RESEARCH ARTICLE

Mantle Cell Lymphoma: A North Indian Tertiary Care Centre Experience

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Abstract

Background: Mantle cell lymphoma (MCL) is an aggressive non-Hodgkin's lymphoma, with a pathognomonic chromosomal translocation t (11;14). Prognosis is uniformly dismal but there is a paucity of information on MCL from India. **Materials and methods:** We retrospectively analysed clinicopathological information on all treated patients with MCL at our centre. STATA 14.0 was used for analysis. Survival was assessed by Kaplan-Meier analysis and the Cox's proportional hazards method. Statistical significance was defined as a P value of < 0.05. **Results:** Fifty-one patients with MCL were reviewed. The median age at presentation was 57.0 years. Extranodal involvement was seen in 39.0 (74.0%) while bone marrow positivity at presentation was found in 27.0 (54.0%). Initial treatment was chemotherapy with or without rituximab. Patients receiving rituximab-based therapy (n = 24) had 5-year progression-free survival (PFS) of 21.0 (88.0%), compared with 14.0 (61.0%) for those not receiving rituximab (n = 23, P = 0.036). Twenty-three patients were alive with a median follow-up of 20.7 months (range 2.5-89.2). PFS at 1 and 2 years was 51.0% and 27.0%, and overall survival (OS) 78.0% and 72.0%, respectively. Use of more than 2.0 lines of therapy, use of bendamustine-rituximab, and high TLC (>10,000.0/cu.mm) significantly affected PFS. **Conclusions:** In our experience, MCL patients from north India have an early age at presentation. When treated with regimens including rituximab results in an improved response rate and PFS. This study provided comprehensive insights into the treatment of MCL in a developing country.

Keywords: Chemotherapy- mantle-cell lymphoma- non-Hodgkin's lymphoma- bendamustine

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Introduction

Mantle cell lymphoma (MCL) accounts for 5-7% of patients with non-Hodgkin's lymphoma (NHL). As per the Surveillance, Epidemiology, and End Results Program (SEER) database, the incidence rate is 0.8/100,000population (Howlader et al., 2015). The frequency is 5.6 % in Indian population as per a retrospective series (Naresh et al., 2000). It is a characteristically aggressive subtype of NHL, with a pathognomonic chromosomal translocation t (11;14). Although the prognosis of MCL was uniformly dismal previously, the introduction of rituximab antibody therapy, small molecules targeting specific signal pathway and autologous stem cell transplantation (SCT) has significantly improved outcome with long-term disease-free survival (Dreyling et al., 2005; Romaguera et al., 2005; Delarue et al., 2013).

The diagnosis of MCL is based on histologic examination and immunophenotyping along with the demonstration of cyclin D1 MCL protein overexpression by immunohistochemistry and/or confirmation by fluorescent in-situ hybridization. (Swerdlow et al., 2016)

This is a retrospective analysis of the clinical features, disease responses and prognosis of newly diagnosed patients with MCL treated in a tertiary care centre in North India.

Materials and Methods

Patient information

The database included search from the digital records and case file of patients with a diagnosis of MCL. We identified 72.0 cases of MCL in our histology records from the year 2010 to 2015. Fifty-one of these received treatment at our centre and had adequate clinical details. The patients who had failed to complete scheduled treatment were excluded from the analysis. Informed and written consent was taken from all patients to allow the use of clinical data for research. This study was approved by the Ethics committee, All India Institute of Medical Science.

Diagnostic and staging procedures

Diagnostic workup includes demographics, clinical history, physical examination and assessment of site

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of involvement and staging at presentation. Complete blood cell count, lactate dehydrogenase (LDH), hepatic enzymes, creatinine and albumin were noted as laboratory parameters at presentation. Radiological investigations included computed tomography scan and positron emission tomography of the whole body. Histopathological slides were retrieved from archives and reviewed. Bone marrow evaluation was performed as a routine for staging purpose and available in 43 cases. Immunophenotyping by flow cytometry (FCM) was available in 12.0 cases. Clinical stage was evaluated in accordance with conventional Ann Arbor criteria. The largest dimension of the largest site of disease was measured and bulky disease was classified as ≥7.5 cm. A number of extranodal disease sites were recorded as ≤1.0 or >1.0. Complete clinical, serological and radiological details were available in 50.0 cases.

Patients had either received rituximab-based regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone).

Clinical response evaluation

Clinical response was classified as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD) based on Modified Cheson's lymphoma response evaluation criteria. The overall response rate (ORR) was calculated including CR and PR (Cheson et al., 2007)

The time period from the beginning of the treatment to the date of demise from any cause or to the date of the last follow-up was defined as overall survival (OS). Progression-free survival (PFS) was defined as the time from the beginning of treatment to disease progression or relapse.

Statistical analysis

Statistical analysis was done using STAT14.0 MP. The Chi-square test was used to analyse the correlation between various treatment regimen and achievement of response to therapy. Survival was calculated by Kaplan-Meier analysis and factors significantly affecting the survival outcomes were analysed by Cox's proportional hazard method. Statistical significance was defined as $P < 0.05$

Results

Patient characteristics

The median age at presentation was 57.0 years (IQR 20.0-88.0). The majority were males, with male to female ratio being 2.4:1. Elderly population (>60.0 years) were 45.0%. The median duration of symptom duration prior to the presentation was three months (IQR 2-6 months).

Nodal involvement is seen in 88.0% of patients. The extranodal involvement was seen in 39/51 (76.0%) patients. Bone marrow was the most common extranodal site of involvement 25.0(59.0%) and others include gastrointestinal system 6/51 (12.0%), soft tissue mass 11/51(22.0%) and bone 5/51(10.0%). B symptoms (fever, night sweat and loss of weight or appetite) were present in 17/50 (34.0%) cases. Most of our patients were

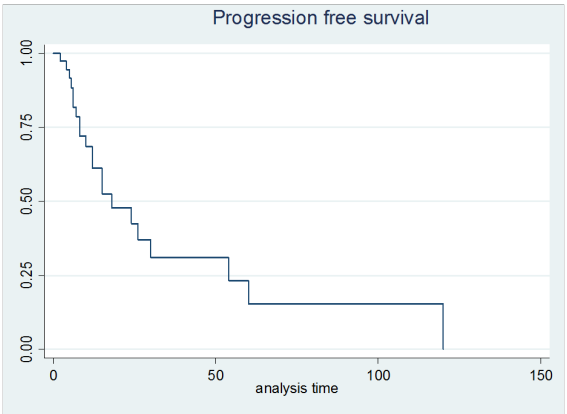

Figure 1. Kaplan Mere Analysis Showing Progression-free survival. The median time to relapse was 8.0 months. The estimated one-year progression-free period(PFS) was 66.0%.

with advanced stage (III/IV) of disease 41/51(80.0%). Bulky disease was present in 22/51(44.0%) of patients. Mantle cell lymphoma international prognostic index low, intermediate and high in 28.0%, 60.0% and 34.0% respectively.

Laboratory parameters of patients were shown in Table 1. Out of 51.0 patients, 30.0% presented with anaemia (<10gm/L), high Lactate dehydrogenase in 26/51 (51.0%) and leucocytosis (>10,000.0/mm3) seen in 19/51(37.0%) patients.

Bone marrow evaluation

Bone marrow infiltration was demonstrated in 25.0 (59.0%) cases. Common patterns of BM involvement were interstitial followed by diffuse and para trabecular deposits. Atypical cells were demonstrated in the peripheral blood film and flow cytometry in of 14/51 (28.0%) patients.

Immuno-phenotyping analysis

Because of close differential with other low grade lymphomas, immunohistochemistry was done to confirm the diagnosis of MCL. CD20 (a B-cell marker) was positive in all cases, along with CD5 and/or cyclin D1 expression. CD23 and CD10 were negative in all cases.

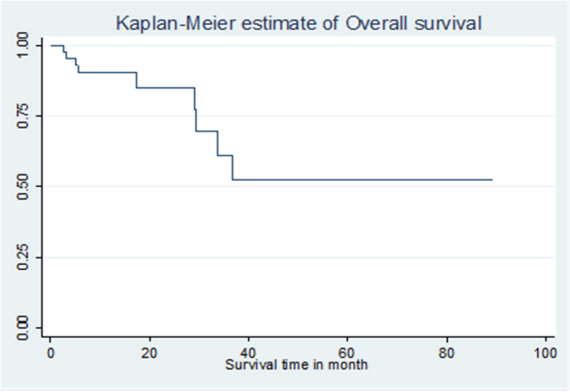

Figure 2. Kaplan-Meier analysis showing survival analysis. The median overall survival time not reached. The estimated the 1-, 2-, and 3-year overall survival rates were 78.0%, 72.0%, and 54.0%, respectively.

Table 1. Laboratory Characteristics of Mantle Cell Lymphoma Patients

Variable (number of patients)	Median	Inter-quartile Range
Haemoglobin gm%(N: 51)	10.8	9.5-12.3
Leucocyte count in mm3/L (n: 51)	8,300	5,900.0-10,800.0
Platelet x103mm3/L (N: 51)	159	123.0-215.0
Absolute lymphocyte count mm3/L (N:51)	3,150	2,192.0-5,000.0
Albumin gm% (N:51)	3.8	3.3-4.2
Lactate Dehydrogenase U/L (N: 51)	374	239.0-456.0

Seven out of 50 cases did not express CD5. None was negative for both CD5 and cyclin D1.

Treatment and outcome

Out of 50.0 cases treated, 23.0 (46.0%) patients received cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) chemotherapy and 24.0 (48.0%) were given rituximab-based chemotherapy (Rituximab-CHOP 30.0%, Bendamustine-Rituximab 14.0%). The median number of cycles received was 5.0 (1.0-9.0). Three patients were managed with best supportive care with close follow-up. One patient underwent surgery and one received upfront radiotherapy. Six patients received radiotherapy with a dose of 45Gy/25 fractions over 5 weeks. The overall response rate and complete response rate with rituximab based and non-rituximab based therapy were 88.0%,67.0% and 61.0%,35.0% respectively. (Table 2) Rituximab-treated patients achieved complete and deeper response with a statistically significance of 0.028 and 0.036 respectively as compared to non-rituximab based therapy in chi-square analysis.

Survival

All follow-ups ended in October 2015, with a median follow-up time of 20.7 months. Total event 28.0 occurred. The median time to relapse was 8 months. The estimated one-year progression-free period (PFS) was 66.0%. (Figure1). The PFS in patients with high/intermediate MIPI and low-risk MIPI is 6.0 month and 9.0 months respectively. Cox's proportional hazard method used for calculation of factors affecting the Progression free survival(PFS). The presence of 'B' symptoms, extranodal site, High LDH, bulky disease, use of bendamustine-rituximab, stage IV disease and high TLC>10,000.0/mm^3 in significantly affected PFS in multivariate analysis.

Kaplan-Meier analysis for overall survival estimated the 1.0-, 2.0-, and 3.0-year OS rates were 78.0%, 72.0%, and 54.0%, respectively. (Figure2). The overall survival rates in the R-CHOP group and conventional chemotherapy group was not statistically significant (P = 0.509). The median OS was not reached in the both the groups. Factors such age </>60 yr, presence of B symptoms, haemoglobin<10 Gm%, hypoalbuminemia had no statistical significance on survival by Cox's proportional hazard method except high LDH.

Discussion

Mantle cell lymphoma is a type of aggressive B-cell NHL with characteristic morphology and distinctive cytogenetic abnormality, t (11;14) (q13; q32). (Li et al. 1999) Approximately 70% tumour cells overexpress cell cycle regulator protein cyclinD1 which leads to dysregulation of G1-S phase of normal cell cycle. (de Boer et al. 1995). The cyclin D1 negative cases were identified by the SOX11 expression which is highly specific for mantle cell lymphoma (Mozos et al., 2009). In our study, 98.0% patients demonstrated cyclin D1 positivity.

Although the clinicopathological description of MCL is well characterised in the European population, there are few studies available from the Indian subcontinent (Argatoff et al., 1997; Bosch et al., 1998). Low-grade lymphoma-like follicular lymphoma and MCL are relatively less common in this part of the world when compared with the west and in the range of 2.0- 3.4% (Naresh et al., 2000). Clinical characteristics in our series were similar to those reported elsewhere. (Naresh et al. 2000) Apart from bone marrow and gastrointestinal tract, orbital soft tissue involvement present in 30.0% cases. With regards to gender profiling, our results are similar to that previously reported. Thirty-nine (80.0%) patients

Table 2. Response Rates of Mantle Cell Lymphoma Patients Receiving Chemotherapy

Response	All patients (N: 47)	Rituximab containing regimen (N: 24)	Non-Rituximab containing regimen (N:24)
CR	24 (51.0%)	16 (67.0%)	8 (35.0%)
Achievement of Complete response		0.03	
PR	11 (23.5%)	5 (21.0%)	6 (26.0%)
SD	3 (6.5%)	1 (4.0%)	2 (8.0%)
PD	9 (19.0%)	2 (8.0%)	7 (31.0%)
ORR (CR+PR)	35 (74.5%)	21 (88.0%)	14 (61.0%)
Achievement of Objective response		0.04	

ORR, objective response rate; CR, complete response; PR, Partial response; SD, stable disease; PD, Progressive disease

presented with advanced stage disease 3.0 or 4.0.

The dedicated MCL-specific prognostic score, MIPI allows characterization of MCL into three prognostic subgroups, the intermediate group and the high-risk group with a median overall survival of 51 and 29 months, respectively (Hoster et al., 2008). Half of our patients belong to the high-risk group (25.0%).

We started using bendamustine for the last 2.0 years with a combination of rituximab. Amongst those patients treated with bendamustine as the first line and subsequent line chemotherapy, the overall response rate was 96.0%. At present, the combination chemo-immunotherapy is the mainstay of mantle cell lymphoma in our centre.

Three patients presented as pure non-nodal leukemic presentation with high leukocyte count. These patients have a low Ki-67 with mutated immunoglobulin heavy chain. They were kept under observation. Presently National Comprehensive Cancer Network (NCCN) recommend observation for mantle cell lymphoma patients with non-nodal leukaemia presentations with low KI67, mutated immunoglobulin and splenomegaly. (NCCN NHL guidelines 2016; Martin et al., 2009) At the time of writing manuscript, all of them were asymptomatic and alive.

The median OS of patients with low-risk MCL who were treated was reported to be 49 months (Hoster et al. 2008; Geisler et al. 2010). Though median OS was not reached in our study, 50.0% of our patients were surviving at the end of 1 year. On multivariate analysis, different parameters like the use of Rituximab, LDH, hypoalbuminemia did not show any impact on the median OS.

This the first comprehensive analysis of Mantle cell lymphoma patients treated at a tertiary cancer care centre of a developing country. Heterogeneity of treatment in our cases was due to inherent reasons like patient compliance and socio-economic factors involved in treatment. To infer, the poor prognosis of our patients can be explained by the presence of adverse prognostic factors like extranodal presentation, higher MIPI score and poor response to chemotherapy. In view of encouraging results, the combination chemo-immunotherapy with bendamustine and rituximab should be the mainstay of mantle cell lymphoma management in developing countries like India.

Clinical Practice Points

Mantle cell lymphoma is a rare B-cell non-Hodgkin's lymphoma. Combination chemotherapy is the cornerstone of treating these patients. In our study of north Indian patients, significant proportions of extranodal disease were present and the overall response to rituximab-based therapy was encouraging.

Combination chemoimmunotherapy is of paramount importance in management, especially in developing countries.

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