Retrospective analysis of mantle cell lymphoma: experience of the “Gruppo Italiano per lo Studio dei Linfomi” (GISL)

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Abstract

Background and Objective. Mantle cell lymphoma is a recently recognized histologic entity with specific biological and clinical features. Clinically, the reported unfavorable outcome of these patients has focused attention on this category of non-Hodgkin’s lymphoma (NHL).

Design and Methods. The slide specimens of 69 NHL patients, originally classified as Working Formulation (WF) group B and E, were reviewed. The clinical features at presentation, response to therapy, response duration and survival were analyzed in cases reclassified as MCL. The correlation between clinical and histologic characteristics and the final outcome was evaluated.

Results. Out of 69 cases, 34 specimens were reclassified as MCL; in 6 patients, previously classified as WF group B, the nodular pattern was confirmed; in 2 instances the blastoid form was recognized. After a median follow-up of 35.7 months, the entire series displayed a median overall survival of 41.2 months; a significantly longer survival was associated with the nodular histologic pattern, IPI score <2, response achievement, and a higher Hb level. The vast majority of patients received anthracycline-containing combination chemotherapy. Complete remission rate was 38.8% and overall response rate was 67.6%; response achievement was significantly influenced only by Hb level. Median response duration was 23.3 months.

Interpretation and Conclusions. The present study confirms the unfavorable clinical course of MCL and the possible need for an alternative therapeutic strategy for this NHL category. Therefore, the correct identification of MCL at diagnosis appears of relevance. ©1998, Ferrata Storti Foundation

Key words: non-Hodgkin’s lymphoma, mantle cell lymphoma, histology, prognosis, response to therapy

Mantle cell lymphoma (MCL), a recently redefined category of non-Hodgkin’s lymphoma (NHL) by the Revised European-American Lymphoma (REAL) classification concerns about 8% of NHL patients with specific clinical, morphologic, immunologic, cytogenetic and molecular characteristics. This entity has been previously recorded among centrocytic NHL in the Kiel classification and considered as low grade, while the Working Formulation (WF) did not recognize MCL as a distinct entity. Moreover, pathologists in the United States included this category among the lymphocytic lymphomas of intermediate grade of differentiation group. The diffuse form represents the commonest MCL histologic pattern. Furthermore, a follicular form has been identified, together with its variant mantle zone lymphoma, which constitutes the initial phase of the disease. Finally, a very rare variant of MCL, the so-called blastoid form, characterized by larger cells and a high mitotic index has been recognized. Whether these different histologic patterns correspond to distinct clinical outcomes is still questioned.

Immunophenotypically, MCL B cells are CD5+, CD23−, a characteristic immunologic pattern distinguishable from follicular (CD5+) and from small lymphocytic lymphoma (CD23+)1. Finally, t(11;14) (q13;q32), detectable in the majority of MCL cases, represents the cytogenetic hallmark of the disease. This translocation involves the bcl-1 oncogene with the consequent overexpression of cyclin D1. Both the unique histologic and biologic features also translate into peculiar clinical characteristics, which differentiate MCL from indolent NHL, because of the former’s aggressive course, and from high grade NHL, considering that no plateau is reached in the survival curve with conventional chemotherapy.

In this study, we reviewed histologic specimens from WF B and E category patients referred to cooperative institutions of the Gruppo Italiano per lo Studio dei Linfomi (GISL), with the aim of describing the clinical features and prognostic factors of those cases redefined as MCL.

Materials and Methods

Patients

We decided to review slide specimens retrospectively from patients previously classified as WF B and E NHL, considering that the majority of MCL might be
included in these subgroups. Out of 69 specimens 34 were reclassified as MCL by a panel of GISL pathologists, according to the currently accepted REAL histologic criteria. In 6 cases (17.6%), all previously classified as WF B NHL, a nodular pattern was confirmed; 28 (82.3%) displayed diffuse growth and 2 (5.9%) exhibited the blastic variant with a diffuse pattern; these last cases belonged to WF group E. Mantle zone histologic architecture cases were not separately evaluated from those with a follicular pattern.

**Staging**

At diagnosis all patients underwent chest x-ray, total body computed tomographic scan, abdominal ultrasound and bone marrow biopsy to establish the stage of the disease. The following clinical and laboratory data were considered for the clinical and prognostic evaluation: age, sex, site of biopsy, performance status (PS) evaluated by the Karnofsky index, systemic symptoms, disease sites, stage and bulk, ESR, lactate dehydrogenase (LDH), hemoglobin (Hb), albumin, iron and fibrinogen. By using the pretreatment risk factors (age, PS, tumor stage, number of extranodal sites, LDH) of the International Prognostic Index (IPI)18 patients were stratified into two risk categories, ranking IPI score 0-2 as low risk and score 3-5 as high risk groups.

**Therapy**

Treatment schedules varied over the years according to GISL controlled clinical trials: aggressive schedules with anthracyclines were used in 30 patients: ProMECE-CytABoM (26 cases), BACOP (1), CEOB (1), chlorambucil plus epidoxorubicin (1), VEMB (1). Less intensive therapy without anthracyclines consisting of chlorambucil with or without interferon was given to the remaining 4 patients.

**Response to therapy**

Complete response (CR) was defined by the disappearance of any detectable sign of disease, partial response (PR) as more than 50% reduction of the initial tumor mass, progression (PD) as the increase of tumor mass while the patient was receiving treatment and no response (NR) as failure to achieve CR or PR.

**Statistical analysis**

The chi-square test (Fisher's exact two-tailed test) for 2x2 tables was used for overall comparison of clinical responders versus non-responders. Survival, calculated from the date of diagnosis, was assessed by the Kaplan and Meier method. Difference in survival between prognostic groups was evaluated in univariate analysis by the log-rank test. For all analyses, the variables age, albumin, iron, Hb, fibrinogen and ESR were transformed into binary variables by using the median as the cut-off value. All calculations were performed using the SAS/STAT software package, release 6.06 of SAS Institute Inc., 1993.
Table 2. Univariate analysis of prognostic variables influencing response achievement.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CR+PR No.</th>
<th>NR+PD No.</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (≤60 v &gt;60)</td>
<td>14 v 9</td>
<td>6 v 4</td>
<td>1.0</td>
</tr>
<tr>
<td>Sex (male v female)</td>
<td>18 v 5</td>
<td>5 v 5</td>
<td>0.2</td>
</tr>
<tr>
<td>Symptoms (A v B)</td>
<td>15 v 8</td>
<td>6 v 4</td>
<td>1.0</td>
</tr>
<tr>
<td>IPI score (0-2 v 3-4)</td>
<td>14 v 8</td>
<td>6 v 4</td>
<td>1.0</td>
</tr>
<tr>
<td>Bulk (yes v no)</td>
<td>3 v 20</td>
<td>2 v 8</td>
<td>0.6</td>
</tr>
<tr>
<td>WF group (B v E)</td>
<td>6 v 17</td>
<td>0 v 10</td>
<td>0.1</td>
</tr>
<tr>
<td>Therapy with anthracycline (yes v no)</td>
<td>18 v 5</td>
<td>9 v 1</td>
<td>0.6</td>
</tr>
<tr>
<td>Albumin, g/dL (≤4.1 v &gt;4.1)</td>
<td>9 v 8</td>
<td>4 v 4</td>
<td>1.0</td>
</tr>
<tr>
<td>Iron, µg % (≤78 v &gt;78)</td>
<td>8 v 11</td>
<td>5 v 2</td>
<td>0.4</td>
</tr>
<tr>
<td>Hb, g/dL (≤12 v &gt;12)</td>
<td>8 v 13</td>
<td>8 v 2</td>
<td>0.054</td>
</tr>
<tr>
<td>Fibrinogen mg % (≤341 v &gt;341)</td>
<td>8 v 10</td>
<td>6 v 3</td>
<td>0.4</td>
</tr>
<tr>
<td>ESR (≤28 v &gt;28)</td>
<td>12 v 9</td>
<td>4 v 5</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Fisher’s exact test.

Table 3. Univariate analysis of prognostic variables for overall survival.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Probability of overall survival</th>
<th>Univariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (≤60 v &gt;60)</td>
<td>0.50 v 0.50</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex (male v female)</td>
<td>0.45 v 0.60</td>
<td>0.4</td>
</tr>
<tr>
<td>Symptoms (A v B)</td>
<td>0.59 v 0.23</td>
<td>0.3</td>
</tr>
<tr>
<td>IPI score (0-2 v 3-4)</td>
<td>0.65 v 0.23</td>
<td>0.0027</td>
</tr>
<tr>
<td>Bulky (yes v no)</td>
<td>0.40 v 0.52</td>
<td>0.7</td>
</tr>
<tr>
<td>WF group (B v E)</td>
<td>0.83 v 0.43</td>
<td>0.054</td>
</tr>
<tr>
<td>Therapy, anthracycline (w v w/o)</td>
<td>0.46 v 0.67</td>
<td>0.3</td>
</tr>
<tr>
<td>Response (CR+PR v NR+PD)</td>
<td>0.65 v 0.20</td>
<td>0.0125</td>
</tr>
<tr>
<td>Albumin, gr. % (≤4.1 v &gt;4.1)</td>
<td>0.29 v 0.58</td>
<td>0.5</td>
</tr>
<tr>
<td>Iron, µg % (≤78 v &gt;78)</td>
<td>0.36 v 0.62</td>
<td>0.2</td>
</tr>
<tr>
<td>Hb, gr % (≤12 v &gt;12)</td>
<td>0.31 v 0.62</td>
<td>0.0204</td>
</tr>
<tr>
<td>Fibrinogen mg % (≤341 v &gt;341)</td>
<td>0.36 v 0.50</td>
<td>1.0</td>
</tr>
<tr>
<td>ESR (≤28 v &gt;28)</td>
<td>0.56 v 0.40</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*Log-Rank test.

Figure 2. Overall survival of MCL patients stratified by histologic subtype (WF B and E) and by IPI simplified score.

Figure 3. Overall survival of MCL patients stratified by Hb value and by response to chemotherapy.
because of toxicity and 1 was lost to follow-up. Among the variables evaluated in this study, only Hb level significantly influenced the response achievement ($p=0.054$ in univariate analysis) (Table 2). Ten patients relapsed and the median length of remission was 23.3 months, 23.4 months for CR and 23.0 for PR. No factor was significantly associated with remission duration. After a median follow-up of 35.7 months 17 patients had died: 13 of disease-related causes, 1 because of toxicity, 2 of infection and 1 of unknown cause. The median overall survival was 41.2 months (Figure 1), with 35.9% of patients alive at 48 months. In univariate analysis (Table 3), a shorter survival was associated with WF group E histology and IPI score $>2$ (Figure 2), absence of response and Hb $\leq 12$ g/dL (Figure 3). Of note, when risk factors considered by the IPI score were separately analyzed, only performance status remained significant ($p=0.035$).

**Discussion**

The histologic, biologic and clinical outcomes have recently focused attention on MCL. In the present study, 69 patients included in GISL controlled clinical studies, originally defined as having B or E histology according to the WF, underwent a review. Thirty-four cases could be reclassified as MCL and their main clinical characteristics and prognostic factors were analyzed. Although diagnostic criteria of MCL have now been well defined, further evaluation and confirmation of its clinical characteristics and prognostic parameters could be useful, in order to improve the therapeutic strategy towards this NHL entity. The clinical features of the present series are in line with those previously reported. $^{12,13,16,19-24}$ Although all patients but four were treated with anthracycline-based protocols, the complete remission rate was 38%, relapses were frequent and median overall survival was rather disappointing (41.2 months). In this regard, the role of anthracyclines in MCL treatment remains controversial. Zucca et al. $^{22}$ found that therapy with anthracyclines may give a benefit in terms of survival over chlorambucil. On the other hand, no other retrospective $^{22,13,16,19-25}$ or randomized $^{20}$ study demonstrated any survival advantage for MCL and centrocytic lymphoma patients treated with an aggressive protocol.

Another matter of debate is the presence of a nodular pattern. In our series 17.6% of cases, originally classified as WF group B, had a longer survival than WF group E patients. Previously, it was reported that a mantle zone pattern is associated with an early clinical presentation, a favorable response to therapy and a longer overall survival as compared to diffuse histology. $^{10,11,26}$ Contrariwise, other authors showed that MCL patients with a nodular pattern, which is defined by pathologists as an intermediate stage between mantle and diffuse growth, had a clinical outcome similar to patients with diffuse histology. $^{13}$ This discrepancy may be due to the fact that in the latter study the mantle zone and follicular histologic patterns were analyzed altogether.

In the present series, the median overall survival was 41 months, comparable to previous experiences in which it ranged between 24 and 60 months. $^{12,13,16,17,21-25,27}$ Several clinical parameters were reported as influencing overall survival in MCL. $^{6,10,12,22-24,27-29}$ In our study, univariate analysis showed that Hb $\geq 12$ g/dL, IPI score $<2$ and response to therapy were significantly associated with a longer survival. Moreover, when a separate univariate analysis of the five IPI components was performed, PS was the only parameter with a significant impact on overall survival.

In conclusion, our study confirms that MCL affects mainly elderly patients in advanced stage of disease and with systemic symptoms. The poor prognosis of these patients is probably due to the biology of MCL cells, which overexpress cyclin D1 and lose, in the more aggressive form, the wild-type p53 gene product. $^{30}$ So far, common experience indicates that MCL is not cured by conventional or purine analog therapy. $^{21-29}$ Moreover, high dose chemo-radiotherapy with peripheral blood stem cell support fails to improve long-term survival in these patients. $^{31-32}$ Alternative approaches, such as immunotherapy$^{1}$ should be urgently evaluated in prospective trials or allogeneic stem cell transplantation. $^{34}$

**Contributions and Acknowledgements**

VCa conceived the study, was responsible for data evaluation and interpretation, literature analysis and writing of the paper; VCl performed the data management at the GISL trial office; FM was responsible for statistical analysis and revised the paper; CS contributed to data collection and analysis; LB, FN, PA contributed with the majority of patients; MB followed the subsequent phases of the study and performed the final revision of the paper; VS supervised the whole study as GISL co-ordinator.

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