Central nervous system involvement in mantle cell lymphoma

A. Ferrer1†, F. Bosch1, N. Villamor3, M. Rozman3, F. Graus2, G. Gutiérrez1, S. Mercadal1, E. Campo3, C. Rozman1, A. López-Guillermo1* & E. Montserrat 1

1Department of Hematology; 2Department of Neurology; and; 3Hematopathology Unit, Hospital Clínic, Postgraduate School of Hematology ‘Farreras Valenti’, Institut d’Investigació Biomedica ‘August Pi i Sunyer’, Barcelona, Spain

Received 17 May 2007; revised 9 August 2007; accepted 13 August 2007

Background: Extranodal involvement, including central nervous system (CNS), is a frequent event in patients with mantle cell lymphoma (MCL). However, the incidence, risk factors, and impact on outcome remain controversial.

Patients and methods: Main clinical, biological, and evolutive features of 82 patients (60 males/22 females; median age: 61 years) diagnosed with MCL (blastoid, 26%) in a single institution were analyzed for risk of CNS involvement and prognosis.

Results: Most patients had advanced stage and intermediate or high-risk International Prognostic Index (IPI). Eleven patients eventually developed CNS involvement with an actuarial 5-year risk of 26% (95% confidence interval 10% to 42%). In one asymptomatic patient, cerebrospinal fluid infiltration was detected at staging maneuvers (1/62; 1.6%). The remaining 10 patients developed neurological symptoms during the course of the disease (median time from diagnosis, 25 months). Initial variables predicting CNS involvement were blastoid histology, high proliferative index measured by Ki-67 staining, high lactate dehydrogenase (LDH) and intermediate- or high-risk IPI. Histological subtype and serum LDH maintained significance in multivariate analysis. Treatment of CNS infiltration consisted of intrathecal chemotherapy (two cases), and intrathecal chemotherapy plus systemic treatment (seven cases). Median survival after CNS involvement was 4.8 months, patients with this complication having shorter survival than those with no CNS disease.

Conclusion: This study confirms the high incidence of CNS involvement in MCL patients. Treatments aimed at preventing this complication are warranted.

Key words: central nervous system involvement, mantle cell lymphoma, prognosis, risk factors

introduction

Mantle cell lymphoma (MCL) is a distinct subtype of non-Hodgkin’s lymphoma derived from mature B cells usually coexpressing CD5 and histologically characterized by a nodular or diffuse proliferation of atypical lymphocytes. Two cytological variants of MCL have been identified, classical and blastoid, the latter including pleomorphic and blastic subtypes [1]. MCL is genetically characterized by 11q13 translocations and Bcl-1 rearrangement. This alteration leads to the overexpression of cyclin D1, which plays an important role in the cell cycle control at the G1–S transition by overcoming the suppressor effect of retinoblastoma protein and p27Kip.

MCL accounts for 5%–10% of lymphomas and particularly occurs in elderly males who, at diagnosis, frequently show advanced disease, generalized lymphadenopathy, and splenomegaly. The disease has an adverse clinical course characterized by a poor response to chemotherapy and a median overall survival (OS) of 3–5 years [2–6].

Extranodal involvement, including bone marrow, gastrointestinal tract, and Waldeyer’s ring, is a well-known feature in patients with MCL. The risk for central nervous system (CNS) infiltration was first reported by Bedotto et al. [7] in 1986 and Ellison et al. [8], and subsequently confirmed by our own group [9] in a series of 22 patients of whom five (22%) eventually had CNS involvement, and by others [10, 11], who reported an overall incidence of 4% and 9%, respectively. However, the incidence, predicting factors, and outcome of CNS involvement in patients with MCL have not been thoroughly investigated in large series of patients from single institutions.

The aim of the present study was to assess the incidence and factors for CNS involvement in patients with MCL diagnosed and followed up at a single institution. In addition, we analyzed the clinical features, therapy, and outcome of patients with MCL once CNS infiltration was detected.
patients and methods

patients

Eighty-two patients diagnosed with MCL from 1988 to 2003 in a single institution were included in this study. Diagnosis of MCL was established according to the World Health Organization criteria [1] and confirmed by histological, immunophenotypic, genetic, and molecular studies. Blastoid variants were recognized based on morphological characteristics.

Initial staging included thoracic, abdominal, pelvic computed tomography (CT), and unilateral bone marrow biopsy (79 patients). Biopsies of other extranodal sites were carried out whenever its involvement was suspected. A comprehensive immunophenotypic analysis of peripheral blood was carried out in 46 patients.

In each patient the following initial data were recorded and evaluated—(i) clinical data: age, gender, performance status according to the Eastern Cooperative Oncology Group scale, and presence of B symptoms (fever, night sweats, weight loss); (ii) histologic data: typical or blastoid, nodular, mantle zone or diffuse variants, and immunohistochemical staining for Ki-67; (iii) hematologic and biochemical parameters: leukocyte and lymphocyte counts, presence of atypical lymphoid cells in peripheral blood, hemoglobin, platelet count and serum lactate dehydrogenase (LDH), and b2-microglobulin levels; (iv) tumor extension data: nodal and extranodal involvement, number of extranodal involved sites, palpable splenomegaly, hepatomegaly, bone marrow infiltration, and Ann Arbor stage; (v) the International Prognostic Index (IPI), as defined by the International Non-Hodgkin’s Lymphoma Prognostic Factors Project.

Complete response (CR) was defined as the total disappearance of tumor masses and disease-related symptoms as well as the normalization of the initial abnormal tests for at least 1 month. Partial response (PR) was considered when tumor masses or organ infiltration decreased by at least 50% along with the disappearance of disease-related symptoms. Patients not included in these categories and early deaths were considered as nonresponders. Informed consent to use the clinical data was required from all the patients in accordance with the local Ethic Committee guidelines.

assessment of CNS involvement

The diagnosis of CNS infiltration was based on clinical findings and on the presence of malignant cells in cerebrospinal fluid (CSF), consistent with the diagnosis of MCL. In the first 20 patients of the present series, who have been previously reported [9], a lumbar puncture was not carried out at diagnosis unless CNS involvement was suspected on clinical grounds. In the subsequent 62 cases, CSF assessment by a lumbar puncture was included as one of the staging maneuvers at diagnosis. Cells from CNS fluid were cytospinned and stained with May-Grunwald-Giemsa for immunohistochemical staining for Ki-67. Data collected at the time of diagnosis of CNS infiltration included neurological symptoms, physical examination findings, diagnostic procedures, stage of the disease, treatment, and response.

statistical methods

Differences among the subgroups of patients were compared with the Fisher’s exact test (two-tailed) or the Student’s t-test. OS was defined as the time from diagnosis to the time of death or last follow-up. Patients still alive were censored at the last known date of contact. The actuarial survival analysis was carried out according to the method described by Kaplan and Meier [12] and differences in survival analyzed by the log-rank test.

Prognostic factors found to be significant in the univariate analysis were included in a multivariate analysis carried out by the stepwise proportional hazard regression method of Cox. The influence of CNS infiltration on survival was assessed in a time-dependent manner by means of the method described by Mantel and Byar [13]. P values <0.05 were considered statistically significant.

results

patient characteristics

The main initial characteristics of the 82 patients are detailed in Table 1. Median age was 61 years (range, 40–84 years) and 73% of patients were males. Fifty-nine of 80 patients (74%) were diagnosed with typical morphologic variant and 21 with blastoid morphology (26%), including pleomorphic (five cases) and blastic (16 cases) subtypes. MCL showed a diffuse growth pattern in 71 cases, nodular in eight, and mantle zone in one case. In two patients with lymph node biopsy-based diagnosis of MCL, the histologic subtype could not be established. Immunohistochemical staining for Ki-67 was available in 46 patients, in 18 of them (39%) being ≥50%. The vast majority of patients presented with advanced disease (92% in stage III–IV). Extranodal involvement was found in 74 patients (90%), including bone marrow infiltration in 64 of 79 patients (81%). The median leukocyte and lymphocyte counts were 8.8 × 109/l (1.1–322 × 109/l) and 2.75 × 109/l (0.50–99 × 109/l), respectively. A lymphocyte count ≥5 × 109/l was observed in 29 cases. Fourteen patients presented with hemoglobin <100 g/l and the platelet count was <100 × 109/l in 18 patients. As per the IPI, 16% patients were of low risk.

Table 1. Main initial characteristics of 82 patients with mantle cell lymphoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥60 years</td>
<td>52</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>73/27</td>
</tr>
<tr>
<td>Morphological variant</td>
<td></td>
</tr>
<tr>
<td>Typical</td>
<td>74</td>
</tr>
<tr>
<td>Blastoid</td>
<td>26</td>
</tr>
<tr>
<td>Ki-67 expression ≥50% (available in 46 patients)</td>
<td>39</td>
</tr>
<tr>
<td>Poor performance status (ECOG ≥2)</td>
<td>28</td>
</tr>
<tr>
<td>B symptoms</td>
<td>35</td>
</tr>
<tr>
<td>Bulky disease</td>
<td>15</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>34</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>49</td>
</tr>
<tr>
<td>Extranodal involvement</td>
<td>90</td>
</tr>
<tr>
<td>Bone marrow infiltration</td>
<td>81</td>
</tr>
<tr>
<td>≥2 extranodal involved sites</td>
<td>40</td>
</tr>
<tr>
<td>Advanced stage (Ann Arbor III–IV)</td>
<td>92</td>
</tr>
<tr>
<td>Increased serum LDH levels (available in 79 patients)</td>
<td>38</td>
</tr>
<tr>
<td>Increased serum b2-microglobulin levels (available in 56 patients)</td>
<td>41</td>
</tr>
<tr>
<td>High/intermediate and high-risk IPI</td>
<td>84</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index.
28% of low-intermediate risk, 34% of high-intermediate risk, and 22% of high risk.

Treatment varied over the time and included chemotherapeutic regimens without anthracyclines in 20 patients (25%) and combination therapy with anthracyclines in 61 (75%). In 16 patients (20%) first-line treatment included high-dose methotrexate (MTX) (Hyper cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, cytarabine regimen) [14], whereas 11 additional patients were treated with this regimen in subsequent recurrences. One patient was not treated because she died before starting therapy. Seventy-nine patients were assessable for response. CR, PR, and failure rates were 17%, 49%, and 34%, respectively. At the time of the last follow-up, 63 patients (77%) had died, with a median OS of 28 months (range, 1–136).

CNS involvement

Eleven of 84 patients (13%) developed CNS involvement. In one asymptomatic patient, CSF infiltration was detected in the lumbar puncture carried out during staging maneuvers. This patient was diagnosed with typical diffuse MCL in a lymph node biopsy. She presented with advanced disease (stage IV), increased serum LDH and β2-microglobulin levels, and a high-risk IPI. The risk of CNS involvement at diagnosis as assessed by systematic lumbar puncture was of 1/62 [1.6%; 95% confidence interval (CI) 0% to 9%].

The remaining 10 patients eventually developed CNS involvement during the course of the disease. Main characteristics of these patients are listed in Table 2. Histology of lymph node biopsies disclosed a typical subtype in six cases (one nodular, five diffuse) and blastoid morphology in five (four blastic, one pleomorphic). All patients had advanced-stage disease, nine patients (82%) presented with bone marrow infiltration, and eight cases (73%) presented with ≥2 extranodal sites involved. Four patients (36%) had B symptoms and a poor performance status. As per the IPI, four patients (36%) were of low-intermediate risk, three (28%) of high-intermediate risk, and four (36%) of high risk. Two of eleven patients (18%) had achieved a CR with first-line combination chemotherapy and a PR was observed in four cases (36%). Development of CNS infiltration was seen at a median time of 25 months from diagnosis (range, 5–130). All 10 patients who developed CNS infiltration during follow-up presented with neurological symptoms: facial palsy in four cases, scialgia in four, diplopia in two, paraparesis in two, and confusional syndrome, trigeminal sensitive symptoms, and upper or lower limbs paresthesias or dysesthesias in one patient each. In two patients (patient 6 and patient 9) the lumbar puncture was not carried out because of their critical status. All except one patient displayed atypical lymphocytes in the CSF, consistent with the diagnosis of MCL. The latter patient (patient 7) was diagnosed with CNS involvement based on the clinical symptoms that improved after intrathecal therapy. In two patients, the flow cytometry analysis of CSF showed a characteristic MCL population (monoclonal B cells CD5 positive, CD23 negative, strong CD20, with relatively intense surface restricted light chain expression). CT or MRI scans were carried out in three patients with negative results in all cases. Three of the 10 patients who developed CNS infiltration during the course of the disease had received chemotherapy containing high-dose MTX (first-line in two cases; salvage therapy in one). At the time of CNS infiltration, five patients were under treatment and the remaining five patients had progressive disease.

risk and factors predicting CNS involvement

The risk of CNS involvement at 5 years was 26% (0.95 CI 10% to 42%) (Figure 1). CNS infiltration was more frequently observed in patients with blastoid histology (P = 0.005) (Figure 2A), Ki-67 expression ≥50% (P = 0.017) (Figure 2B), high LDH serum level (P = 0.006) (Figure 2C) or intermediate- and high-risk IPI (P = 0.05) (Figure 2D). Extranodal

Table 2. Clinical features at diagnosis and outcome of 11 patients with MCL who developed CNS involvement

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/sex</th>
<th>Histological subtype</th>
<th>Stage</th>
<th>IPI</th>
<th>First-line treatment</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>65/F</td>
<td>Typical, diffuse</td>
<td>IVA</td>
<td>H</td>
<td>Hyper-CVAD</td>
<td>Fa</td>
</tr>
<tr>
<td>2</td>
<td>61/F</td>
<td>Blastosíde</td>
<td>IVA</td>
<td>H</td>
<td>CHOP</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>54/M</td>
<td>Blastosíde</td>
<td>IVA</td>
<td>I/H</td>
<td>Hyper-CVAD</td>
<td>Fa</td>
</tr>
<tr>
<td>4</td>
<td>63/M</td>
<td>Blastosíde</td>
<td>IVA</td>
<td>I/H</td>
<td>CHOP</td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
<td>63/M</td>
<td>Blastosíde</td>
<td>IVA</td>
<td>I/H</td>
<td>Hyper-CVAD</td>
<td>Fa</td>
</tr>
<tr>
<td>6</td>
<td>54/M</td>
<td>Typical, diffuse</td>
<td>IVA</td>
<td>I/H</td>
<td>CHOP</td>
<td>Fa</td>
</tr>
<tr>
<td>7</td>
<td>53/M</td>
<td>Blastosíde, pleomorific</td>
<td>IVA</td>
<td>L/I</td>
<td>Hyper-CVAD</td>
<td>PR</td>
</tr>
<tr>
<td>8</td>
<td>63/F</td>
<td>Typical, diffuse</td>
<td>IVA</td>
<td>L/I</td>
<td>CHOP</td>
<td>CR</td>
</tr>
<tr>
<td>9</td>
<td>70/M</td>
<td>Typical, nodular</td>
<td>IVA</td>
<td>L/I</td>
<td>CHOP</td>
<td>CR</td>
</tr>
<tr>
<td>10</td>
<td>47/F</td>
<td>Typical, diffuse</td>
<td>IVA</td>
<td>L/I</td>
<td>CHOP</td>
<td>Fa</td>
</tr>
<tr>
<td>11</td>
<td>51/F</td>
<td>Typical, diffuse</td>
<td>IVA</td>
<td>L/I</td>
<td>Chlorambucil + prednison</td>
<td>PR</td>
</tr>
</tbody>
</table>

MCL, mantle cell lymphoma; CNS, central nervous system; IPI, International Prognostic Index; F, female; H, high; Hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, cytarabine; Fa, failure; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PR, partial response; M, male; I/H, intermediate/high; L/I, low/intermediate; CR, complete response.

*CNS involvement at diagnosis.
involvement of ≥2 sites showed a trend to higher risk \((P = 0.06)\). The treatment given to the patients (high-dose MTX regimens versus other) did not show predictive value for CNS involvement. In a multivariate analysis including the histologic subtype (blastoid versus nonblastoid), LDH serum level (normal versus high), and extranodal sites involved (<2 versus ≥2), the histologic subtype \([P = 0.03; \text{relative risk (RR): } 4.8]\) and LDH serum level \((P = 0.02; \text{RR: } 4.8)\) were the most important variables to predict CNS involvement. Given the number of missing data, Ki-67 immunohistochemistry staining was not included in the model. When the IPI (low versus low intermediate versus intermediate high versus high) was included in the analysis, histology and LDH levels retained their prognostic significance.

treatment and outcome of the patients
The most relevant features of patients developing CNS involvement are summarized in Table 3. All but two patients (patient 6 and patient 9) were treated with intrathecal chemotherapy (MTX 10 mg, hydrocortisone 20 mg, cytarabine 30 mg). In addition, seven patients (patients 1–5, 7, and 11) received combination chemotherapy that included high-dose MTX in four cases (patients 1, 2, 5, and 7).

All the patients with CNS infiltration died, with a median survival from the time of CNS involvement of 3 months.
The cause of death was systemic progression of MCL in all cases but in one case (patient 1 died of sepsis). To analyze the impact of CNS infiltration on OS, we first carried out a raw comparison between the median OS of patients with and without CNS involvement (24 versus 29 months, respectively; \(P > 0.1, \text{NS}\)). Subsequently, CNS infiltration was analyzed as a time-dependent variable; patients developing CNS involvement showed a significantly poorer OS (\(P < 0.001; \text{RR: 4.7}\)).

**discussion**

The reported incidence of CNS involvement in patients with lymphoma varies from 2% to 27% in different series [15–22]. This wide variation is most likely explained by patients’ inclusion criteria, different histologic subtypes, and methods to assess CNS infiltration [23]. In some aggressive lymphomas, such as lymphoblastic lymphoma or Burkitt’s lymphoma, CNS infiltration is a well-known feature in the natural history of the disease, whereas, on the contrary, CNS infiltration is virtually absent in indolent lymphomas and, if present, it is usually related to histologic transformation [24, 25]. The incidence in different studies of CNS involvement in patients with MCL is also highly variable, ranging from 4% to 22%. The first reports describing this complication were published two decades ago [7, 8]. Subsequently, other series describing the presenting and evolutive features of patients with MCL were reported but in all these studies little attention was paid to CNS disease, this being considered an infrequent event with an incidence inferior to 10%. As a result, CNS assessment has not been part of the routine initial work-up in patients with MCL.

In the present series, CNS involvement was found in one of 62 asymptomatic patients at diagnosis (1.6%). In all, 11 of 82 patients developed CNS infiltration during their clinical course, with an actuarial risk at 5 years of 26%. Discrepancies between our series and others are not easy to explain, but they could be due in part to differences in the duration of the follow-up. Risk factors for a higher probability of CNS involvement were blastic subtype, high Ki-67 immunostaining, high serum LDH levels, and high-risk IPI. Of note, most of these variables are in fact related to the proliferation of the disease.

The most frequent clinical manifestations of CNS involvement included signs and symptoms related to high intracranial pressure or meningeal infiltration, and mainly consisted in mental status changes, headache, and cranial nerve palsies. Nevertheless, signs and symptoms of CNS involvement may be very subtle, warranting a high degree of suspicion of CNS infiltration.

The mechanisms by which MCL involves the CNS are not completely understood. The possibility of histologic transformation into a more aggressive lymphoma type or of progression from typical to blastoid histology cannot be completely ruled out. However, none of our six patients diagnosed with typical MCL presented with signs to suspect...
such an event and, in addition, three of them showed lymphoid cells of typical MCL in the CSF. On the other hand, it is well known that cellular adhesion molecules (CAM) are involved in the pattern of growth and dissemination of lymphoproliferative disorders [26–30]. MCL is characterized by low levels or absence of L-selectin and CD11c, low expression of CD11a/CD18 (Leukocyte function antigen (LFA)-1), and high levels of CD44, CD54 (Intracellular adhesion molecule-1), and VLA-5 [31, 32]. In this regard, the lack of expression of LFA-1 has been related to lymphoma dissemination and aggressive behavior [30, 33]. Moreover, the strong expression of VLA-5 has been associated with extranodal involvement [30]. However, no correlation between the pattern of CAM and CNS involvement has been found yet in MCL [9].

In conclusion, CNS involvement is a frequent complication in patients with MCL. Blastoid histology, high proliferative index measured by Ki-67 immunostaining, high serum LDH or intermediate and high-risk IPI are associated with a higher risk to develop this complication. The fact that in most cases CNS involvement occurs late in the course of the disease as part of a generalized clinical relapse or progression indicates that better therapies for MCL are urgently needed. Whether there is a role for CNS prophylaxis in patients with MCL should be investigated as part of potentially more effective treatments for this type of lymphoma.

funding
Spanish Ministry of Health (FIS PI 03/0473, V-2006-RET2051-0 (Red de Cáncer)).

references