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Araştırma Makalesi / Research Article

Clinicaland Laboratory Characteristics of Our Mantle Cell Lymphoma Patients: A Cross Sectional Study

Mantle Hücreli Lenfoma Hastalarımızın Klinik ve Laboratuvar Özellikleri: Kesitsel Bir Çalışma

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Abstract

Mantlecelllymphoma (MCL) compriseslessthan 10% of non-Hodgkin'slymphomacases. Majorindependent risk factorsareidentified as the MCL International Prognostic Index (MIPI) and Ki-67 proliferationindex of tumor. Theaim of thisstudy is retrospectivelyevaluate MCL patientstreatedandfollowed-up in ourdepartment. MaterialsandMethods: Thisstudyincluded 27 MCL patientsmedicalrecords of whomcould be reached. Thedatawasreviewedtofigureout MIPI score, bone marrowinvolvement, extranodalinvolvement, treatmentprotocols, treatmentresponse, relapsestatus, andtransplanthistory. Patientswerefollowed-upfor a meanduration of 64.4 (1-246) months. Subsequenttothefirst-linetreatment, completeresponsewasachieved in 17 (63%) andpartialresponsewasachieved in 3 (11%) patients, whereas 7 (26%) patientsexperienceddiseaseprogression. Median PFS followingfirst-linetreatmentwas 29 (3-120) months. Based on theclassificationby MIPI scoring, low-risk patients had significantlylongermediansurvivalthanthat of high-risk patients (194 monthsvs 126 months, p=0.04), andthepatients at moderate-risk had significantlylonger PFS comparedtohigh-risk patients (41month vs 3 months, p=0.025). Medianage, stage III-IV, andshortduration of PFS in patientswithhigh MIPI scorewereourfindings in parallelwithavailableliterature. R-hyper-CVAD/MTX-AraCwasmostlypreferredfirst-linetreatment at ourcenterwith a shortermedian PFS comparedtoliterature. Giventheexpandinguse of target-driventherapiesfor MCL, webelieveourresultsarenoteworthy in comparing-suchtherapieswithpre-existingtherapies.

Keywords: Mantle cell lymphoma, treatment, prognosis

Özet

Mantle hücreli lenfoma (MHL), Hodgkin dışı lenfoma vakalarının %10'dan daha azını oluşturur. Başlıca bağımsız risk faktörleri; MHL Uluslararası Prognostik İndeksi (MIPI) ve Ki-67 tümör proliferasyonu indeksidir. Bu çalışmanın amacı; bölümümüzde takip ve tedavisi yapılan MHL hastalarının geriye dönük olarak değerlendirilmesidir. Çalışmaya tıbbi kayıtlarına ulaşılabilen toplam 27 MHL hastası dahil edildi. Bu veriler incelenerek hastaların, MIPI skoru, kemik iliği tutulumu, ekstranodal tutulum, tedavi protokolleri, tedaviye yanıtı, nüks durumu ve nakil öyküsü kaydedildi. Bulgular: Hastalar ortalama 64,4 (1-246) ay süreyle takip edilmişti. Hastaların 5'ine (%18) otolog, 2'sine (%8) allogeneikhematopoietik kök hücre nakli yapılmıştı. Birinci basamak tedavi sonrası 17 (%63) hastada tam yanıt, 3 (%11) hastada kısmi yanıt elde edilirken 7 (%26) hastada progresyon saptandı. Birinci basamak tedavi sonrası medyan progresyonsuzsağkalım 29 (3-120) ay olarak hesaplandı. MIPI skorlamasına göre düşük riskli hasta grubunun medyan sağkalımı, yüksek riskli hasta grubuna göre daha uzun (194 ay vs 126 ay, p=0.04), orta riskli hasta grubunun progresyonsuzsağkalımı yüksek riskli hasta grubuna göre daha uzun (41 ay vs 3 ay, p=0.025) bulundu. Sonuç olarak, çalışmamızda hastaların medyan tanı yaşı, çoğunun evre III-IV olması, MIPI skoru yüksek hastalarda progresyonsuzsağkalımın kısa olması literatürle uyumlu bulgular olarak saptandı. Merkezimizde en çok tercih edilen birinci basamak tedavi R-hyper-CVAD/MTX-AraC olup literatüre kıyasla medyan progresyonsuz sağ kalım süresi daha kısa bulundu. MHL'de giderek artan hedefe yönelik tedavi kullanımı dikkate alındığında, bu tür tedavilerle eskiden beri mevcut olan tedavilerin kıyaslanması açısından sonuçlarımızın önemli olduğu kanaatindeyiz.

Anahtar Kelimeler: Mantle hücreli lenfoma, tedavi, prognoz

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1. Introduction

Mantle cell lymphoma (MCL) comprises less than 10% of non-Hodgkin's lymphoma cases and has a heterogeneous clinical manifestation along a spectrum from indolent to aggressive. It is characterized by the presence of t (11;14) translocation. Usually, MCL arises in males and presents with advanced stage.1Immunophenotyping of patients reveals IgM, IgD, CD20, CD5, and cyclin D1 expression whereas negative for CD10 and Bcl-6. Pan-B-cell antigens CD19, CD20, CD5, and FMC7 are frequently expressed, with rare cases tested negative for CD5 and positive for CD23.2Certain clinical and biological features are of prognostic importance for MCL. Among them, major independent risk factors were identified as the MCL International Prognostic Index (MIPI) and Ki-67 proliferation index of the tumor.3 MCL treatment has improved over the last 20 years attaining prolongation of survival. Today, chemoimmunotherapy with or without consolidation of autologous stem cell transplantation is regarded as the standard of care.4,5 The aim of this study is to retrospectively evaluate MCL patients treated and followed-up in our department.

2. Materials and Methods

This study included 27 MCL patients medical records of whom could be reached. Patient data was retrieved by retrospective screening of patient charts and/or hospital records.

The data was reviewed to figure out age, gender, MIPI score, presence of B-symptoms, bone marrow involvement, extranodal involvement, treatment protocols, treatment response, relapse status, and transplant history for each patient.

Statistics

All statistical analyses were performed by using SPSS v.21.0 (IBM Corp., Armonk, NY, USA). Categorical and continuous variables was expressed in percent (%) and as median (range). Primary endpoints of the study were overall survival (OS) and progression-free survival (PFS). Survival analyses were done through Kaplan-Meier method and inter-group differences were compared using log-rank test. A p-value < 0.05 was considered statistically significant.

3. Results

Of the patients, 10 (37%) were females and 17 (63%) were males. Median age at the time of diagnosis was 63 (40-91) years. Laboratory findings and clinical features of the patients at diagnosis were summarized in Tables 1 and 2, respectively.

Table 1. Laboratoryfindings at diagnosis

	Median (min-max)
Hemoglobin (g/dL)	11.9 (7.6-16.9)
White blood cell count (/mm^3)	7400 (2000-134000)
Absolute neutrophil count (/mm^3)	4500 (1200-13370)
Absolute lymphocyte count (/mm^3)	1900 (320-120000)
Platelets (/mm^3)	215000 (37000-402000)
Erytrocytesedimentation rate (mm/h)	34 (4-104)
Lactate dehydrogenase (LDH) (U/L)	377 (208-1046)
Blood ureanitrogen (BUN) (mg/dL)	15.1 (5.4-38)
Creatinine (mg/dL)	0.83 (0.52-2.6)
Uricacid (mg/dL)	6.1 (3.9-13.7)
Total protein (g/dL)	7 (5.38-9)
Albumin (g/dL)	4.2 (3.25-5.2)
Aspartate aminotransferase (U/L)	22 (11-52)
Alanine aminotransferase (U/L)	14 (5-80)
Alkaline phosphatase (U/L)	146 (21-518)
Gamma-glutamyltransferase (U/L)	23.8 (10-83)
Beta-2 microglobulin (mg/dL)	0.5 (0.16-9.03)

Table 2. Clinical features of patients

	Number of Patients (%) n=27 (100%)
B-symptoms	
Yes	13 (48%)
No	14 (52%)
Bone marrowinvolvement	
Yes	12 (44%)
No	15 (56%)
EasternCooperativeOncologyGroup (ECOG) performancescore	
0	12 (45%)
1	14 (52%)
≥2	1 (3%)
Lactatedehydrogenase (LDH)	
≥1	16 (59%)
<1	11 (41%)
Ki-67 index	n=10 (100%)
<30%	5 (50%)
≥30%	5 (50%)
Extranodalinvolvement	
Yes	19 (70%)
No	8 (30%)
Splenomegaly	
Yes	7 (26%)
No	20 (74%)
t (11;14)	n=7 (100%)
Positive	6 (86%)
Negative	1 (14%)

MCL was classified at diagnosis as stage II in 2 (8%), stage III in 7 (26%), and stage IV in 18 (66%) patients. From the point of MIPI score, 6 (22%) patients had low risk, 11 (41%) had moderate risk, and 10 (37%) had high risk. Patients were followed-up for a mean duration of 64.4 (1-246) months during which 9 (33%) died, 17 (63%) survived, and one patient was lost to follow-up. Breakdown of deaths by cause was as follows: infection in 4 (2 fungal pneumonia, one bacterial pneumonia, and one hepatosplenic candidiasis), disease progression in 4, and alveolar hemorrhage in one out of 9 deaths.

Of the patients, 5 (18%) underwent autologous and 2 (8%) underwent allogeneic hematopoietic stem cell transplantation (HSCT). Diagnostic tissues of the patients were collected from lymph node in 18 (67%), gastrointestinal tract in 4 (14%), bone marrow in 2 (7%), nasopharynx in other 2 (7%), and eyelid in the last one (3%) patient. Group of patients who died were compared to those who survived, with no significant difference in hemoglobin, leukocyte, platelet, or lactate dehydrogenase (LDH) values at the time of diagnosis.

Regimens given to our patients as first-line treatment modalities were: R-hyper-CVAD/MTX-AraC (rituximab plus hyper-fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with high-dose methotrexate-cytarabine) in 10 (36%), R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone) likewise in 10 (36%), R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisolone) in 4 (16%), sequential R-CHOP/R-DHAP (rituximab plus cisplatin, high-dose citarabine, dexamethasone) in 2 (8%) and R-Bendamustine in one (4%) patient. Subsequent to the first-line treatment, complete response (CR) was achieved in 17 (63%) and partial response was achieved in 3 (11%) patients, whereas 7 (26%) patients experienced disease progression. PFS following the first-line treatment lasted for a median term of 29 (3-120) months. Out of 17 patients, in whom CR was attained with first-line treatment, disease relapsed in 8 (47%) patients.

Of 8 relapses, 6 (75%) were administered BORID (bortezomib, rituximab, and dexamethasone) and one (13%) was administered R-hyper-CVAD/MTX-AraC regimen, the last patient was lost before salvage therapy could be administered. Subsequent to the second-line treatment, 4 (50%) patients demonstrated CR and 3(38%) patients suffered disease progression.

Based on the classification by MIPI scoring, low-risk patients had a significantly longer median survival than that of high-risk patients (194 months vs 126 months, p=0.04) (Figure 1), and the patients at moderate-risk had significantly longer PFS compared to high-risk patients (41 month vs 3 months, p=0.025) (Figure 1).

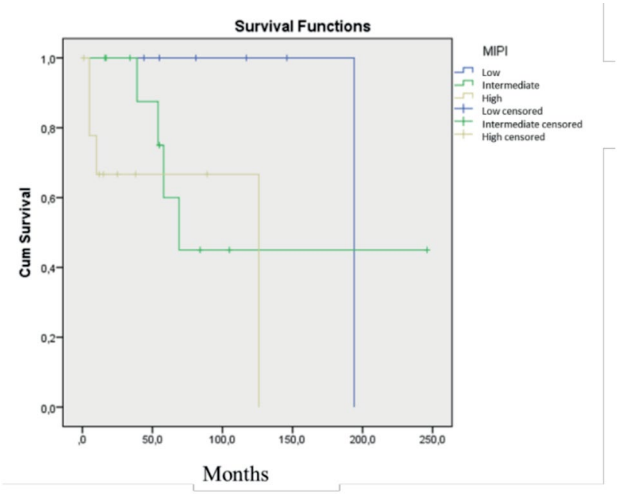

Figure 1. Curve of overall survival by MIPI score

Median survival was longer in patients whose diagnostic work-up included lymph node examination than those whose diagnostic work-up included bone marrow examination (126 months vs 10 months, p=0.031). Similarly, median survival was longer in patients with diagnostic tissue examination collected from gastrointestinal tract than those with diagnostic bone marrow examination (58 months vs 10 months, p=0.046) (Figure 2). Median PFS was also significantly longer in patients with diagnostic lymph node examination compared to those with diagnostic bone marrow examination (41 months vs 3 months, p=0.025)

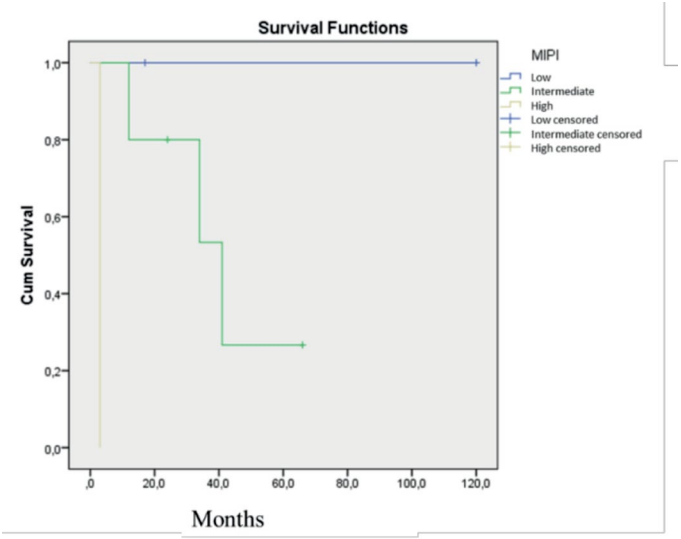

Figure 2. Curve of progression-free survival by MIPI score

Review of Eastern Cooperative Oncology Group (ECOG) performance scores of patients turned out that there were no patient with ECOG performance score of 3 or 4. Group of patients with ECOG performance score 0 had pursued a significantly longer median survival (194 months vs 69 months, p=0.003) and PFS (p=0.023) compared to the patients with ECOG performance score of 1.

Most of the patients who underwent HSCT remained in complete remission, nevertheless, HSCT was not found to have a significant effect on median survival (194 months vs 126 months, p=0.074).

4. Discussion

Although used to be referred to as a low-grade and slow-progressing lymphoma previously, MCL is today considered as an aggressive, incurable lymphoma incorporating the worst characteristics of low to high stage lymphomas. Almost all MCL cases require systemic treatment.6 Due to the emergence of novel targeted therapies, place of autologous HSCT in the event of first complete remission has become debatable.

MCL usually arises at advanced age, with an incidence rate increasing directly proportional to increasing age. Median age at diagnosis in our study was 63 years, in compliance with the previous literature.7,8 MCL is 2- to 3-fold more common in males compared to females.9 Consistently, males were affected 1.7 times as frequently as females in our study.

B-symptoms are detected in 40-50% of patients.10 In line with the literature data, 14 (52%) of our patients had B-symptoms at diagnosis.

Examination for splenomegaly revealed 7 (26%) of our patients had splenomegaly which is less than the figures mentioned in literature (40-60%) (10). We suppose this might be related to the variations of methods employed in splenomegaly examination.

In most of the former studies, as much as 70%, or higher, of patients were diagnosed at an advanced disease stage.11 Likewise, 92% of our patients were diagnosed at stage III or IV.

MIPI score is a well-established determinant of prognosis.12 In consistency with the former results in literature, when our patients were classified according to their MIPI scores, low-risk patient group had a significantly longer median survival (p=0.04) than that of high-risk patients and also the patients at moderate-risk had significantly longer PFS (p=0.025) compared to high-risk patients.13

Ki-67 proliferation index is identified as one of the factors with highest prognostic value14, however, only 10 patient in our cohort had documented Ki-67 proliferation index and therefore, we were not able to conduct survival analysis for Ki-67 proliferation index.

We suppose that the longer PFS in our patient group with diagnostic lymph node examination than the patient group with diagnostic bone marrow examination is attributable to the more advanced disease stage in patients who have bone marrow involvement at diagnosis.

Our patients had received 2 most used first-line treatment regimens according to the literature15 (R-hyper-CVAD/MTX-AraC, 36% and R-CHOP, 36%). Among the 10 receivers of each of R-hyper-CVAD/MTX-AraC and R-CHOP, CR was attained in 7 (70%) and 5 (50%), respectively and in harmony with previous results.11,16 Our shorter median PFS following first-line therapy (29 months) in comparison to the literature data is a likely result of difference in characteristics and size of patient population.17

Comparison between the groups who had been administered R-CHOP and R-hyper-CVAD/MTX-AraC as first-line treatment did not indicate any significant difference in overall survival (p=0.812) or PFS survival (p=0.458), as also noted in previous literature.12

In the patient subgroup in whom disease relapsed and thereupon BORID treatment was applied, CR was reached in 50%, similar to the figures in previous literature.18

Most of our patients who had undergone HSCT remained in complete remission. However, on contrary to literature data (8,17), HSCT did not act significantly on median survival (p=0.074) which we believe is due to our small number of patients who underwent HSCT.

5. Conclusion

Median age at diagnosis, predominant disease status of stage III-IV at diagnosis, and short duration of PFS in patients with high MIPI score were our findings in parallel with available literature. R-hyper-CVAD/MTX-AraC was the mostly preferred first-line treatment at our center. In light of our shorter median PFS compared to the literature data, it behooves our center to re-consider our first-line treatment preferences. Although majority of HSCT recipients in our cohort remained in complete remission, HSCT did not play a significant role on median survival. On the other hand, due to the small number of transplant recipients we rather abstain from making an overall conclusion on this matter. Given the expanding use of target-driven therapies for MCL, we believe our results are noteworthy in comparing such therapies with the pre-existing therapies.

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