Monoclonal B-Cell Lymphocytosis: Update on Diagnosis, Clinical Outcome, and Counseling

Sameer A. Parikh, MD, Neil E. Kay, MD, and Tait D. Shanafelt, MD

Abstract: Monoclonal B-cell lymphocytosis (MBL) is a clonal B-cell disorder characterized by less than 5 × 10^9/L B lymphocytes in the peripheral blood, with a characteristic immunophenotype and no lymphadenopathy or organomegaly. The vast majority of MBL cases express the immunophenotype of chronic lymphocytic leukemia (CLL; CLL-like MBL), although non-CLL MBL also exists. CLL-like MBL, which is the focus of this review, is divided into low-count MBL (median B-cell count: 0.001 × 10^9/L, typically identified in population-based screening studies using highly sensitive flow cytometry assays) and high-count MBL (clinical MBL, median B-cell count: 2.9 × 10^9/L, typically identified during the workup of low-level lymphocytosis). Low-count MBL has an exceedingly small risk of progression to CLL, and these patients do not require any specific follow-up. In contrast, patients with high-count MBL have a 1% to 2% per year risk of progression to CLL requiring therapy, as well as a higher risk of infectious complications and secondary malignancies. Although the overall survival of high-count MBL patients collectively is similar to the age- and sex-matched general population, 5-year survival for CD38+ high-count MBL is approximately 10% to 20% lower than the general population. This review summarizes key concepts in the classification, diagnosis, and biology of CLL-like MBL and addresses several important issues in clinical management.

Background and Definitions

The 1996 National Cancer Institute-Working Group (NCI-WG) criteria defined chronic lymphocytic leukemia (CLL) as a clonal lymphoproliferative disorder characterized by more than 5 × 10^9/L lymphocytes in the peripheral blood that coexpress CD19, CD5, and CD23, and have weak expression of CD20, CD79b, and surface immunoglobulin. In the past 25 years, widespread use of 3- and 4-color flow cytometry has made it possible to detect monoclonal B cells at very low levels in apparently healthy individuals. In a public health study conducted by the US Centers for Public Health, the prevalence of monoclonal B-cell lymphocytosis was found to be approximately 0.2% in the general population. This finding highlights the importance of understanding the natural history and clinical implications of MBL.
Disease Control in the 1990s, 11 out of 1926 (0.6%) individuals in the general population aged 40 to 76 years were found to have a clonal population of B cells with a CLL phenotype. Subsequent studies also identified clonal B-cell populations with a non-CLL phenotype, such as other low-grade non-Hodgkin lymphomas (eg, marginal zone lymphoma). Using biospecimens from the observational cohort of the PLCO (Prostate, Lung, Colon, and Ovary Cancer Screening Trial) study, investigators were able to demonstrate the presence of a monoclonal B-cell lymphocytosis (MBL) clone in virtually all patients (44 out of 45) who subsequently developed CLL. This study convincingly demonstrated that CLL is almost always preceded by MBL. In 2005, the International Familial CLL Consortium proposed the term monoclonal B-cell lymphocytosis to describe very low levels of circulating monoclonal B cells that were identified by means of immunophenotypic characterization in the peripheral blood of apparently healthy subjects. In alignment with this proposal, the 2008 International Working Group of CLL (IWCLL) revised the diagnostic criteria for CLL and also formally recognized MBL as a separate entity. The requirement for a diagnosis of CLL was modified from a chronic absolute lymphocytosis of more than $5 \times 10^9/L$ to an absolute count of more than $5.0 \times 10^9/L$ monoclonal B cells with a CLL immunophenotype in the peripheral blood in the absence of disease-related symptoms or cytopenias, or tissue involvement other than the bone marrow. A diagnosis of small lymphocytic lymphoma (SLL) indicated the presence of lymphadenopathy or splenomegaly due to infiltrating CLL cells, with less than $5 \times 10^9/L$ CLL-type cells in the blood. Patients with a clonal B-cell process consistent with MBL but without a CLL immunophenotype were classified as having the non-CLL phenotype MBL if they were CD5+; if they did not express CD5, they were classified as CD5−ve MBL. The natural history and management of non-CLL phenotype MBL and CD5−ve MBL are distinct from CLL-like MBL, but are beyond the focus of this review. The current diagnostic criteria for MBL are summarized in Table 1.

**Prevalence**

The size of the B-cell clone has a significant impact on its clinical relevance, making it important to distinguish between low-count MBL (typically identified through population screening) and high-count MBL (recognized during the evaluation of low-level lymphocytosis). Early population-based screening studies using 2-color flow cytometry identified a monoclonal B-cell population in 0.1% to 3% of the general population. Subsequent studies using 4- to 8-color flow cytometry identified MBL in up to 6% of the general population. A large population-based study utilizing 8-color flow cytometry to examine $5 \times 10^9/L$ B cells per patient found that 73 out of 608 patients (12%) older than 40 years had CLL-phenotype MBL. Table 2 summarizes all published studies that have reported on the prevalence of MBL to date.

**Table 1. Diagnostic Criteria for Monoclonal B-Cell Lymphocytosis**

<table>
<thead>
<tr>
<th>Documentation of clonal B-cell population by 1 or more of the following:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light chain restriction, $k: \lambda$ ratio $&gt;3:1$ or $&lt;0.3:1$ or $&gt;25%$</td>
</tr>
<tr>
<td>B cells lacking or expressing low-level surface immunoglobulin</td>
</tr>
<tr>
<td>Heavy chain monoclonal IGHV rearrangements</td>
</tr>
<tr>
<td>Absolute B-cell count $&lt;5 \times 10^9/L$</td>
</tr>
<tr>
<td>Presence of a disease-specific immunophenotype*</td>
</tr>
<tr>
<td>No other features of a lymphoproliferative disorder or autoimmune/infectious condition:</td>
</tr>
<tr>
<td>Normal physical examination (no organomegaly or lymphadenopathy)</td>
</tr>
<tr>
<td>Absence of B symptoms, such as fatigue, night sweats, or weight loss</td>
</tr>
<tr>
<td>No evidence of an underlying autoimmune/infectious disease</td>
</tr>
</tbody>
</table>

*CLL-like phenotype MBL cells coexpress CD5, CD19, CD23, CD20 (dim), and surface immunoglobulin (dim). Atypical-CLL phenotype MBL cells express CD5 with CD19, but are either CD23− or express CD20 (bright) or surface immunoglobulin (bright). Non-CLL phenotype MBL cells do not express CD5, but are CD20+, and express surface immunoglobulin (bright). It is important to exclude mantle cell lymphoma, which characteristically has t(11;14).

CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain; MBL, monoclonal B-cell lymphocytosis.

The median B-cell count in the peripheral blood of patients with low-count MBL is only $0.001 \times 10^9/L$. This is in contrast to the median B-cell count of $2.9 \times 10^9/L$ observed in high-count MBL. More than 95% of patients with high-count MBL have an absolute B-cell count of more than $0.45 \times 10^9/L$. Given these facts, as well as the important differences in the biology and outcomes of patients with low- and high-count MBL, a threshold of $0.5 \times 10^9/L$ has been proposed in order to distinguish between these conditions.

Prospective studies following patients with both low- and high-count MBL for an extended period are needed in order to confirm the biologic and prognostic importance of this threshold. The change in the lower boundary of what constitutes CLL (from an absolute lymphocyte count [ALC] of $\geq 5 \times 10^9/L$ to a B-cell count of $\geq 5 \times 10^9/L$) reclassified many patients who were previously considered to have CLL as having high-count MBL. A population-based study in Olmsted County, Minnesota evaluated the incidence of CLL and high-count MBL from 2000 to 2010. The incidence of high-count MBL was 3.5 per...
100,000 individuals, according to the IWCLL 2008 criteria. Of the 123 patients who were classified as having Rai stage 0 CLL by the NCI-WG 1996 criteria, 36 patients were reclassified as MBL by the IWCLL 2008 criteria. This reclassification also shifted the stage distribution at diagnosis for those who remained in the CLL category, with an increased proportion of patients with Rai stage 1 or 2 disease at diagnosis. Reclassifying some of the lowest risk patients from Rai stage 0 to MBL also changed the natural history of those patients who remained in the Rai stage 0 category under IWCLL 2008, resulting in a shorter time to first treatment.

### Risk Factors for Developing MBL

Few risk factors for the development of MBL or CLL have been identified. Consistent with the fact that CLL has the strongest family history of any hematologic cancer, the prevalence of MBL in families where at least 2 first-degree relatives are affected by CLL (eg, familial CLL; MBL prevalence, 12% to 18%) is 2- to 3-fold higher than that of the general population. Studies suggest that relatives of patients with sporadic CLL also have an increased prevalence of MBL. Increasing age and male sex are associated with an increased risk of developing MBL.
Several groups have identified heritable germline gene polymorphisms associated with increased risk of CLL. and initial studies suggest that these single nucleotide polymorphisms may confer this risk by increasing the likelihood of developing MBL.

Recent studies have shown that up to one-third of patients with CLL will demonstrate stereotyped B-cell receptors (BCR), characterized by nonrandom combinations of immunoglobulin heavy-chain variable (IGHV) genes. Structural similarity of these BCRs suggests that such receptors may bind to a similar yet unidentified antigen(s), with potential relevance to disease pathogenesis. Approximately 25% of CLL patients demonstrate stereotyped complementarity determining region 3 (CDR3) sequences, compared with less than 5% of patients with low-count MBL. One recent study found CDR3 stereotypy in 5.5% of patients with low-count MBL, compared with 22% of high-count MBL patients and 20% of patients with Rai stage 0 CLL.

Chronic infections may also contribute to the risk of developing CLL in some patients. In a population-based study of 4249 CLL patients conducted in Denmark from 1977 to 1997, prior history of pneumonia was associated with significantly increased risk for CLL (odds ratio [OR], 1.4) compared with 15,690 frequency-matched controls. Analysis from the Surveillance, Epidemiology and End Results (SEER) database also suggested that patients with CLL (n=10,171) were at increased risk for sinusitis, pharyngitis, bronchitis, pneumonia, influenza, cellulitis, and herpes zoster (OR range, 1.08-1.24) relative to 122,531 frequency-matched controls. A link between infection and risk of CLL was also observed in a nationwide analysis of 4 million adult males who were admitted to Veterans Affairs hospitals. In a recent study, MBL was detected in 28.5% of patients (35 out of 123) with chronic hepatitis C virus (HCV), with a trend toward increased frequency among patients with more advanced disease. Interestingly, the distribution of cases among the subtypes of MBL differed in HCV-infected patients relative to the general population. All phenotypes occurred at a higher frequency in the HCV-infected patients than in the uninfected control group. Although CLL-like MBL accounts for approximately 70% of cases in the general population, only 37% of the HCV patients with MBL had this phenotype. Atypical CLL and non-CLL types of MBL constituted 46% and 17% of the cases, respectively. The authors concluded that persistence of the HCV antigen may signal through the BCR chronically, resulting in clonal expansion of B cells. Additional research to determine which specific antigenic stimuli can lead to MBL is ongoing, and will likely provide clues to the stimuli that lead to CLL.

**Biologic Insights**

Although both CLL-like MBL and CLL share the same immunophenotypic markers, studies that describe their underlying biologic differences are limited. It was initially thought that low-count MBL was always a monoclonal process; however, single-cell analytic studies have showed that low-count MBL can be oligoclonal or polyclonal. A recent study identified constitutive activation of lymphoid enhancer binding factor-1 (LEF-1) and the Wnt pathway in patients with CLL and MBL (absolute B-cell count of 0.7-2.4 × 10^9/L), but not in normal B cells, suggesting that the Wnt signaling pathway may be active and play a role in the pathogenesis of MBL and CLL. The IGHV gene usage profile and genetic abnormalities detected by the fluorescence in situ hybridization (FISH) risk category are generally similar among patients with high-count MBL and Rai stage 0 CLL (Table 3), although they are markedly different in patients with low-count MBL. In low-count MBL, both IGHV 4-34 and IGHV 3-23 genes are underrepresented and IGHV 1-69 usage is absent, whereas these IGHV gene families are much more common in CLL.

In addition to the known common recurrent genetic alterations identified by FISH, recent genetic studies in CLL using massively parallel sequencing have identified novel mutations in NOTCH1, SF3B1, MYD88, ZMYM3, MAPK1, FBXW7, and DDX3X genes. Of these, NOTCH1 (present in approximately 10% to 15% of CLL patients) and SF3B1 (present in approximately 10% to 15% of CLL patients) have been shown to be independent predictors of poor outcomes in CLL patients. A small study of 63 high-count MBL patients, SF3B1 mutation was detected in only 1 patient (1.5%), and 2 patients (3.2%) harbored NOTCH1 mutations. A recent study evaluated the IGHV gene repertoire and FISH risk category in low-risk MBL, high-risk MBL, and CLL. Investigators demonstrated that low-count MBL clones appear to display a much lower frequency of chromosomal alterations that are restricted to del(13q) and trisomy 12, with a high prevalence of IGHV-mutated cases. In contrast, del(11q) was seen more often in high-count MBL, and del(17p) and NOTCH1 mutations were only found in CLL. These data support the notion that evolution from low-count MBL to high-count MBL—and subsequently CLL—occurs in a stepwise fashion, with gradual acquisition of high-risk genetic abnormalities.

**General Approach to the Workup of Lymphocytosis**

A general approach to evaluating patients with lymphocytosis is shown in the Figure. It is important for clinicians to recognize that patients found to have non-CLL...
phenotype MBL require a complete evaluation for an underlying lymphoproliferative disorder appropriate for the histologic profile of the clonal B cells. For most cases of non-CLL phenotype MBL, this involves the typical non-Hodgkin lymphoma staging evaluation, including computed tomography (CT) scans of the chest, abdomen, and pelvis, as well as bilateral bone marrow biopsy.

Prior to classifying patients as having CLL phenotype MBL, it is important to consider whether they may have SLL (Table 1 and Figure). One study examined the clinicopathologic features of 36 patients incidentally found to have extramedullary tissue biopsies containing CLL-type cells (and who had <5 × 10^9/L peripheral blood monoclonal B cells). Lymph node biopsies were performed in order to evaluate lymphadenopathy in 20 patients and for staging of a nonhematologic neoplasm in 16 patients. After a median follow-up of 23 months, 21 untreated patients had stable or no lymphadenopathy, 3 had regressed lymphadenopathy, and 12 patients had developed progressive lymphadenopathy and/or received treatment for CLL/SLL. Features associated with disease progression included lymph nodes larger than 15 mm and the presence of proliferation centers in the biopsied tissue.

It is well recognized that CT scans at the time of diagnosis will upstage approximately 25% of patients with newly diagnosed, Rai stage 0 CLL. One recent study of 240 patients with Binet stage A CLL (according to the 1996 NCI-WG criteria) evaluated the effects of whole-body CT on disease classification. Of the 240 cases of Binet stage A CLL, 69 patients had high-count MBL when classified using the 2008 IWCLL guidelines. CT scans identified a lymph node larger than 1.5 cm in 29 patients with high-count MBL, resulting in reclassification to SLL. After a median follow-up of 35 months, however, only 5 of the 66 patients with high-count MBL had progressed to CLL requiring therapy, with no difference observed among MBL patients who were reclassified as having SLL based on imaging. Collectively, these studies suggest that there may be a “nodal equivalent” of MBL, but indicate that there is no current clinical justification for routine CT scans in patients with CLL-phenotype MBL.

There are limited data on the clinical management of patients with MBL. Ideally, these patients should be seen by a hematologist/oncologist at least once for a review of systems and a physical examination, with particular attention to a thorough family history. A bone marrow aspirate and biopsy is not required at the time of diagnosis. Additionally, there are no formal recommendations to test for various prognostic markers available to predict time to treatment and overall survival (as are available in CLL) for patients with MBL, outside of a research setting. Low-count MBL patients have an exceedingly low risk of progression to CLL requiring therapy, and therefore could be followed by their regular primary care physician for routine medical care. Patients with high-count MBL should be made aware of B-type symptoms, including fevers, night sweats, weight loss, and fatigue. They should also be informed of the risks of progression to CLL requiring therapy (which is approximately 1% to 2% of cases per year). Annual follow-up by a hematologist/oncologist is generally advised in order to monitor the B-cell clone size and assess for clinical progression of disease. General recommendations for follow-up of MBL are summarized in Table 5.

### Key Questions Regarding the Natural History and Clinical Management of Patients With MBL

**What Is the Natural History of MBL?**

Since the prevalence of low-count MBL is at least 100 times more than that of CLL, it is apparent that only a
subset of patients with low-count MBL progress to overt CLL. Few studies have longitudinally examined the progression of low-count MBL. After a median follow-up of 34 months, Fazi and colleagues evaluated 76 low-count MBL patients with 5-color flow cytometry and demonstrated that 90% of patients were stable over time. In another study of 78 patients with low-count MBL, expansion of CLL cells occurred in 7.5% of patients after a median follow-up of 65 months. No low-count MBL patients had progressed to CLL that required therapy.

More studies have evaluated clinical outcomes in patients with high-count MBL than in low-count MBL. Given that the threshold to distinguish high-count MBL from Rai stage 0 CLL was somewhat arbitrarily selected, rather than focusing on what proportion of MBL patients progress to meet criteria for a CLL diagnosis, a more appropriate and clinically relevant question is: What is the rate of progression of high-count MBL to CLL requiring therapy? Several studies have reported the rate of progression of high-count MBL to CLL requiring treatment and are summarized in Table 4. The median duration of follow-up in these studies ranged from 1.5 years to 6.7 years. The rate of progression to CLL requiring treatment was heterogeneous and ranged from 0% to 5% per year. The vast majority of these studies were retrospective; as such, accurate determination of clinical features in some patients was not always possible. Also, it appeared in some of the studies that the rate of progressive CLL requiring treatment was higher in the first few years following diagnosis. Based on the number of patients

Figure. A schematic approach to incidentally-discovered lymphocytosis.

* Treat the underlying infectious and autoimmune condition appropriately; if lymphocytosis does not resolve, consider peripheral blood flow cytometry
† Phenotype of CLL cells is as follows: positive for CD19, CD5, and CD23; and weak expression of CD20, CD79b, and surface immunoglobulin

ALC, absolute-lymphocyte count; CLL, chronic lymphocytic leukemia; IWCLL, International Working Group of CLL; MBL, monoclonal B-cell lymphocytosis; SLL, small lymphocytic leukemia.
What Are the Risk Factors of Progression From MBL to CLL Requiring Therapy?

Whereas the risk factors for disease progression in CLL (eg, non-del(13q14) FISH abnormality, unmutated IGHV, and positive expression of CD38, ZAP-70, and CD49d) have been well defined, there are limited studies examining the role of these risk factors on the natural history of high-count MBL. In a retrospective study from the Mayo Clinic involving 302 high-count MBL patients, expression of CD38 was associated with faster progression, but there were insufficient events to assess the impact of IGHV mutation, ZAP-70 expression, or chromosomal abnormalities.\(^{17}\) Rossi and associates studied the impact of several prognostic markers among 123 patients with high-count MBL, and found that IGHV mutation analysis, CD38 and CD49d expression, and FISH analysis predicted for a faster time to progression on univariable analysis.\(^{16}\) However, on multivariable analysis, only high-risk FISH category (trisomy 12 or del(17p)) remained significant (median time to CLL requiring therapy in unmutated IGHV, 1.9 years vs not reached; \(P=.02\).\(^{49}\)

Several studies have also reported on overall survival in patients with high-count MBL.\(^{12,52}\) In the UK series of high-count MBL, 62 out of 185 patients (34%) died after 6.7 years of follow-up. However, only 4 deaths (2%) were attributed to progressive CLL.\(^{12}\) In a retrospective study of 312 patients with high-count MBL seen at the Mayo Clinic, overall survival was not significantly different from that of age- and sex-matched controls in the general population.\(^{52}\) This is in contrast to patients with Rai stage 0 CLL, whose overall survival was significantly inferior to that of the general population. Notably, however, the survival of patients with high-count MBL relative to the population was influenced by biologic characteristics of the B-cell clone. Patients with high-count MBL who were negative for CD38 had a survival identical to that of the general population, but 5-year survival for CD38+ high-count MBL patients was approximately 10% to 20% lower than that of the general population.

Together, these findings lend support to considering both the B-cell count\(^ {27,28}\) and biologic characteristics of the clone in future efforts to better determine the exact association of the diagnostic criteria for MBL to clinical outcome.

Bennett and colleagues reported on the outcomes of patients with low-count MBL detected during routine screening of normal 60- to 80-year-old patients seen in the clinic.\(^ {57}\) They identified 78 patients with low-count MBL and 126 age-matched controls that did not have any abnor-
mal circulating B cells. Among those for whom follow-up data were available, there were 9 deaths (23%) in the MBL group compared with 36 deaths (29%) among controls, after a median follow-up of 5.5 years. This report suggests that patients with low-count MBL have no significant difference in overall survival when compared with those among an age-matched general population.

Are Patients With MBL at Increased Risk of Other Complications Associated with CLL?

MBL and Infections Infections are a major source of morbidity and mortality in patients with CLL, and are directly or indirectly related to the cause of death in 30% to 50% of CLL patients. In addition to hypogammaglobulinemia that is thought to occur from defective functioning of the nonmalignant B cells, there have been reports of abnormalities in T-cell function, as well as neutrophil and monocyte function. Recent studies evaluating the risk of infection in high-count MBL suggest that these individuals are at a higher risk for infectious complications. In a case control study from the Mayo Clinic, infection risk was compared among local cohorts of patients with high-count MBL (n=154), newly diagnosed CLL (n=174), and adult patients seen in the general medicine clinic (n=689). After a median follow-up of 4 years for patients with MBL and CLL and 3 years for controls, hospitalization owing to serious infections was noted to occur more among patients with MBL (16%) and CLL (18%) than among controls (2.6%). In a Cox proportional hazard analysis of all 1017 patients (controls, MBL, and CLL), male sex (hazard ratio [HR], 2.3), major comorbid health problems (HR, 1.7), the presence of CLL (HR, 3.2), treatment for progressive CLL (HR, 2.4), and the presence of MBL (HR, 3.0) were independently associated with risk of hospitalization for infection. In contrast, patients with low-count MBL did not seem to have a higher risk for developing infections when compared with the general population.

MBL and Secondary Malignancy An association between CLL and increased risk of secondary cancers has long been recognized. In a large retrospective study of 16,367 CLL patients enrolled in the SEER program who were followed for 5.2 years, 11% of patients developed a second solid tumor. This rate was significantly higher than that of the general population (odds ratio, 1.20). In a more recent study of more than 2.3 million patients with various solid malignancies enrolled in the SEER database, overall survival was compared in patients with and without preexisting CLL. After adjusting for age, sex, race, and disease stage, patients with cancers of the breast, colorectum, kidney, prostate, and lung had an inferior overall survival if they had preexisting CLL, compared with patients without a diagnosis of CLL.

Whether patients with high-count MBL are at an increased risk for secondary malignancies has also been explored. A recent study evaluated the risk of secondary nonhematologic cancers among locally-dwelling patients with MBL (n=125), CLL (n=153), and controls (n=596) seen in the general medicine clinic at the Mayo Clinic from 2004 to 2009. After a median follow-up of 4.2 years, 16% of patients with MBL developed nonhematologic malignancies, compared with 4% of controls (HR, 5.0). The MBL cohort had a higher incidence of cancer of the breast, lung, and nervous system than the control cohort. In contrast to these findings in patients with high-count MBL, 78 patients with low-count MBL identified in a hospital outpatient clinic did not appear to have a higher risk of developing a secondary nonhematologic malignancy.

Collectively, these observations regarding risk for serious infection and secondary malignancy suggest that there is a clinical phenotype to high-count MBL that goes beyond the risk for progression to CLL. Indeed, the findings suggest that the risk of hospitalization for infection and/or secondary malignancy may be higher than the likelihood of progression to CLL requiring treatment. Further follow-up and validation of these preliminary findings will hopefully allow us to derive more insight into the risk of nonhematologic malignancy and infection among patients with both high-count MBL and low-count MBL.

Can Patients With MBL Serve as Stem Cell Transplant Donors?

Allogeneic transplant is now a well-established therapy for patients with CLL. For CLL patients who meet the international consensus criteria for transplantation, a matched sibling is the preferred donor source. As previously discussed, CLL has a strong genetic predisposition, with approximately 10% of patients having 1 or more first-degree relative affected by CLL. Moreover, approximately 15% to 18% of patients from CLL families and 15% of relatives older than 60 years of age with sporadic CLL (ie, nonfamilial) have MBL. Accordingly, approximately 1 out of every 7 relatives undergoing human leukocyte antigen typing to serve as a sibling donor may have unrecognized MBL if evaluated using sensitive screening assays. A number of cases of transfer of MBL donor clones to CLL patients undergoing transplant have been reported. Although identifying an MBL clone in a given donor among patients with multiple matched siblings may allow for more optimal selection among multiple suitable donors, the more difficult and important question of whether this should preclude a sibling donor in favor of an unrelated donor in a patient who has only 1 matched sibling (or preclude transplantation altogether) remains uncertain. Cases of transfer of a CLL-like
clone to unrelated donors to children undergoing stem cell transplant have also been documented, thus raising the broader question of whether all patients preparing to donate stem cells (including unrelated donors) should be screened for MBL.66

**Conclusion**

The formal recognition of MBL as a separate diagnostic entity in the 2008 IWCLL guidelines has made it important for practicing hematologists/oncologists to be familiar with MBL. Two distinct types of MBL exist: one that is detected using highly sensitive flow cytometry assays in population screenings (owing to lymphocytosis) and the other detected in a healthcare setting. New evidence suggests that the clonal B-cell biologic characteristics (eg, IGHV mutation status, chromosomal abnormalities detected by FISH, and IGHV gene usage) of high-count MBL closely mirror those of Rai stage 0 CLL, whereas low-count MBL has a distinct clinical and biologic profile. Patients with high-count MBL progress at a rate of 1% to 2% per year to CLL requiring therapy, whereas individuals with low-count MBL have a very low risk of progression. Recent studies suggest that the risks of serious infection and/or secondary malignancy among patients with high-count MBL are greater than the likelihood that they will progress to CLL requiring treatment. Additional studies are needed in order to better understand the risks of infection, secondary malignancies, and appropriate clinical management of patients with MBL.

**References**

5. Nieto WG, Teodosio C, Lopez A, et al; Primary Health Care Group of Sala-
7. Marti GE, Rawstron AC, Ghiu E, et al; International Familial CLL Consor-
12. Rawstron AC, Bennett FL, O’Connor SJ, et al. Monoclonal B-cell lymphocy-
14. Nieto WG, Almeida J, Romero A, et al; Primary Health Care Group of Sala-
22. Manso DM, Izad MJ, Scidoni CA, de Oliveira FM, Rago EM, Falcão RP. Monoclonal B-cell lymphocytosis in first-degree relatives of patients with sporadic (non-
25. Crowther-Swanepoel D, Corre T, Lloyd A, et al. Inherited genetic susceptibil-
27. Vardi A, Dagklis A, Scarlò L, et al. Immunogenetics shows that not all MBL are equal: the larger the clone, the more similar to CLL. *Blood*. 2013;121(22):4521-4528.
30. Landgren O,_Gridley G, Cheek D, Caporaso NE, Morris Brown L. Acquired immune-related and inflammatory conditions and subsequent chronic lympho-
32. Lanaus MC, Allgood SD, Volkheimer AD, et al. Single-cell analysis reveals oligoclonal-
33. Gutierrez A Jr, Tschumper RC, Wu X, et al. LEF-1 is a prosurvival factor in chronic lymphocytic leukemia and is expressed in the preleukemic state of mono-
clonal B-cell lymphocytosis in first-degree relatives of patients with sporadic (non-
34. Molica S, Mauro FR, Giannarelli D, et al. Differentiating chronic lymphocytic leukemia from monoclonal B-lymphocytosis according to clinical outcome: on-
35. Lanasa MC, Allgood SD, Volkheimer AD, et al. Single-cell analysis reveals oligoclonal-