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ORIGINAL ARTICLE

Mantle cell lymphoma: a Turkish Multi-Center Study

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Summary

Purpose: *Mantle Cell Lymphoma (MCL) is a B-cell neoplasm with CCND1 [t(11;14)(q13;q32), cyclin D1] translocation. The guidelines recommend various treatment options based on age, performance status and comorbidities. Our purpose was to analyze the clinical features and evaluate prognostic factors for survival of 78 MCL patients.*

Methods: *We retrospectively analyzed all MCL patients in two reference Hematology Departments between January 2001 and September 2018.*

Results: *The patient median age was 62 years (34-86) and 78.2% of them were male. The treatment regimens were R-CHOP in 42.3%, R-Bendamustine in 26.9%, HyperCVAD in 9% and R-CHOP/R-DHAP alternating in 7.7%. Only 13 patients underwent autologous stem cell transplantation. Median overall survival (OS) was 77.8 months (53.8-101.8) and median disease-free survival (DFS) was 20.6 months (14.2-26.9), all patients included. Univariate analysis showed that MCL International Prognostic Index and neutrophil count effected OS in all groups (p=0.047 and p=0.001). Multivariate analysis showed that the neutrophil count at diagnosis was independent prognostic risk factor (HR=0.209, 95% confidence interval 0.069-0.629, p=0.005) for OS. The median OS was 77.8 months in absolute neutrophil count (ANC) less than 7.5×10³/μL and 14.8 months in ANC more than 7.5×10³/μL (p=0.001).*

Conclusions: *Median OS is somewhat prolonged in the last years with new treatment approaches but MCL is still an incurable disease. The first choice of treatment in MCL patients was R-CHOP. Higher neutrophil count at the time of diagnosis has a detrimental effect on OS.*

Key words: *mantle cell lymphoma, neutrophil, prognostic score*

Introduction

Mantle cell lymphoma (MCL) is a B-cell neoplasm with CCND1 [t(11;14) (q13;q32), cyclin D1] translocation. It accounts for 3-6% all Non-Hodgkin lymphomas and the disease has poor prognosis. MCL is a heterogeneous disease. There are two different type (classical and leukemic non-nodal MCL) in the World Health Organization 2016 updated classification [1]. Clinically, most patients have lymphadenopathy, hepatosplenomegaly and bone marrow involvement. The majority of patients has extranodal disease, usually gastointestinal involvement [2]. There are different prognostic scores, the most used is the Mantle Cell Lymphoma International Prognostic Index (MIPI) score (MIPI-c score) [3,4]. There are four independent prognostic factor in defining MIPI score: lactate dehidrogenase (LDH), white blood cell count (WBC), age, performance status and Ki-67 proliferation index [5,6]. Blastoid cytology was related with worse PFS and OS in MIPI-c. Additionaly, there are genetic abnormalities associated with poor prognosis, such as deletion of TP53 and CDKN2A [7].

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The guidelines suggest various treatment options based on age, performance status (fitness status) and comorbities [8]. Autologous stem cell transplantation (ASCT) is standard first-line treatment in younger fit patients [9]. For elderly patients, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) or bendamustin-rituximab (BR) are recommended [8]. In the present study, we aimed to analyze the clinical characteristics and evaluate prognostic factors of MCL patients.

Methods

In this is retrospective study, we analyzed all MCL patients in two reference Hematology Departments between January 2001 and September 2018. All patients gave informed consent to be included in the study. This study complied with the Declaration of Helsinki. The diagnosis of MCL was established by local hematopathologists. Patient age, gender, presence of B symptoms, date of diagnosis, leukocyte, lymphocyte, neutrophil, monocyte count, hemoglobin level, platelet counts at diagnosis, cyclin D1 and SOX-11 results (immunohistochemical staining) and cytogenetic analysis results were retrospectively analyzed. Karyotype analyses were performed on bone marrow cells in both centers. G-banded technique was used, culture for 24h at 37°C without stimulation. Additionally, bone marrow involvement, stage, extranodal involvement sites, and MIPI score were analyzed [4]. In addition, first treatment choices, watch and wait, R-CHOP (rituximab 375mg/m^2 on day 1, cyclophosphamide 750 mg/m^2 on day 1, doxorubicin 50 mg/m^2 on day 1, vincristine 1.4 mg/m^2 on day 1 and oral prednisone 100 mg/m^2 days 1-5), R-CHOP/R-DHAP alternating (3 cycles R-CHOP alternating with 3 cycles rituximab, cisplatin, cytosine arabinoside, and dexamethasone), R-HyperCVAD (rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone), MA (high-dose methotrexate 1 g/m^2 on day 1 and cytarabine 3 g/m^2 q12h days 2,3), BR (rituximab, bendamustine), R-CVP (rituximab 375mg/m^2 on day 1, cyclophosphamide 1000 mg/m^2 on day 1, vincristine 2 mg on day 1, oral prednisone 100 mg/m^2 days 1-5), R-ICE (rituximab, etoposide, carboplatin, ifosfamide, mesna), R-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin), R-GCVP (rituximab, gemcitabine, cyclophosphamide, vincristine, oral prednisone) were recorded. Treatment response, status of autologous stem cell transplantation (ASCT), relapse status, salvage regimen (if any) and date of last communication were recorded. Primary refractory disease (stable disease) was defined as disease progression or failing to attain a complete response (CR) during first-line chemotherapy [10]. Relapsed disease was defined as disease progression after disappearance of all clinical and radiographic evidence of disease for more than two months [10]. Salvage regimen was indicated when no response to first induction therapy or relapsed status was achieved.

Statistics

Categorical and continuous data were expressed as percents (%) and medians (range) and were compared by the chi-square (x^2) and Mann-Whitney U tests, respectively. The primary endpoints of the study were OS and DFS. Survival analyses were computed by the Kaplan-Meier method and log-rank test was performed to evaluate differences between groups. OS was calculated from diagnosis to the date of death from of any cause. Patients who were alive at last follow-up were censored at this time for OS computations. DFS was calculated in patients who attained CR from the time of CR to relapse or death in remission. Parameters related to survival were investigated by Cox regression univariate and multivariate analyses. In univariate analysis, significant parameters at $p<0.1$ were incorporated into multivariate analyses. The analysis was performed with the IBM SPSS Statistics for Windows, version 23.0 (Armonk, NY) and statistical significance was set at $p<0.05$.

Results

Patient characteristics

In a total of 78 patients, the median age was 62 years (34-86) and 78.2% of the patients were male. The median number of neutrophils, lymphocytes, monocytes at diagnosis was 3.8 (0.7-45)×10^3/μL, 3.1 (0.5-91.6)×10^3/μL and 0.5 (0.1-47.1)×10^3/μL, respectively. According to the clinical stage, 80.8%, 10.3%, 6.4%, 2.6% of patients had stage 4, 3, 2 and 1, respectively. Out of the total patients 83.3% had extranodal organ involvement, and the most common extranodal involvement sites were spleen, bone marrow and gastrointestinal system. Data on baseline clinical characteristics are presented in Table 1.

There were only 9 patients with cytogenetic analyses evaluated. One of 9 patients had deletion on chromosome 7 and another one had deletion on Y chromosome. The cytogenetic analyses of other patients were with normal karyotype. SOX-11 analysis was performed on only 10 patients. Eight patients were SOX-11 positive.

Treatment regimens

For initial therapy, only one patient had no chemotherapy because of age and general condition. The other treatment choices were 42.3% R-CHOP, 26.9% BR, 9% HyperCVAD, 7.7% R-CHOP/R-DHAP alternating and other regimen, as shown in Table 1. Only 13 patients underwent ASCT, with conditioning regimen mitoxantrone and melphalan. Only one patient received carmustine, etoposide, cytarabine, and melphalan (BEAM) for ASCT. Response to initial chemotherapy: 55.3%, 23.7%, 14.5%, 5.3%, 1.3% of patients attained CR, PR, SD,

Table 1. Patient clinical characteristics (n=78)

Characteristics	*Values*
Age (years), median (range)	62 (34-86)
Male, n (%)	61 (78.2)
Neutrophil, median (range) ×10³/μL	3.8 (0.7-45.1)
Lymphocyte, median (range) ×10³/μL	3.1 (0.5-91.6)
Monocyte, median (range) ×10³/μL	0.5 (0.1-47.1)
Platelet, median (range) ×10³/μL	202 (55-402)
Patients with B symptoms, n (%)	46 (59)
Clinical stage, n (%)	
I	2 (2.6)
II	5 (6.4)
III	8 (10.3)
IV	63 (80.8)
Extranodal disease, n (%)	65 (83.3)
Disease involved organ, n (%)	
Spleen	31/65 (47.6)
Bone marrow	18/65 (27.6)
Gastrointestinal system	10/65 (15.3)
Waldayer ring	1/65 (1.5)
Bulky mediastinal mass	1/65 (1.5)
Spleen and bulky mediastinal disease	3/65 (4.5)
Spleen and waldeyer ring	1/65 (1.5)
MIPI score, n (%)	
Low risk	21 (26.9)
Intermediate risk	22 (28.2)
High risk	34 (43.6)
N/A	1 (1.3)
Induction treatment regimen, n (%)	
R-CHOP	33 (42.3)
BR	21 (26.9)
HyperCVAD (without R)	7 (9)
R-CHOP/R-DHAP	6 (7.7)
R-HyperCVAD	3 (3.8)
HDMTX-cytarabin (MA)	1 (1.3)
R-CVP/(CVP,without R)	1/1 (1.3/1.3)
R-ICE	1 (1.3)
R-CVA	1 (1.3)
R-GCVP	1 (1.3)
No treatment	1 (1.3)
N/A	1 (1.3)
Response of initial regimen, n (%)	
Complete remission	42(55.3)
Partial response	18 (23.7)
Stable disease	11 (14.5)
Progressive disease	1 (1.3)
N/A	4 (5.3)
ASCT	13/77 (16.8)

MIPI: Mantle Cell Lymphoma International Prognostic Index; R-CHOP: rituximab + cyclophosphamide+doxorubicin + vincristine + oral prednisone; R-CHOP/R-DHAP alternating: 3 cycles R-CHOP alternating with 3 cycles rituximab + cisplatin + cytosine arabinoside + dexamethasone; R-HyperCVAD: rituximab + hyperfractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone; MA: high-dose methotrexate + cytarabine; BR: rituximab + bendamustine; R-CVP: rituximab + cyclophosphamide + vincristine + oral prednisone; R-ICE: rituximab + etoposide + carboplatin + ifosfamide + mesna; R-CVAD: rituximab + cyclophosphamide + vincristine + doxorubicin; R-GCVP: rituximab + gemcitabine + cyclophosphamide + vincristine + oral prednisone

no evaluation, PD, respectively. Two patients died after chemotherapy and another two didn't come to hospital for evaluation, totally four patients (5.3%) were lost to follow-up.

There were 32 (41%) patients with relapses. Two patients did not receive salvage regimen because of their general condition. Salvage regimens were given to 33 patients. Three patients had salvage chemotherapy because of SD (no relapse). Salvage regimens were HyperCVAD with R/without R (4/4 patients) and MA 3 patients, HyperCVAD/MA alternating 1 patient. Ifosfamide, etoposide and carboplatin (ICE) was given to 3 patients (1 with rituximab). DHAP regimen was given to 3 patients (1 with rituximab, 1 without rituximab, 1 alternating with CHOP). Bortezomib-containing regimens were given to 4 patients; only bortezomib to 1 patient, with rituximab to 2 patients, with fludarabine-cyclophosphamide to 1 patient. Ibrutinib was given only to 3 patients. Bendamustine with R was given to 3 patients. Fludarabine, cyclophosphamide, rituximab were given to 1 patient, and CVP to 1 patient. Because of poor general status, rituximab was only given for salvage to 2 patients (1 with cyclophosphamide).

Survival outcomes

The median OS was 77.8 (53.8-101.8) months (Figure 1), and median DFS was 20.6 months (14.2-26.9). The 3-year OS and DFS rates were 64.3% and 52.9% in the ASCT group and 63.6% and 39.9% in the non-ASCT group (p=0.193 and p=0.569, respectively).

The univariate analysis showed that MIPI and neutrophil count impacted OS (p=0.047 and p=0.001). The median OS was not reached in the low MIPI group vs. 33.5 months in intermediate

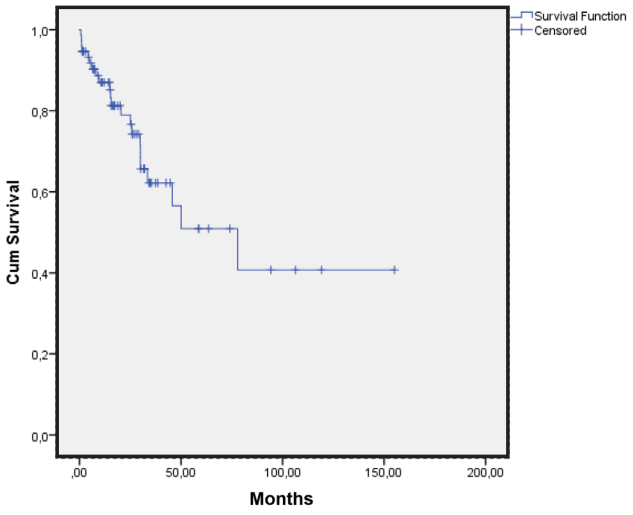

Figure 1. Overall survival of all patients.

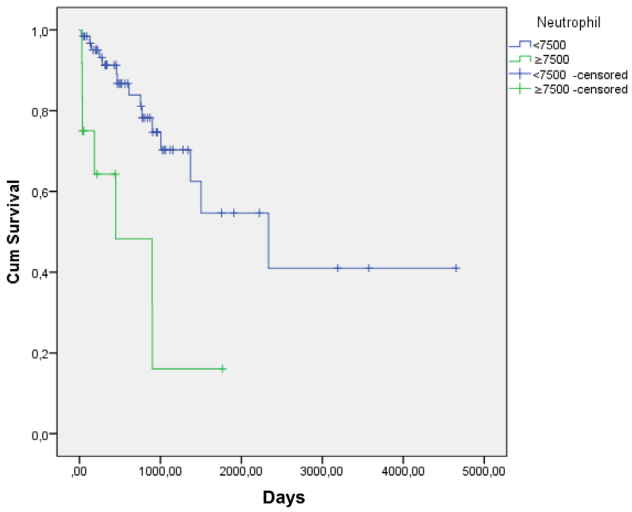

Figure 2. Overall survival rates according to two neutrophil groups (p=0.001).

MIPI group and 45.6 months in high MIPI group (p=0.047). The median OS was significantly higher in patients with ANC less than 7.5×10^3/μL compared to higher than 7.5×10^3/μL (77.8 vs. 14.8 months, p=0.001) (Figure 2). The other factors (age, gender, stage, bone marrow involvement, extranodal involvement, extranodal disease sites, lymphocyte, monocyte, platelet count and initial chemotherapy) did not impact ASCT OS. The multivariate analyses showed that the high neutrophil count at diagnosis was independent worse prognostic risk factor for OS (p=0.005).

The univariate analysis showed that age <65 marginally affected DFS (p=0.074). The other factors [gender, stage, MIPI score, bone marrow involvement, extranodal involvement, extranodal disease sites (spleen, gastrointestinal tract), lymphocyte, monocyte, neutrophil, platelet count and ASCT] had not affected DFS. The univariate analysis showed that initial chemotherapy had no impact on DFS (p=0.13). DFS according to treatment regimen: the patients who received R-CHOP/R-DHAP alternating, R-CHOP, BR, and HyperCVAD with or without R had 6.8 (14.2-30.3), 22.2 (11.8-13.9), 12.9 (8.7-37.8) and 23.3 (13.4-27.7) months, respectively.

The multivariate analyses showed that age <65 remained marginally significant for DFS (p=0.074).

Discussion

Survival has been prolonged in recent years with new treatment modalities, but MCL is still an incurable disease. Currently, the median OS is 4-5 years [11]. If a patient has good performance status, no B symptoms, normal LDH, nonbulky disease, leukemic non-nodal variant and low Ki-67, the watch and wait policy can be followed [12]. In the present study, there was only one patient in the watch and wait policy.

The most commonly used treatment strategy is consolidation with ASCT. There are several chemotherapy regimens for younger patients such as R-CHOP and high-dose cytarabine [13] and R-CHOP/R-DHAP alternating [14]. In the literature, using chemotherapy with high dose cytarabine and ASCT shows significant effect on OS for young patients than R-CHOP alone [14]. In the present study, most of the patients received R-CHOP and secondly BR. Before ASCT, R-HyperCVAD/MA regimen was also used. In a recent study, Alwasadi et al showed that the median OS duration in the ASCT group was 68 months [15]. They found higher OS and PFS rates in the ASCT group. In this study, the most preferred regimen for salvage was HyperCVAD. The median DFS was 20.6 months in the present. Since the median age was 62 years in our study, most clinicians opted not to give high-dose cytarabine.

The majority of MCL patients are elderly [16-18]. Rummel et al showed that BR is better than R-CHOP on PFS for indolent lymphomas, especially MCL. In this retrospective study, R-CHOP showed somewhat similar DFS when compared to BR (p=0.36).

R-CHOP was superior to rituximab, fludarabine, cyclophosphamide (R-FC) in the elderly patients [19]. In the present study, we preferred BR in most of the patients as salvage treatment. Ibrutinib, lenalidomide, bortezomib are used with variable success in relapsing patients [20-23]. In our study, only few patients received ibrutinib and bortezomib.

Hoster et al found the MIPI score from three randomized trials. They performed Cox regression analyses without granulocyte number because of high number of multivariate numbers. They performed univariate analyses and they found granulocyte number was significant on OS. In multivariate analyses they did improve MIPI score with white blood cell count because of missing data on granulocytes [4]. We analyzed univariate and multivariate Cox regression analyses and found that if the neutrophil count was higher than 7.5×10^3/μL, the patients had significantly shortened survival. In this study, it was shown that the number of increased neutrophils at the time of diagnosis was significantly detrimental on OS when multivariate analyses performed.

This study is crucial in terms of taking a snapshot of the MCL approach at the two major Turkish referral centers. However, the study has

some limitations because it was designed in a retrospective manner and had small number of study participants.

In conclusion, the first choice of treatment in the MCL patients was R-CHOP in this multicenter Turkish study. The higher number of neutrophil count at the time of diagnosis has a detrimental effect on OS. In order to better elucidate the value of the prognostic indices and treatment approaches with novel agents, larger randomized controlled studies are needed.

Author contributions

M.O., E.K., M.T. and H.G. contributed to design; M.O., O.M. and E.K. contributed to data collection; M.O., U.Y.M. and H.G. wrote the main manuscript text; M.O. and U.Y.M. prepared table and figures. All authors reviewed the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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