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Monoclonal B Cell Lymphocytosis: Clinical and Population Perspectives

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Abstract

Monoclonal B Cell Lymphocytosis (MBL) refers to clones of CLL-like cells that exhibit CLL characteristics that fall short of the numbers required for CLL diagnosis. Data from large CLL kindreds document increased prevalence of MBL suggesting a genetic contribution to its etiology. The molecular features that favor progression of MBL to CLL are poorly understood but an elevated B-cell count is a risk factor for progression. An important consideration when evaluating volunteers from CLL families who are willing to donate bone marrow is that MBL be ruled out since the MBL donor clone could result in a second CLL in the recipient. Further studies of MBL are needed to identify the molecular features and how they evolve during progression. Published 2010 Wiley-Liss, Inc.

Keywords

chronic lymphocytic leukemia; monoclonal B cell lymphocytosis; population; lymphocytosis

Five years after the formal description of monoclonal B cell lymphocytosis (MBL) as a uniform nomenclature for CLL-like cells clones that fall short of the numbers required for CLL diagnosis (1,2), the clinical, demographic and molecular features have begun to come into better focus. This report examines offers a clinical perspective on the controversies and suggests studies required for further progress. We discuss the definition, population features, clinical features, molecular components, and finally some recommendations for research directions.

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DEFINITION

The original MBL definition (2) consolidated numerous earlier reports of B-cell clones (3,4) noted in diverse settings and distinguished an entity limited to monoclonal B-cell expansions with CLL-like characteristics that did not meet the absolute lymphocyte count (ALC) threshold for CLL. Some related and more rare subgroups (e.g., those with CD20 bright, CD5-cells) were included as distinct subgroups (1,2,5). However, there is an ongoing issue as to whether these should be separated to provide a more CLL-specific MBL definition (6).

A recent revision of the definition of CLL has altered the ALC ceiling (7). The revised CLL definition requires an absolute B-lymphocyte count of greater than 5000 cells per cubic milliliter. This has important implications regarding the prevalence of MBL and CLL and the likelihood of a precursor state (MBL) progressing to CLL. Based on this classification change alone, numbers of CLL cases will decrease (because some individuals previously classified as having CLL will now be reclassified as MBL), MBL cases will increase, and the probability of progression to overt CLL will increase.

What are the optimum CLL-like cell counts to use for the definition of MBL? On the upper side, MBL become CLL (by definition) at the threshold of 5000 ALC per mm^3 (8). Optimally, such a threshold should be based on a definition that is clinically accessible and one that offers the best possible separation between subjects who will have a benign outcome and those who will suffer morbidity or mortality from the condition (7).

On the lower side (the border with the “normal” state), MBL has been divided into “low count” and “high count” based on the projected likelihood of progression to CLL (9,10). How should the definition be refined to reflect these distinctions? What features distinguish MBL that progresses from that likely to remain benign? Some studies suggest the absolute b-cell count (ALC) is more important than the percentage of clonal B cells (10); further studies are needed to refine this issue.

What immunophenotyping protocols should be used for standard clinical documentation, and what is recommended for research investigation? This determines in part how frequent MBL is in the general population (11–13) and how it varies in key subgroups such as families (14,15)? While the reported age-adjusted population prevalence has been consistent, altered protocols predictably result in detection of lower (16) or higher (11) rates. For example, the highest population prevalence of MBL is reported by Nieto using an eight color/antibody approach (11). Examples of low prevalence findings were reported in the early hazardous waste site studies, recently reviewed by Vogt et al. (16).

More “sensitive” approaches are by definition less specific, i.e., a smaller proportion of those with more broadly defined MBL will progress to CLL. However, as mentioned earlier, the recent change in the definition CLL has the effect of reclassifying some individuals with a historic CLL diagnosis as MBL. As these individuals are at the top of the B-cell count range, their risk of progression is correspondingly higher. It is desirable to define the entity so that it identifies as accurately as possible those at risk of progression to CLL and allows studies to focus on the molecular features that confer risk. Elucidating the earliest changes

associated with risk can allow a mechanistic basis for crafting biologically rational interventions.

POPULATION FEATURES

From an epidemiologic perspective MBL has strong parallels with CLL based on previously cytological similarities. It shares the only known demographic risk factors with CLL in that it is more common in the elderly, in males and in high-risk B cell malignancy (CLL) kindreds; MBL precedes virtually all cases of CLL (17) and MBL has strong parallels with monoclonal gammopathy of unknown significance (MGUS) and multiple myeloma (MM) as a B-cell precursor (18); The etiologic origin of MBL is a mystery. Does it derive from a dysregulated antigen response or is it induced by some currently obscure extrinsic environmental or infectious insult? While no extrinsic risk factors for CLL are established, there is suggestive evidence for herbicides and radiation, although the evidence is controversial (19). Even more obscure are risk factors for MBL and the factors that determine progression of MBL to CLL. Examining the frequency of MBL and its outcome in groups exposed to these agents with careful exposure assessment and appropriate biomarkers is a future priority (19–21).

While every population studied exhibits a male excess of CLL, in MBL the gender difference seems to be less pronounced. Further study is needed to understand if there is a real dichotomy by gender and what it implies about progression.

CLL exhibits a marked pattern of ethnic variation. This leukemia is strikingly less frequent in Asians (20,22). Moreover, migration studies implicate inherited factors as having a dominant role as individuals who migrate to the west from Asia retain their original risk profile, a pattern distinct from other malignancies such as breast and colon where western lifestyle imposes increased risk on Asians once they adopt Western diet and other exposure patterns. Some evidence suggests lymphoma rates are increasing in Asia for selected B cell malignancies and further study of both precursor and CLL in diverse geographic settings is needed.

Does MBL share the genetic susceptibility increasingly well documented for CLL in both population samples (23,24) and in families (14,25)? Is the prevalence of MBL also elevated in relatives of individuals with other B cell malignancies such as Waldenström's Macroglobulinemia, MM, or NHL? Our family data from a large sample of high risk CLL kindreds from the genetic epidemiology of CLL consortium clearly document an increased prevalence of MBL with the expected age and gender distribution. The prevalence of MBL in adults from these high risk families is 17% (26). Do the B cell precursor states MBL and MGUS share characteristics, for example, elevated levels of free light chains (FLC)? We recently assayed monoclonal (M)-proteins, kappa/lambda, FLCs in prediagnostic blood obtained up to 9.8 years before CLL diagnosis (27). The prevalence of an abnormal FLC ratio, M-protein, and hypogammaglobulinemia before CLL diagnosis was 38%, 13%, and 3%, respectively. M-proteins and abnormal FLC ratios were detected up to 9.8 years before CLL diagnosis in a total of 48 persons (44%). Hypogammaglobulinemia was not present until 3 years before the diagnosis of CLL. Among 37 patients with information on tumor cell

immunophenotype, an association between immunophenotype and involved FLC (P = 0.024) was observed.

CLINICAL

The “Low count MBL” with normal blood absolute B-cell count has limited potential to progress to CLL (28). Among individuals with “high count” MBL, Rawston’s group has reported the most extensive follow-up to date on a group of MBL subjects. Although only 1% progress to require treatment every year, a considerably larger proportion exhibit an increasing ALC and therefore progress to a formal CLL diagnosis (12). Although data suggest that MBL that progress to CLL are likely to have a more indolent course, perhaps based on a higher proportion of “mutated” phenotype and lower rates of the more deleterious cytogenetic abnormalities (11q- and 17p-), the observation by the Leeds group that over 1/3 of MBL died (62/185) over a 6.7 year follow-up period raises questions even though only four of the deaths in this group were ascribed to CLL (13).

What clinical studies if any are indicated when MBL is identified, and what are the ethical considerations for research when someone is identified with MBL (2,29–31)?

The majority of patients presenting to a clinical practice for MBL are identified due to an abnormal blood count, usually lymphocytosis. Clinical CLL-like MBL is identified in ~10% of cases referred for investigation of lymphocytosis (12). Additionally, there are increasing numbers of individuals previously diagnosed with CLL who were reclassified as MBL due to the 2008 update to CLL diagnostic criteria which is based on the B-threshold of 5×10^9/L (7). MBL is a diagnos is require an of evaluation exclusion; by all individuals hematologist–oncologist including a relevant history and physical exam to exclude those with lymphadenopathy and organomegaly. The medical history should take into account family history and patients should be educated regarding key symptoms such as lymph node enlargement, fatigue, night sweats, bleeding and infections. Shanafelt has reviewed the suggested clinical management of MBL (32). Monitoring of subjects with MBL is similar that for patients with low stage CLL and requires infrequent (e.g., yearly) interview, physical examination and blood analysis. There are no known modifiable risk factors and beneficial early interventions (prevention or treatment) are currently unknown for MBL/CLL, emphasizing the need for further investigation in populations.

There is limited data on outcomes of the rarer variant forms of MBL, atypical-CLL-MBL and non-CLL-MBL. These variants may have greater tissue or bone marrow involvement than blood levels suggest (2). The discovery of CD5-MBL mandates a workup to exclude other B cell malignancies such as NHL (33,34) including primary splenic marginal zone lymphoma/Waldenstrom’s macroglobulinemia (35). Evaluation should include standard clinical testing and imaging (chest X-Ray, abdominal ultrasound, and possibly, computerized tomographic studies of the chest, abdomen, and pelvis). A rapid rise in the ALC or other clinical findings may warrant diagnostic/prognostic bone marrow aspirate and biopsy.

Once the diagnosis of “clinical” or “high-count” CLL-like MBL (cMBL) is established, the primary concern is progression to CLL. Although CLL is likely universally preceded in all

cases by MBL (17), the overall proportion of cMBL subjects who that progress to clinically significant CLL is small and similar to the rate of progression of MGUS to MM (~1% per year) (13). Population based MBL (pMBL) or “low-count” MBL are unlikely to progress. Very few atypical MBL have been identified and followed longitudinally, so it is not known how often they progress to overt CLL. Absent this data, the best routine management is a standard work-up and yearly follow-up (13,30,31). What predicts progression to CLL and more importantly—CLL that requires treatment? Shanafelt has specifically compared the influence of B-cell count vs. ALC on risk of experiencing an adverse outcome. The influence of these is similar, but the influence of an elevated B-cell count is slightly superior. It is interesting that T and NK-cells counts had the opposite effects of B-cell count on outcome. This suggests we should more closely examine this potential source of effect modification in future studies (30). Rawston followed 185 subjects with lymphocytosis with a median follow-up of 6.7 years. Progressive lymphocytosis occurred in 28%, progression to CLL in 15% and the need for chemotherapy in 7%. The absolute B cell count was the only prognostic factor clearly indicative of progression, and Kaplan-Meier estimates of the percentage of patients with stable disease showed that those with B cell counts >4000/mm^3 had higher risk than did those with B cell counts in the ranges of 1900–4000/mm^3 or <1900/mm^3 (13). Rawston studied outcomes in 111 patients over a median of 3.7 years follow-up in a population referred for investigation of mild lymphocytosis. Overall, 35% (39/111) progressed to a lymphocyte count >10 × 10^9/l after a median 1.8 years from presentation, and 12% (13/111) to a lymphocyte count >30 × 10^9/L after a median 4.1 years. In the subset that progressed (n = 47), doubling time was either slow (34/47, over 3 years), rapid 7/47 (median 0.7 yrs) or bi-phasic (median 3.5 years after initial stable). The “bi-phasic” group might be of greatest interest for future biomarker studies that could potentially identify a critical oncogenic event in a similar sample (12). The modest proportion that exhibit this pattern (i.e., ~15% cMBL) mean that a substantial sample will be required to identify the subgroup with this pattern for intense biomarker investigation.

Rossi has compared some feature of Rai Stage 0 CLL and cMBL. MBL subjects had better humoral immune capacity, lower infection risk, lower prevalence of the adverse cytogenetic features (del11q22-q23, del17p13, and TP53 mutations), slower lymphocyte doubling time and longer tumor free survival than did Rai 0 CLL. Although CD38, ZAP-70, CD49d, and IGHV mutation status all predicted treatment free survival as univariate factors, the presence of trisomyþ12 or del17p13 were the sole independent predictors of the eventual need for treatment in cMBL (n = 123 cMBL vs. n = 154 Rai 0) (36). Shanafelt found that CD38 expression was also associated with cMBL outcome. Fung followed 46 MBL for a median of 2.5 years and observed no progression in comparison to 21% of 112 Rai 0 and 52% of 54 Rai 1 (albeit, the CLL group had longer median follow-up of ~5 years) (37).

In general, we can conclude that the absolute B cell count is currently the most important easily accessible predictor (13,31) while CD38 expression correlated with the need for therapy in some studies (10,37). Other prognostic parameters used in CLL (e.g., IGHV mutation status, CD49 expression and cytogenetics) may be important but more data is needed (37). It is important for this field to have larger consolidated studies that include validated sets of markers [i.e., ZAP-70, IGVH mutation status, FISH (10) and CD-38 expression] to address the independent and combined effects of these markers on

progression. This should be a clear future goal for studies by consortiums since it will be difficult for any one group to achieve the required study size.

There are ethical concerns with regard to population screening for MBL. Identification of this condition imposes concerns (albeit small) for potential development of CLL. There is currently no known preventive intervention or early treatment option to prevent conversion of MBL to CLL. Once an individual acquires this “label”, insurance might become more expensive or unavailable. Informing subjects with screen detected MBL of their status could cause anxiety and the unintended consequences of employment and insurance discrimination. Also, the clinical benefit of early detection of MBL is not clear. Researchers should share meaningful information with subjects, but what is meaningful? If the absolute B cell count is an important marker of progression, those without lymphocytosis are very unlikely to progress, i.e., low count MBL is likely at very low risk for progression. For cMBL, both consent and laboratory quality control (i.e., were studies done under CLIA laboratory conditions?) become issues. Ultimately, MBL may closely resemble MGUS, a precursor for another incurable B cell malignancy with a similar low but documented risk of progression with regard to the need to inform subjects. MBL will also need to be included in new diagnostic codes to enhances tracking and insurance compensation and to distinguish it from both CLL and lymphocytosis. As some CLL patients are reclassified as MBL based on the new 2008 CLL classification, new Rai stage 0 patients will have worse prognosis than in the original classification since these new Rai 0 CLL will have higher ALCs and greater risk of progression (38).

The situation in “high risk” families is a bit more clear. Individuals in families with multiple cases of CLL in blood relatives share increased risk for developing CLL although the specific inherited genes that distinguish those at highest risk remain unknown. Although a number of groups have documented the increased incidence of MBL in unaffected first degree relatives of CLL cases in these families, we do not know the degree to which MBL identifies individuals within kindreds that are at highest risk of progression to overt CLL. Close follow-up of these families over extended periods for these outcomes is needed but given the numbers under observation and the “expected” rate of progression it will take some time to get answers (39).

There is concern for volunteers from CLL families who donate bone marrow who themselves have MBL. CLL family members have an increased chance of having unrecognized MBL despite normal physical examinations and normal standard blood counts. There is both the theoretical and actual concern for transfer of MBL and leukemia stem cells to recipients, especially in the setting of an immunodepressed recipient. Several occurrences of transfer of MBL donor clones to a CLL patient undergoing transplant resulting in a second CLL in the recipient have been documented (40–42). Three case studies of potential population-screened MBL donors and a detailed review of ethical issues can be found in Hardy et al. (29). A small study of 13 HLA-identical siblings evaluated for stem cell transplant identified MBL in 15.4%, a rate similar to the prevalence of MBL in unaffected first degree relatives of CLL patients (43). In light of their findings and the case studies noted above, Del Giudice et al. recommend that flow cytometric analysis of peripheral blood be added to eligibility screening of HLA-matched siblings to prevent transfer of MBL clone

to the recipient. There would be comparable concern regarding nonfamilial MBL individuals serving as donors. Currently we are not aware of information to address this but as flow screening on prospective donors accumulates, we will be able to more accurately assess this.

MOLECULAR

There has been limited study to date of the molecular features of MBL, and how they evolve during progression to CLL. For example, the immunoglobulin gene repertoire in MBL is different from CLL (for example, VH 169, commonly observed in CLL, is lacking in MBL) and the stereotyped heavy chain regions observed in as many as 30% of CLL cases are present in far fewer individuals with MBL (9,10,13,30).

The study of MBL offers the opportunity to identify the earliest changes that characterize CLL. Prospective observation of MBL cases may also reveal the specific molecular alterations that signal progression. Eventually, such studies should provide mechanistic insight and may eventually lead to identification of targets for early intervention/treatment. This work sets the stage for a new assault on the key molecular, genetic, and etiologic features that have been so elusive in CLL.

Refining the understanding of MBL and CLL in high risk CLL kindreds will allow dissection of the genetic architecture of CLL in relation to the larger group of lymphoproliferative malignancies. MBL, the CLL precursor condition is much more common than CLL. Thus it offers a more efficient way to investigate early but potentially critical steps towards developing CLL.

All of these factors suggest that the detailed follow-up study of individuals from populations and families with MBL, and the detailed observation of their epidemiological, clinical, and molecular characteristics over time will be most informative.

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