p=0.73) according to the MIPI score. When the MIPI score was compared in 2 groups, low, medium, and high risk, no significant relationship was found with overall survival (p=0.30). Main prognostic factors: Cox regression analysis results of the association of absolute monocyte count, ECOG, LDH, and MIPI with overall survival are given in Table 2. There was no statistically significant relationship between absolute monocyte count and disease-free survival (p=0.06). There was no significant relationship between LDH level and disease-free survival (p=0.27). There was no significant difference between disease-free survival in the low-intermediate (p=0.56) and intermediate-high risk group (p=0.84) according to the MIPI score. When the MIPI score was compared in two groups, low, medium, and high risk, no significant relationship was found with disease-free survival (p=0.53). According to the ECOG performance score, there was no significant difference in disease-free survival between patients with scores of 0 and 1 (p=0.63) and 2 and 3 (p=0.99). The relationship with disease-free survival was examined in two groups, ECOG performance status 0.1 and 2.3. There was no statistically significant relationship between performance status and disease-free survival times (p=0.89). Cox regression analysis results of the relationship of absolute monocyte count, ECOG, LDH, and MIPI with disease-free survival are given in Table 3. Additionally, the absolute monocyte count was grouped as > 0.5 x 10^9/l and ≤ 0.5 x 10^9/l, and no significant statistical relationship was found between the overall survival and disease-free survival (p=0.31) times, respectively (Figs. 3 and 4, respectively). A moderately sig-

Table 2. Relationship of AMC, Hazar Ratio, CI 95%, p Value with the overall survival

Variable	Hazar Ratio	CI 95%	p
AMC	1.38	0.18-10.25	0.75
ECOG	0.28	0.02-3.15	0.3
LDH	1.00	0.99 – 1.01	0.16
MIPI	3.5	0.31-38.6	0.3

AMC: Absolute Monocyte Count; ECOG: Eastern Cooperative Oncology Group; LDH: Lactate Dehydrogenase; MIPI: Mantle Cell Lymphoma International Prognostic Index.

Table 3. Relationship of AMC, Hazar Ratio, CI 95%, p Value with the disease-free survival

Variable	Hazar Ratio	CI 95%	p
AMC	20.03	1.05–38	0.06
ECOG	1.7	0.18–15.4	0.89
LDH	1.00	0.99–1.00	0.27
MIPI	0.5	0.05–4.32	0.53

AMC: Absolute Monocyte Count; ECOG: Eastern Cooperative Oncology Group; LDH: Lactate Dehydrogenase; MIPI: Mantle Cell Lymphoma International Prognostic Index.

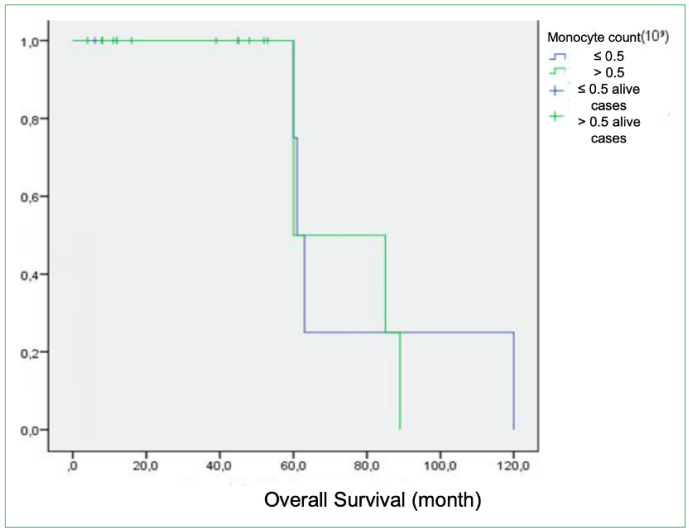

Figure 3. Relationship between AMC and overall survival.

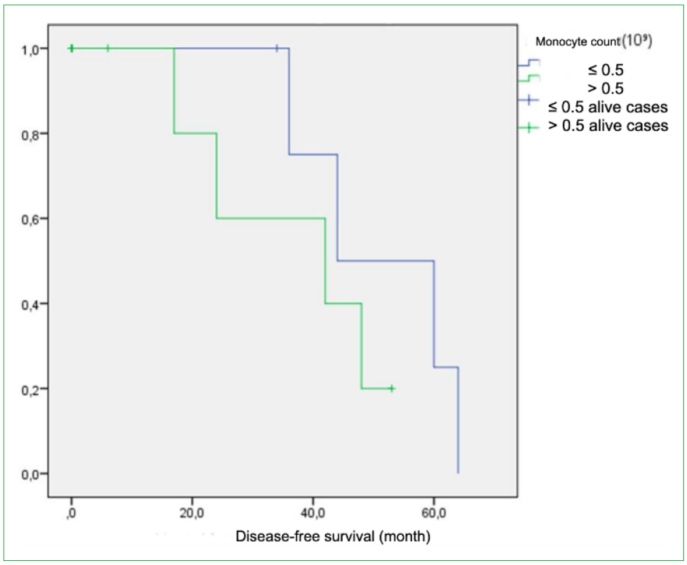

Figure 4. Relationship between AMC and disease-free survival.

nificant correlation was detected between LDH, which has prognostic value, and absolute monocyte count (r=0.499; p=0.015), but no significant correlation was found between MIPI and absolute monocyte count (p=0.27).

Discussion and Conclusion

The clinical course of mantle cell lymphoma is heterogeneous; an indolent course may be observed in some patients, and an aggressive course may be observed in others. Prognostic scoring that can predict this clinical heterogeneity has been determined. The MIPI scoring system, which is the most useful of these and uses age, performance status, LDH, and leukocyte count to predict prognosis, cannot explain the clinical discrepancy in patients due to some deficiencies. In the original MIPI scoring study, AMC was found to be associated with short survival, but COX regression analysis was not applied due to a lack of data.[13] Absolute monocyte counts above the mean value have been associated with poor survival in many lymphoma subtypes.[8] In the study conducted by Kathrin Aprile et al., the absolute monocyte count at diagnosis was the determining factor for the effectiveness of the immune system, and a low monocyte count was found to be associated with more prolonged overall and disease-free survival.[10] Additionally, in this study, a simple M2 scoring system is presented using the absolute monocyte count and β-2 microglobulin level at diagnosis. A statistically significant longer overall and disease-free survival was observed in patients with low scores determined according to this scoring system. In our study, no significant difference was found between the absolute monocyte count at diagnosis and overall and disease-free survival rates. In addition to the study of Kathrin Aprile et al. which showed the prognostic value of AMC in 97 MCL patients, another study by Young et al. supported the findings by showing the prognostic value of the absolute monocyte count at diagnosis in 103 MCL patients.[14] In this study, high monocyte count was also associated with advanced disease, leukocytosis, and short overall survival. As a result, in both studies, the absolute monocyte count at diagnosis was recommended to be used as an inexpensive, easily accessible prognostic marker in addition to MIPI. In our study, no significant relationship was found between the absolute monocyte count at diagnosis and overall survival and disease-free survival. In the study conducted by Kathrin Aprile et al., patients with absolute monocyte counts > 0.5 x 10^9/l and ≤ 0.5 x 10^9/l at diagnosis were found to be associated with statistically significant short and long overall survival, respectively.[10] In our study, when the relationship between overall and disease-free survival was examined in two groups, > 0.5 x 10^9/l and ≤ 0.5 x 10^9/l, according to the monocyte count, no significant relationship was found. Interestingly, a moderately significant correlation was detected between LDH level, whose prognostic value has been proven in previous studies, and absolute monocyte count. This hints at the prognostic power of both markers. Studies have found that advanced age, high LDH, and poor performance score (ECOG) in the MIPI scoring system are associated with shorter disease-free and overall survival.[15] In our study, no statistically significant effect of performance score and LDH level on overall and disease-free survival was detected. Average overall survival and 5-year survival can be predicted in low, intermediate, and high-risk groups determined using the MIPI scoring system.[13] In our study, no significant difference was found between the low-risk group and the low-medium-risk group or between the high-medium-risk group and the high-risk group in terms of overall and disease-free survival.

As a result, neither MIPI nor absolute monocyte count could be shown to have a prognostic power in determining overall and disease-free survival in our study. We thought that the reason why both MIPI, a proven prognostic tool, and the absolute monocyte count, which has been proven and recommended in recent studies, could not determine the overall and disease-free survival rates in our study was related to the fact that a small number of MCL patients (n=23) were evaluated in the study. Studies including larger numbers of patients with MCL are needed to evaluate the prognostic power of AMC and MIPI prognostic markers. The finding of a moderately significant correlation between LDH level, whose prognostic value has been proven in our study, and absolute monocyte count can be considered as a factor implying the prognostic power of these two markers.

Disclosures

Ethics Committee Approval: Istanbul University Faculty of Medicine Clinical Research Ethics Committee (No:2015/1116).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.N., A.A.; Design – M.N., A.A.; Supervision – M.N.; Materials – M.N., A.A.; Data collection and/or processing – A.A.; Analysis and/or interpretation – A.A.; Literature search – M.N., A.A.; Writing – M.N., A.A.

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