Clinical progression and outcome of patients with monoclonal B-cell lymphocytosis

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Abstract
Monoclonal B-cell lymphocytosis (MBL) is a clonal lymphoproliferation with the immunophenotype of chronic lymphocytic leukemia (CLL) but a B-lymphocyte count of less than 5 × 10⁹/l and no lymphadenopathy, organomegaly, cytopenias or symptoms. We performed a retrospective analysis of patients with MBL (n = 46), Rai stage 0 CLL (n = 112) and Rai stage ≥1 CLL (n = 54). Median follow-up and range was 30 (0.1 – 120) months for MBL, 60 (0.1 – 309) months for stage 0 CLL and 54 (0.1 – 309) months for stage ≥1 CLL. None of the MBL patients required treatment compared with 24 of 112 (21%) stage 0 CLL and 28 of 54 (52%) stage ≥1 CLL patients (p < 0.0003). No MBL underwent aggressive transformation compared with 1 of 112 (0.8%) stage 0 CLL and 6 of 54 (11%) stage ≥1 CLL patients (p < 0.0003). Progression-free survival (PFS) appeared improved in MBL compared to stage 0 CLL, although this did not reach statistical significant (p = 0.07) due to the relatively short follow-up in the MBL group; two year PFS was 97.2% for MBL, 93.1% for stage 0 CLL, and 68% for stage ≥1 CLL patients (p < 0.0001 for stage ≥1 CLL compared with MBL and stage 0 CLL). This is the first study of outcome in MBL which demonstrates that patients have an improved disease course compared to stage 0 CLL patients. Over a median 2.5 years of follow-up, no MBL patients required treatment or died of CLL-related causes.

Keywords: Monoclonal B-cell lymphocytosis, MBL, CLL, clonal lymphocytosis

Introduction
Monoclonal B-cell lymphocytosis (MBL) is a clonal lymphoproliferation of B-cells that has the immunophenotype of chronic lymphocytic leukemia (CLL) but an absolute lymphocyte count below that required for a diagnosis of CLL [1]; the lymphocyte count set out in CLL diagnostic guidelines by the National Cancer Institute (NCI) is more than 5 × 10⁹ lymphocytes/l [2]. Improvement in accuracy of diagnosis was made possible by the standard use of analysis for cell markers by immunophenotyping and flow cytometry, which has enabled greater certainty in detection of a truly clonal lymphoproliferation [3,4]. CLL is an indolent lymphoproliferative disorder that is usually sporadic [5], more common in elderly patients, and many patients with CLL will not develop active disease that requires treatment [6–9].

With the increasing use of regular laboratory monitoring in recent years, as well as access to immunophenotyping, cases of MBL are detected more frequently than in the past. However, the amount of data documenting the clinical course and outcome of MBL has not kept pace with the number of new diagnoses [6]. There is little information describing the clinical course of MBL, its prognostic factors or characteristics, and its relationship to CLL [10]. Here we present a retrospective study of 214 patients with clonal lymphoproliferation in keeping with CLL, 46
of whom presented with MBL. This report compares the clinical characteristics, progression, and outcome of patients with MBL and CLL seen at a single institution in Vancouver, Canada.

Patients and methods

Patients with clonal lymphocytosis in keeping with CLL seen at St. Paul's Hospital in Vancouver, Canada, who had immunophenotyping data available, were identified from a search of the Hematology practice database. Clinical and laboratory features of 214 patients were abstracted by chart review. All patients had lymphocytosis that was sustained for at least three months. MBL was defined as clonal B-cell lymphocytosis with an absolute B lymphocyte count less than $5 \times 10^{9}$/l but with morphology and an immunophenotype in keeping with CLL, and with no lymphadenopathy, organomegaly, cytopenias or symptoms attributable to the lymphoproliferation. The B lymphocyte count was determined by multiplying the CD19 or CD20 fraction, obtained from flow cytometry data, by the absolute lymphocyte count. Data collected on the characteristics of patients included: age at diagnosis; gender; date of diagnosis; lymphocyte count at diagnosis (LCD); B-lymphocyte count at diagnosis; Eastern Cooperative Oncology Group Performance Status (ECOG PS); Rai CLL stage; date of first treatment, primary treatment, indication and response; complications of therapy; treatment at progression; lymphocyte doubling time (LDT, see below); CD38 expression; ZAP-70 expression; immunoglobulin heavy chain variable region gene mutation status (IgHV); karyotype, fluorescence in situ hybridization (FISH) analysis; immunophenotype by flow cytometry or immunohistochemistry; immunoglobulin light chain restriction. Rai CLL stage was 0 in 112 patients, stage 1 (27), stage 2 (25), stage 3 (0), stage 4 (2). Clonality was determined by immunoglobulin light chain restriction. Rai CLL stage was 0 in 112 patients, stage 1 (27), stage 2 (25), stage 3 (0), stage 4 (2).

Patients with MBL or stage 0 CLL were censored at the last known date of contact. Richter's transformation was defined as a change in clinical behavior of the CLL associated with biopsy proof of aggressive non-Hodgkin's lymphoma. Prolymphocytic transformation was defined as a change in clinical behavior associated with at least 55 per cent of lymphoid cells having the features of prolymphocytes on evaluation of peripheral blood morphology [13]. PFS and OS were determined by the Kaplan–Meier method and the significance of differences in actuarial survival by the log-rank method employing SPSS for Windows, version 13.0. TTT, PFS and OS were compared in subgroups defined by MBL vs. CLL and age, gender, Rai stage, LCD, LDT, CD38 expression, transformation events, and mortality. Cox regression analysis was performed using SPSS for Windows, version 13.0.

This study was conducted in accordance with the requirements of the St. Paul's Hospital Institutional Research Ethics Board.

Results

Baseline clinical and laboratory features of 214 patients with B-cell clonal lymphoproliferation in keeping with CLL, follow-up and significant events are shown in Table I. MBL was present in 46 patients and CLL in 168. Immunophenotyping performed by flow cytometry was available in all patients, and clonality was determined by immunoglobulin light chain restriction. Rai CLL stage was 0 in 112 patients, stage 1 (27), stage 2 (25), stage 3 (0), stage 4 (2). Documented ECOG PS was 0 in 206 patients, and 1 in 8 patients; no patients had a PS of over 1.

The median lymphocyte count at diagnosis was significantly lower in MBL patients ($p < 0.0001$), undoubtedly a result of diagnostic criteria. The male to female ratio was significantly higher in patients with stage 1 or greater CLL compared to those with MBL or stage 0 CLL ($p < 0.0001$). There were more patients with a LDT of 12 months or less in both CLL groups compared to MBL ($p < 0.03$). Most patients were diagnosed in the era prior to which CD38, ZAP-70 and IgHV were known to be prognostic factors and were routinely available laboratory investigations. Analysis for CD38 was available in only 10 (4.7%) of patients, ZAP-70 expression in three (1.4%), IgHV in none, classical cytogenetic analysis in 11 (5.1%), and fluorescence in situ hybridization (FISH) in 8 (3.7%). Thus, data on these factors were available in a limited number of cases, restricting analysis.

At a median follow-up of 30 (0–119.6) months for MBL patients and 59.8 (0369) months for CLL, no
patients with MBL required treatment, a significant difference from either CLL group ($p < 0.0001$, Table I). Primary indications for treatment in CLL patients were: bulky disease or systemic symptoms, 21; infiltrative cytopenias, 8; transformed disease, 7; cutaneous infiltration, 4; autoimmune hemolytic anemia, 4; immune mediated thrombocytopenia, 2; leucocytosis only, 1; not documented, 2. No patient with MBL underwent transformation to aggressive disease (Richter's transformation or PLL) as compared to six patients with CLL (1, Richter's; 3, PLL; and 2, unspecified; $p < 0.003$).

Progression free survival (PFS) showed a trend for improvement in MBL patients compared to either CLL group and is shown in Figure 1; two-year PFS for MBL was 97.2% compared to 93.1% for stage 0 CLL ($p < 0.07$ compared to MBL) and 67.8% for CLL stage 1 or greater ($p < 0.0001$ compared to the MBL and stage 0 CLL). Since PFS between stage 0 CLL and MBL did not reach significance, other factors influencing PFS between these groups were not analyzed further.

The two-year overall survival (OS) for patients with MBL was 97.2% compared to 99.1% for stage 0 CLL and 90.1% for CLL stage 1 or greater ($p = NS$, see Figure 2). There were two deaths in the MBL group, both of unknown causes. In the stage 0 CLL group, there were 23 deaths; 6 were CLL-related, 4 were CLL-unrelated, and 8 were of unknown causes.

Table I. Baseline clinical and laboratory features of 214 patients with clonal lymphocytosis in keeping with CLL.

<table>
<thead>
<tr>
<th></th>
<th>MBL</th>
<th>CLL STAGE 0</th>
<th>CLL STAGE &gt; 1</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n$</td>
<td>46</td>
<td>112</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Median age (range) (years)</td>
<td>65.5 (43–86)</td>
<td>61 (34–80)</td>
<td>62 (30–86)</td>
<td>NS</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>1.0</td>
<td>0.8</td>
<td>10.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Median (range) lymphocyte count at diagnosis ($\times 10^9/l$)</td>
<td>5 (3–9)</td>
<td>12 (3–187)</td>
<td>12 (3–295)</td>
<td>ND</td>
</tr>
<tr>
<td>Lymphocyte doubling time (months) $\leq 12$</td>
<td>3 (6.5)</td>
<td>16 (14)</td>
<td>11 (20)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>&gt;12</td>
<td>42 (93.5)</td>
<td>100 (86)</td>
<td>44 (80)</td>
</tr>
<tr>
<td>Median follow up duration (range) (months)</td>
<td>30 (0.1–120)</td>
<td>60 (0.1–305)</td>
<td>54 (0–309)</td>
<td></td>
</tr>
<tr>
<td>Patients requiring treatment, $n$ (%)</td>
<td>0</td>
<td>24 (10.3)</td>
<td>28 (51)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Transformation, $n$ (%)</td>
<td>0</td>
<td>1 (0.8)</td>
<td>6 (10.9)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

CLL, chronic lymphocytic leukemia; MBL, monoclonal B-cell lymphocytosis; ND, not done; NS, not significant.

Figure 1. Progression-free survival of 214 patients with lymphoproliferation in keeping with CLL according to MBL, CLL Rai stage 0, and CLL stage 1 or more. $p < 0.07$ for MBL vs. CLL stage 0, and $p < 0.0001$ for CLL stage 1 or greater vs. the other groups.
Discussion

In the era of readily available determination of cell surface marker expression by immunophenotyping, patients with a clonal lymphoproliferative process consistent with CLL, but a minimally elevated lymphocyte count and no other signs or symptoms of CLL, present regularly to medical attention. At diagnosis, patients are naturally concerned about what to expect in the future in terms of rapidity of disease progression or transformation requiring treatment, and survival. It is well documented that for patients with CLL, Rai stage is associated with clinical outcome [2,14] and other co-morbidities may also have an influence. In this series, the majority of patients were either Rai CLL stage 0 or MBL and had an ECOG PS of 0 (n = 203, 95%).

The study, then, is essentially a comparison between a group of patients with MBL and a group of patients who had largely early stage and asymptomatic CLL. Clinical and laboratory factors that were used to compare the MBL and CLL that showed no significant difference between groups included age at diagnosis. Although the male to female ratios were similar in the MBL and stage 0 CLL groups at 1.0 and 0.8, respectively, there was a marked male predominance in CLL of stage 1 or greater, with a male to female ratio of 10 (p < 0.0001). The lymphocyte count at diagnosis was lower in the MBL group, a result of diagnostic criteria, and showed no difference between CLL groups. The most striking finding was that no MBL patient went on to require treatment, and none underwent transformation to aggressive NHL or PLL. These differences were significant; but the possibility that they were influenced by shorter follow-up in the MBL group cannot be ruled out (median follow-up 30, 60, and 54 months for MBL, stage 0 CLL and CLL stages 1 or more, respectively). It is possible that the differences in outcome seen might be attributable to the LCD. In a similar analysis of patients with CLL that remained clinically stable for at least 72 months, we found that the most significant presenting feature predicting for stability was the LCD (Hillier et al., submitted for publication), and this is in keeping with the results of other analyses [15,16]. The MBL category takes into account, however, not only the lymphocyte count but also a lack of lymphadenopathy, organomegaly, cytopenias and symptoms.

In a comparison between MBL and stage 0 CLL, MBL patients had better PFS, although this difference failed to reach statistical significance; two-year PFS were 97.2% and 93.1%, respectively (p < 0.07). Although there was no significant difference in OS between MBL and Rai stage 0 CLL, this may be because the stage 0 CLL had a low median lymphocyte count (12 x 10^9/l), and thus had very similar presenting features to the patients with MBL. However, there are pre-clinical data to suggest that
MBL may differ from CLL in terms of cell surface markers, response to stimulation of lymphocytes, circulating cytokine levels, and immune cell populations present, all of which could potentially affect clonal cell growth and clinical outcome [17 – 22]. One striking finding in this series was the difference in transformation to aggressive non-Hodgkin’s lymphoma or PLL, which occurred in no patients with MBL and six patients with CLL (p < 0.003). These results suggest that patients with MBL may have a more indolent clinical course with fewer transformations, a lower requirement for treatment, and better progression-free survival than do patients with CLL, including Rai stage 0. Although other series of patients with MBL have been reported [1,23,24], this is to our knowledge the first series demonstrating superior clinical outcome for patients with MBL compared to CLL.

Acknowledgements

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References