Original Article

Clinical profile, treatment, and outcomes of patients with mantle cell lymphoma treated in a tertiary care center in South India

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ABSTRACT

Introduction: Mantle cell lymphoma has an aggressive course, with unfavorable outcomes. **Subjects and Methods:** A retrospective analysis was undertaken and 77 cases were identified between 2009 and 2014. **Results:** Median age was 55 years with a male to female ratio of 6:1. Patients with pure nodal disease at presentation were fewer than with extranodal disease (53.2%). Most common extranodal site was bone marrow. A number of patients with low-, low-intermediate, high-intermediate, and high-risk International Prognostic Index (IPI) scores were 6, 24, 22, and 25. Treatment consisted of cyclophosphamide,hydroxydaunorubicin, oncovin, prednisolone (CHOP) or R-CHOP regimens. Median survival was 21 months. Median overall survival with early and advanced disease was 31 and 18 months ($P = 0.02$). Patients who received R-CHOP survived better than those given CHOP, 30 and 16 months ($P = 0.0002$). There was no difference in survival with respect to age, gender, extranodal, or bone marrow involvement. **Conclusions:** Most patients presented with extranodal disease, advanced stage, and high IPI. Although rituximab has improved survival, intensive chemotherapy would be required to improve survival.

Key words: CHOP, mantle cell lymphoma, R-CHOP

INTRODUCTION

Mantle cell lymphoma (MCL) is a distinct subtype of B-cell non-Hodgkin's lymphoma (NHL) and comprises 4%–9% of NHL.[1-4] MCL is considered as an intermediate grade lymphoma with an aggressive course. It is associated with unfavorable outcomes and a survival of 2–5 years[5,6] due to advanced presentation and poor treatment responses. On a molecular level, MCL is characterized by the t(11;14) (q13;32) translocation, resulting in an overexpression of cyclin D1 due to a rearrangement involving the BCL-1 gene locus.[1,7,8] Anthracycline-based chemotherapy that has improved overall survival (OS) in high-grade lymphomas, however, has failed to show benefit in MCL.[9,10] We here present the clinical profile, treatment, and outcomes of patients treated with this lymphoma at our center.

SUBJECTS AND METHODS

A retrospective analysis was undertaken at Kidwai Memorial Institute of Oncology, a tertiary care centre in South India. The patients diagnosed histopathologically (confirmed by

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immunohistochemistry) with MCL between the years 2009 and 2014 were analyzed. Evaluation included hemogram, biochemistry, serology, lymph node excision biopsy/core biopsy of the presenting extranodal site, unilateral bone marrow aspiration/biopsy, with either whole-body positron emission tomography-computed tomography (CT) or CT imaging. Formalin-fixed paraffin-embedded sections were utilized for immunohistochemistry. These tissues were stained with conventional hematoxylin-eosin and immunostaining. Follow-up was done as per the standard criteria. The survival analysis was done by Kaplan–Meier analysis, using the log-rank test.

RESULTS

A total of 77 patients were identified and analyzed; the results are as in Table 1. The median age of the cohort was 55 years (35–72) with a six times male preponderance. 37 (48%) patients had B-symptoms at presentation. 46.8% of the patients presented with pure nodal disease and 53.2% with extranodal disease. Most common sites of extranodal involvement were bone marrow followed by intestine, stomach, spine, and lungs [Table 1]. 27 (35.06%) patients presented with bone marrow involvement. Five (26%) of those with extranodal disease had more than one extranodal site involved. The number of patients who presented in stages I, II, III, and IV involvement were 3 (3.9%), 13 (16.8%), 28 (36.4%), and 33 (42.9%), respectively. The number of patients with low, low-intermediate, high-intermediate, and high risk International Prognostic Index (IPI) scores was 6 (7.7%), 24 (31.2%), 22 (28.6%), and 25 (32.5%), respectively.

All our patients were CD20 positive. Treatment administered consisted of primarily anthracycline-based chemotherapy, constituted by either CHOP or R-CHOP regimens. None of our patients received the recommended intensive chemotherapeutic regimens such as hyper-CVAD/rituximab-high dose methotrexate-cytosine arabinoside/fludarabine-based chemotherapy. Stem cell transplantation that is recommended following first-line chemotherapy[9-11] was also not done in any patient.

The median survival of the entire cohort was 21 months with stage-wise survival being 47, 24, 19, and 13 months for stages I, II, III, and IV, respectively [Table 2]. The median OS with early (stages I and II) (n = 16) and advanced disease (stages III and IV) (n = 61) was 31 and 18 months, respectively (P = 0.02) [Figure 1]. Similarly, the patients who received R-CHOP had significantly better survival than those with received CHOP chemotherapy, 30 and 16 months (P = 0.0002) [Figure 2]. There was no significant difference in survival with respect to gender, extranodal involvement, or bone marrow involvement.

Table 1: Clinical characteristics

Characteristic	*n* (%)
Age (median)	55 (35-72) years
Sex	
Male	66 (85.7)
Female	11 (14.3)
B symptoms	
Yes	37 (48)
No	40 (52)
Stage	
I	3 (3.9)
II	13 (16.8)
III	28 (36.4)
IV	33 (42.9)
Nodal	36 (46.8)
Extranodal	41 (53.2)
1 site	34 (82.9)
>1 site	7 (17.1)
BM	27
Intestine	10
Stomach	6
Spine	2
Lungs	2
Thyroid	1
Medial canthus of eye	1
Hard palate	1
Pelvis	1
Omentum	1
IPI	
Low	6 (7.7)
Low-intermediate	24 (31.2)
High-intermediate	22 (28.6)
High	25 (32.5)

BM: Bone marrow, IPI: International prognostic index

Table 2: Survival outcomes

Characteristic	*n* (%)	Median OS (months)	*P*
OS (median)	77	21	
Age (years)			
<60	57 (74)	21	0.07
>60	20 (26)	18	
Sex			
Male	66 (85)	21	0.58
Female	11 (15)	21	
Nodal disease	36 (46.8)	24	0.28
Extranodal disease	41 (53.2)	18	
Stage wise survival			
Early Stage (I and II)	16 (20.7)	31	0.02
Advanced Stage (III and IV)	61 (79.3)	18	
Marrow involved			
Yes	27 (35.06)	13	0.116
No	50 (64.93)	24	
R-CHOP	25 (32.5)	30	0.0002
CHOP	52 (67.5)	16	

OS: Overall survival

DISCUSSION

MCL is an aggressive malignant lymphoma that is seen to present in the elderly. Our study showed the median age of presentation as 55 years, which is in concordance with another Indian study by Baheti *et al.*[1] [Table 3] that documented a median age of 57 years. This seems almost

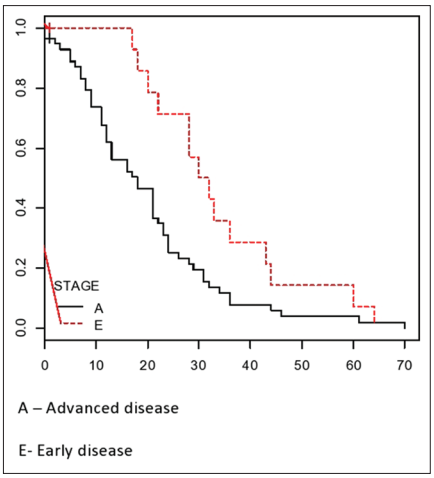

Figure 1: Survival analysis comparing early versus advanced stage arms

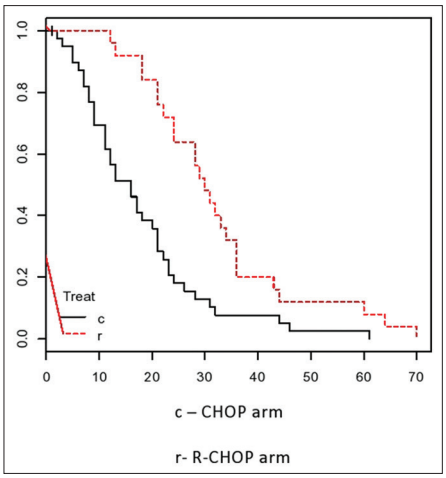

Figure 2: Comparing survival between R-CHOP versus CHOP chemotherapy arms

a decade earlier than other studies that have a median age at presentation of 63–64 years.[12-15]

Our study showed a higher incidence in males compared to females with a ratio of 6:1. This is in concurrence with published literature.[1,12,13,15] The reason for preponderance to this extent in males is still not known.

Most of our patients presented at an advanced stage, with almost 80% of our population presenting with Stage III and IV disease. This finding concurs with other studies[12-15] and is also probably responsible for the poorer outcomes seen with this disease.

48% of our patients presented with B symptoms, slightly higher than other studies that have documented B symptoms of 19%–32%.[1,12,13,15]

Most of our patients presented with a low-intermediate to high IPI due to advanced stage and poorer performance status at presentation.

The most common extranodal sites of presentation were the bone marrow followed by the bowel. This is similar to other studies that have documented these sites as their most frequent extranodal sites of involvement.[12-15] Stomach, lungs, and spine were other uncommon sites of involvement. This is similar to other studies that have documented them as less frequent sites of involvement.[1,12]

Our patients are treated with anthracycline-based chemotherapy, with CHOP or rituximab with CHOP. More intensive regimens such as hyper-CVAD or cytarabine-based chemotherapy, although recommended, are not used in our setup due to poor performance status, lower tolerability, and due to affordability issues to make arrangements for supportive care required during administration of intensive chemotherapy.

The median survival of our patients was 21 months, much lower than documented in other studies, wherein the survival ranges from 30 to 48 months.[1,12-16] A lower survival has been noted despite the stage of presentation and use of anthracycline-based chemotherapy, which is as in most studies. Those who received rituximab-based chemotherapy seemed to do better than those who did not in our study - 30 versus 16 months. However, the number of those who received rituximab-based chemotherapy was fewer in number, than who did not, which would probably explain the poorer outcome of our entire study population. Rituximab has been shown to increase complete remission rates,[10] however, has not conclusively shown to improve the overall survival. Our analysis shows that rituximab seems to add substantial survival benefit.

Various factors have been attributed to being prognostic in this disease, which have varied across different studies. Studies have uniformly identified factors such as advanced age, poorer performance status as poor prognostic factors.[14-16] Factors such as IPI, morphology, bone marrow, and peripheral blood involvement have been contributory prognostic factors only in few.[1,12-16] The modality of treatment used seemed to have no impact on outcome.[14,15] Our study revealed that age <60 years, rituximab-based anthracycline chemotherapy, and early stage of presentation were associated with significantly better survival outcomes. Factors such as extranodal/bone marrow involvement and gender had no impact on outcome of these patients.

CONCLUSIONS

MCL continues to be a malignant lymphoma with an aggressive course with poor survival. Most of the patients presented with extranodal disease, advanced stage, and high

Table 3: Comparison with other studies

Study	Age (years)	Sex	Stage	Nodal/ extranodal (%)	Extranodal sites	B-symptoms (%)	OS (months)	Poor prognostic factors	Not prognostic
Our study	55	6 to 1	Table 1	75/25	Intestine > stomach > spine, lungs BM - 35.06%	48	21	Advanced stage, nonrituximab-based chemotherapy, age >60 years	Sex, BM involvement, extranodal involvement
Argatoff *et al.*[12]	63	7 to 3	I - 5 (6) II - 6 (6) III - 11 (14) IV - 57 (71)	75/25	Waldeyer's ring > intestine > orbit, salivary gland, stomach BM - 63%	24	43	Poor PS, blastic transformation, peripheral blood involvement, >20 mitosis/hpf	Architectural pattern or BM involvement
Weisenburger *et al.*[13]	64	3 to 1	I/II - 25% III/IV - 75%	>1 extranodal site - 9	BM involved in 60%	32	38	BM involvement, stage III/IV, B symptoms, poor PS, high IPI, cytology, and growth pattern	Other extranodal sites, mitotic rate
Samaha *et al.*[14]	63		87% advanced		GI - 18% and peripheral blood - 36% BM - 79%		3.12 years	Older age, BM involvement, hemoglobin <12 mg%, poor PS, peripheral blood involvement	IPI, treatment modalities
Baheti *et al.*[1]	57	3.9 to 1	-	35/65	Spleen > bowel > lungs > skin/ subcutaneous tissue	19	48	-	Morphology, sites of involvement
Zucca *et al.*[15]	64	2 to 1	IV - 72%		BM - 58%	31	42	Poor PS, age >65 years, high IPI, elevated LDH, and B2-microglobulin	Chemotherapy in high risk IPI
Danish group[16]	-	-	-	-	-	-	30	Age, anemia, and splenomegaly	IPI, Ann Arbor staging

BM: Bone marrow, IPI: International prognostic index, PS: Performance status, LDH: Lactic dehydrogenase, GI: Gastrointestinal, OS: Overall survival

IPI. Although rituximab-based chemotherapy improved survival outcomes in our study, it was significantly lower as compared to that with intensive regimens recommended for treatment of MCL. Therefore, whenever possible, recommended intensive regimens (e.g., hyper-CVAD) should be the mainstay of therapy.

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Conflicts of interest

There are no conflicts of interest.

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