Central nervous system involvement in mantle cell lymphoma: clinical features, prognostic factors and outcomes from the European Mantle Cell Lymphoma Network†


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Background: Central nervous system (CNS) involvement in mantle cell lymphoma (MCL) is uncommon, and the manifestations and natural history are not well described.

Patients and methods: We present the data on 57 patients with MCL who developed CNS involvement, from a database of 1396 consecutively treated patients at 14 institutions.

Results: The crude incidence of CNS involvement was 4.1%, with 0.9% having CNS involvement at diagnosis. Blastoid histology, B-symptoms, elevated lactate dehydrogenase, Eastern Cooperative Group performance status ≥2 and a high Mantle Cell Lymphoma International Prognostic Index score were enriched in the cohort with CNS involvement, and the presence of ≥1 of these features defined a high-risk subset (an actuarial risk of CNS involvement 15% at 5 years) in a single-institution subset. The median time to CNS relapse was 15.2 months, and the median survival from time of CNS diagnosis was 3.7 months. The white blood cell count at diagnosis <10.9 × 10⁹/l, treatment of CNS involvement with high-dose anti-metabolites, consolidation with stem cell transplant and achievement of complete response were all associated with improved survival.

Conclusions: In MCL, CNS involvement is uncommon, although some features may predict risk. Once manifest outlook is poor; however, some patients who receive intensive therapy survive longer than 12 months.

Key words: mantle cell lymphoma, central nervous system, prognosis

introduction

Mantle cell lymphoma (MCL) comprises 5% of non-Hodgkin lymphoma. The median age of onset is around 60 years, with a male predominance and median survival of 4–5 years [1]. Extranodal manifestations are common with blood, bone marrow and gastrointestinal involvement prominent [2, 3].

The risk of central nervous system (CNS) involvement in MCL is not well studied, without consensus on recommended CNS staging procedures. We, and others, have previously reported series comprising 4–11 cases [4–8]. The aim of this study was to comprehensively assess the frequency, clinical features, treatment and outcomes of patients with CNS involvement of MCL.
methods

We conducted a multicentre, retrospective case series through 14 sites within the European Mantle Cell Lymphoma Network (EMCLN). Each site fulfilled their individual institutional requirements for a review of medical records. We requested that sites report (i) the total number of MCL cases and (ii) the number with CNS involvement diagnosed at any time during follow-up from their databases. We have included updated data from 15 previously reported cases (11 from ref. [5] and 4 from ref. [6]), with the remaining 42 cases previously unreported. The initial diagnosis of MCL was based on published histological, immunophenotypic and molecular criteria [1]. Although no centralised pathology review was carried out, cyclin D1 expression by immunohistochemistry (IHC) and/or t(11:14) by fluorescence in situ hybridization or conventional karyotype analysis was required for inclusion. Member sites of the EMCLN have considerable experience in the diagnosis and treatment of MCL, through numerous prior clinical [9–11] and pathological [2, 12, 13] studies. Staging required a minimum of computed tomography (CT) scan of the body, physical examination and bone marrow biopsy. Due to the retrospective design, baseline CNS staging, positron emission tomography-CT and endoscopy were not mandatory.

We collected the following data on patients with CNS involvement:

baseline characteristics

Demographics date of diagnosis, stage, histological subtype, Ki-67 (IHC), total lymphocyte and leukocyte counts, B-symptoms, Eastern Cooperative Group (ECOG) performance status, serum lactate dehydrogenase (LDH), β2-microglobulin, bulk (defined as maximal nodal diameter >10 cm), number and sites of extranodal involvement. Mantle Cell Lymphoma International Prognostic Index (MIPI) was derived as published [14].

disease features at diagnosis of CNS involvement

Date of proven CNS involvement, disease status (i.e. initial diagnosis, isolated CNS relapse, concurrent systemic relapse), neurological symptoms, cerebrospinal fluid (CSF) features, imaging findings and prior treatment.

treatment of CNS disease and outcome

Chemotherapy regimen including the use of intrathecal chemotherapy, radiotherapy, response to therapy (investigator determined according to standard criteria [15]), outcome at the last follow-up, date of relapse/death and cause of death.

CNS involvement was defined by at least one of (i) histologically confirmed CNS involvement, (ii) neuroimaging findings compatible with CNS involvement with lymphoma, in conjunction with consistent clinical presentation and the absence of other clinically feasible diagnosis or (iii) positive CSF (lymphoma cells detected by cytology and/or flow cytometry). Correction for peripheral blood contamination was carried out according to the discretion of each individual laboratory: methods for diagnosing peripheral blood contamination included the simultaneous analysis of peripheral blood by flow cytometry, comparison of the red-cell to white-cell ratio and the presence of granulocyte clusters.

statistical methods

Survival times were calculated using the Kaplan–Meier method [16], with comparisons carried out using the log-rank test. Time to CNS relapse was defined as time from original diagnosis of MCL to date of proven CNS involvement. Patients with CNS involvement at diagnosis (defined as proven within 1 month of initial diagnosis) were excluded from the ‘time-to-relapse’ analysis. The 95% confidence intervals (95% CIs) for survival analyses were asymmetric, and proportions were calculated using the modified Wald method. Statistical analysis was carried out using GraphPad Prism (San Diego, CA), and P-values <0.05 were considered significant. As the study was exploratory in nature, no correction was made for multiple comparisons.

results

In total, 1396 patients with MCL were screened, with 57 identified as having CNS involvement. Thirteen patients had CNS involvement at diagnosis and 44 at relapse. Thus, the crude incidence of CNS involvement was 0.9% (95% CI 0.5%–1.6%) at diagnosis and 4.1% (95% CI 3.2%–5.2%) overall. The median follow-up of the cohort with CNS relapse was 17 (range 0.2–170) months from initial diagnosis.

baseline characteristics

Fifty-three (93%) had at least one site of extranodal involvement, with 61% having ≥2 sites; the most common of which at initial diagnosis were bone marrow (90%), blood (77%), liver (14%) and lung (11%). Ki-67 by IHC was carried out in 27 (47%) patients; 70% expressed Ki-67 in >30% of cells. Mantle Cell Lymphoma International Prognostic Index score was evaluable in 72%; low, intermediate and high scores were seen in 10 (24%), 6 (15%) and 25 (61%) cases, respectively. In 37% of patients, relapses were isolated to the CNS and in 63%, it was concurrent with systemic relapse.

We compared baseline features in patients with CNS involvement to a series of 105 consecutive patients with MCL treated at Peter MacCallum Cancer Centre (PMCC) from January 1994 to June 2012 without the development of CNS involvement at the most recent follow-up (Table 1). These patients were used as a comparator, because complete data from the remainder of the cohort were unavailable. Blastoid histology, B-symptoms, increased serum LDH, ECOG performance status ≥2 and a high MIPI score were more frequent in the cohort with CNS involvement. We analysed the actuarial risk of CNS involvement among 112 patients at PMCC according to baseline characteristics to derive a predictive risk model. Among the 44 ‘high-risk’ patients (defined as ≥1 of the above-risk factors), the actuarial risk of CNS involvement was 15% at 5 years, compared with 0% in the 68 ‘low-risk’ patients (defined by the absence of high-risk features), P = 0.0005 (Figure 1).

clinical features at time of CNS involvement

Symptoms at presentation varied, but included weakness (28%), confusion (24%), ocular disturbance (20%) and headache (19%). CSF cytology was positive in 86% of cases, and flow cytometry in 91%. One case negative by cytology was positive by flow cytometry. The median CSF cell count (n = 37) was 79 (range 0–41 093) cells/μl. The CSF protein (n = 29) was raised in 69% of cases. CSF LDH was infrequently measured (n = 10), but was elevated in 90%.

Neuroimaging was carried out in 47 (82%) cases. Patients with normal imaging had CNS disease proven by positive CSF cytology and/or flow cytometry; therefore, leptomeningeal disease [positive cytology with no/normal neuroimaging (n = 26), or leptomeningeal abnormalities (n = 15), total n = 41...
Median LDH/ULN (range) 1.26 (0.1
Serum LDH > normal 38/51 (75%) 16/50 (32%) <0.0001

Table 1. Baseline characteristics of patients with CNS involvement (pooled from 14 institutions), compared with patients with mantle cell lymphoma treated at Peter MacCallum Cancer Centre (PMCC) without central nervous system involvement

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>CNS involved cohort (current study)</th>
<th>CNS not involved (PMCC)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>57</td>
<td>105</td>
<td>–</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>61 (38–82)</td>
<td>63 (30–85)</td>
<td>0.28</td>
</tr>
<tr>
<td>Male</td>
<td>70%</td>
<td>73 (70%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Blastoid histology</td>
<td>28%</td>
<td>8/84 (10%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>53%</td>
<td>11/70 (16%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stage IV</td>
<td>91%</td>
<td>65/91 (71%)</td>
<td>0.006</td>
</tr>
<tr>
<td>β2-microglobulin &gt; normal</td>
<td>17/22 (77%)</td>
<td>20/34 (59%)</td>
<td>–</td>
</tr>
<tr>
<td>Median β2-microglobulin/ ULN (range)</td>
<td>2.0 (0.5–7.3)</td>
<td>1.08 (0.6–5.2)</td>
<td>0.079</td>
</tr>
<tr>
<td>Serum LDH &gt; normal</td>
<td>38/51 (75%)</td>
<td>16/50 (32%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median LDH/ULN (range)</td>
<td>1.26 (0.1–11.9)</td>
<td>0.84 (0.52–1.65)</td>
<td>–</td>
</tr>
<tr>
<td>Median WBC, ×109/l (range)</td>
<td>10.9 (2.8–351)</td>
<td>8.0 (4.1–470)</td>
<td>0.058</td>
</tr>
<tr>
<td>ECOG ≥2</td>
<td>16/43 (30%)</td>
<td>12/68 (18%)</td>
<td>0.026</td>
</tr>
<tr>
<td>Ki-67 ≥30%</td>
<td>70%</td>
<td>4/8 (50%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Median Ki-67 (range)</td>
<td>53.5% (5–90%)</td>
<td>22.5% (8–80%)</td>
<td>0.44</td>
</tr>
<tr>
<td>High MIPI score (≥6)</td>
<td>25/41 (61%)</td>
<td>14/50 (28%)</td>
<td>0.0018</td>
</tr>
</tbody>
</table>

CNS: central nervous system; LDH: lactate dehydrogenase; ULN: upper limit of normal; WBC: white blood cell count; ECOG: Eastern Cooperative Oncology Group; MIPI: Mantle Cell Lymphoma International Prognostic Index.

Figure 1. Actuarial CNS involvement free survival for ‘high-risk’ patients according to baseline characteristics at one institution, n = 44. ‘High-risk’ patients defined by one or more of: serum lactate dehydrogenase increased, Eastern Cooperative Group performance status 2 or more, B symptoms and blastoid histology. ‘Low-risk’ defined by the absence of high-risk features.

(72%) was more frequent than parenchymal (n = 17, 29%), though seven patients with leptomeningeal disease also had parenchymal lesions. Of 17 patients with parenchymal lesions, 10 also harboured MCL cells in the CSF. Therefore, isolated parenchymal CNS disease constituted just 12% of cases.

The median number of prior chemotherapy regimens was 2 (range 0–6) with 60% previously exposed to a CHOP (combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone)-like regimen, 38% rituximab (with chemotherapy), 18% hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) and 20% receiving prior intrathecal chemotherapy. Therefore, previous treatment with CNS penetrating doses of anti-metabolites and intrathecal prophylaxis did not completely protect from subsequent CNS relapse. Of the CNS relapses, 48% occurred at first relapse, 25% at second, 20% were primary refractory and 7% at third or subsequent relapse. The median time to CNS relapse was 15 (range 2–167) months (supplementary Figure S1, available at Annals of Oncology online); 78% occurred within 36 months of initial diagnosis, and the remaining 22% were spaced over many years (up to 14 years from diagnosis).

We compared 34 patients with early relapse (<36 months from initial diagnosis) with 10 with late (≥36 months) and found no differences in baseline characteristics or survival (data not shown).

CNS-directed treatment strategies and outcomes

Once CNS involvement was confirmed, treatment strategies included chemotherapy alone in 72%, combined chemoradiotherapy in 13%, radiotherapy alone in 4% and palliative care in 10%. The most frequently used chemotherapy strategy contained high-dose methotrexate (defined as ≥3 g/m², or ≥2 g/m² if age >60) and/or cytarabine (defined as ≥3 g/m²) in 40%, in various forms including alone, as part of (R) hyper-CVAD or maxichop/high dose cytarabine. Rituximab was incorporated in 13% and intrathecal therapy in 79%. Intrathecal therapy consisted of methotrexate, cytarabine and steroid in 15 cases, methotrexate and cytarabine in 12 cases and methotrexate alone in 9. Liposomal cytarabine was employed in three cases.

Of 47 patients with data, eight (17%) received autologous stem cell transplant in consolidation and one (2%) allogeneic. The conditioning regimens for the autologous transplants were BEAM (busulfan, etoposide, cytarabine, melphalan) in six and busphalan–melphalan in two. The allogeneic transplant was reduced the intensity conditioning with fludarabine and total body irradiation. Seven of these patients had received high-dose methotrexate or cytarabine containing regimens as CNS treatment. The median age of these nine patients was 56 (range 38–67) years. Three had prior autologous stem cell transplantation. Patients consolidated with high-dose chemotherapy and stem cell rescue had attained both systemic [complete remission (CR) in 6] and CNS [CR n = 4 and partial remission (PR) n = 2] responses. Two patients received whole-brain radiotherapy following transplant. Among patients not receiving transplant, treatment ranged in intensity from high-dose cytarabine and/or methotrexate to palliative care, with no significant differences in response rates.

The median overall survival from time of CNS involvement was 3.7 (range 0.2–69.3) months (supplementary Figure S2, available at Annals of Oncology online). Nine patients were alive at time of reporting with a median follow-up from time of CNS event of 15.2 (range 6.6–69.3) months (supplementary Figure S2, available at Annals of Oncology online), with the remaining 47 having died (42 with progressive disease, 4 of sepsis and 1 cause unknown). The only long-term survivors from time of CNS diagnosis received high-dose anti-metabolite...
therapy and transplant (supplementary Figure S3, available at *Annals of Oncology* online).

Eight patients survived ≥12 months from recognition of CNS involvement. Comparing the baseline data of these patients with those surviving <12 months showed no significant differences in age, white-cell count, LDH or pattern of relapse, although median Ki-67 staining (24% versus 53%; *P* = 0.04) and MIPI score (*P* = 0.02, Mann–Whitney test) were lower in those surviving ≥12 months.

**prognostic factors**

Four factors (WBC <10.9 × 10⁹/L at baseline, treatment of CNS disease with high dose anti-metabolites, consolidation with stem cell transplant and achievement of CNS complete response to chemotherapy) in univariate analysis were associated with improved overall survival from time of CNS involvement (supplementary Table S1, available at *Annals of Oncology* online). Although age alone (≥60 versus <60 years) was not associated with outcome, the cohort treated with chemotherapy regimens containing high-dose anti-metabolites had median age of 56 versus 64 years in those not treated with these agents (*P* = 0.006). B-symptoms, number of extranodal sites, LDH, ECOG, bulky disease, positive neuroimaging findings and CSF cell count/protein were not associated with survival. There was no difference in survival between patients with proven histological/cytological involvement and those without (10 versus 4 months; *P* = 0.62). Benefit of prior treatment with rituximab approached, but did not reach statistical significance (hazard ratio 0.47, 95% CI 0.21–1.05; *P* = 0.065).

**discussion**

We have presented the largest collection of cases of patients with MCL and CNS involvement reported to date. The crude incidence of 4.1% suggests that CNS involvement is uncommon in the clinical course of MCL, being towards the lower end of previously published estimates (supplementary Table S2, available at *Annals of Oncology* online). However, due to non-uniform staging procedures, the true incidence of asymptomatic CNS disease may be under-reported.

Comparison with a CNS non-involved cohort of patients identified blastoid histology, B-symptoms, increased serum LDH, poor ECOG performance status and a high MIPI score as possible indicators of CNS risk. Though not derived from the entire cohort, we nevertheless developed a predictive risk model for CNS involvement based on the presence of ≥1 high-risk feature(s) at baseline. In the absence of any risk features, we did not observe cases of CNS involvement, while 15% of patients with risk features developed CNS involvement by 5 years. Thus, our results support the findings of previous investigators that highly proliferative MCL is a risk factor for CNS involvement [2, 3, 17, 18].

Given that blood involvement at diagnosis is common [3], we recommend that patients with high risk of CNS involvement undergo CSF assessment once the peripheral blood lymphoma cells are cleared, acknowledging that delaying initial CSF sampling until after clearance risks underestimating the presence of CNS involvement if CNS-penetrating doses of anti-metabolites have been used before CSF sampling. We also recommend performing flow cytometry on CSF, due to the improved sensitivity over cytology alone [19–21]. If traumatic tap occurs, performing blood count, film and blood flow cytometry can assist the pathologist in differentiating sample contamination from true CNS involvement.

Given our findings, we recommend that CNS prophylaxis be given to patients at high risk for CNS involvement, particularly when the primary chemotherapy strategy does not contain CNS-penetrating doses of methotrexate or cytarabine. As has been discussed extensively in the diffuse large B-cell lymphoma (DLBCL) literature [22], the effectiveness of CNS prophylaxis cannot be readily determined from retrospective studies. It is clear that despite prophylaxis, some patients developed CNS relapse. Only prospective, randomised allocation of CNS prophylaxis is able to determine the benefit of such an approach.

One observation to emerge from this study is the predilection of MCL to result in leptomeningeal disease in apparent contrast to DLBCL, where parenchymal relapse is more frequent. In a meta-analysis of 28 studies by Siegal and Goldschmidt [23], 59% of 693 cases of CNS relapse in patients with DLBCL were parenchymal with 41% leptomeningeal.

The treatment approaches, once CNS involvement was established, that were associated with superior overall survival were therapy with CNS-penetrating doses of anti-metabolites, and consolidation with stem cell transplantation. Stem cell transplantation was the only strategy that provided remissions >12 months, making this approach the therapeutic goal for patients with adequate performance status and organ function. However, this group of patients were younger, had better performance status, achieved at least PR and sustained their responses long enough to undergo transplantation.

Our data have weaknesses. As a pooled retrospective multicentre case series, CNS staging, investigation and management policies varied widely between centres, and this non-uniform data collection lessens the quality and reliability of data. In particular, primary treatment strategies varied considerably, and the majority of patients did not receive rituximab. We are unable to provide an analysis of frontline therapy and risk of CNS relapse, which would be of interest. Our predictive index is based on comparison with a single-institution cohort of patients, some of whom were treated before the era of highly active regimens containing CNS-penetrating doses of anti-metabolites. As such, prospective validation in a larger cohort should be a goal of future studies in the field.

**conclusion**

CNS involvement is an unusual site of extranodal involvement in the course of MCL. Baseline features that are markers of highly kinetic disease appear to predict risk. Once established, CNS involvement carries a poor prognosis. Until randomised prospective trials are conducted that specifically address the issue of CNS prophylaxis, the optimum method and effectiveness of this approach remain unproven.
authors’ contributions

CYC coordinated data collection, carried out statistical analysis, made the figures and tables and wrote the paper. JFS designed the research, analysed results and wrote the paper. AG designed the case report form and collected data. EG, AC, JFS, MP contributed patients and collected data. All authors reviewed and approved the final manuscript.

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disclosure

The authors have declared no conflicts of interest.

references