Precursors to Lymphoproliferative Malignancies
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Abstract

We review monoclonal B-cell lymphocytosis (MBL) as a precursor to chronic lymphocytic leukemia and monoclonal gammopathy of undetermined significance (MGUS) as a precursor to plasma cell disorders. These conditions are present in the general population and increase with age. These precursors aggregate with lymphoproliferative malignancies in families suggesting shared inheritance. MBL and MGUS may share some of the same risk factors as their related malignancies but data are limited. Although these conditions are characterized by enhanced risk for the associated malignancy, the majority of individuals with these conditions do not progress to malignancy. A key focus for current work is to identify markers that predict progression to malignancy. Cancer Epidemiol Biomarkers Prev; 22(4); 533–9. ©2013 AACR.

Introduction, Definition, and History

Hematologic neoplasms are classified according to cell lineage. The use of the term “precursors” with respect to these malignancies includes a broad range of conditions. We will focus on the precursors that are premalignant lymphoproliferative conditions. We will discuss monoclonal B-cell lymphocytosis (MBL) as a precursor to chronic lymphocytic leukemia (CLL) and monoclonal gammopathy of undetermined significance (MGUS) as a precursor to multiple myeloma and Waldenström macroglobulinemia. Lymphoid malignancies show significant familial aggregation (1–5). Many studies of MBL and MGUS have been conducted in the setting of high-risk families; these have shown the coaggregation of the precursors with their related malignancies (6, 7). In addition, CLL, Waldenström macroglobulinemia, and other lymphomas often aggregate together in families suggesting that they may share common etiologic pathways. Moreover, expression studies have shown that Waldenström macroglobulinemia is more closely related to CLL than either of them are related to multiple myeloma (8), although one study showed that each subtype could be distinguished (9). To date, such studies that directly compare these B-cell lineage diseases are limited. Genetic, epidemiologic, and molecular studies of MBL and MGUS provide opportunities to elucidate disease mechanisms and define common etiologic pathways.

Monoclonal B-cell lymphocytosis

MBL is detected by multicolor flow cytometry of lymphocytes and is defined as a monoclonal B-cell population with cell surface markers consistent with CLL in an individual that does not meet the criteria for CLL. These monoclonal populations were first noted in studies of unaffected relatives in families segregating for CLL (10). A large cross-sectional study was started in 1995 to evaluate by flow cytometry individuals living near hazardous waste sites in the United States compared to controls. This study found evidence of an MBL phenotype in several individuals, the prevalence being significantly higher in those living near the hazardous waste sites (11). Other researchers described monoclonal B-cell findings in different clinical settings and for a number of years there was no standard nomenclature or definition. In 2005, the International Familial CLL Consortium published diagnostic criteria for MBL (12). Briefly, diagnosis requires detection of a monoclonal B-cell population with overall k:λ ratio of >3:1 or <0.3:1, or >25% of B cells lacking or expressing low-level surface immunoglobulin, and with a disease-specific immunophenotype. The monoclonal population must be stable. Other lymphoproliferative disorders or symptoms indicative of CLL must be excluded. The B-lymphocyte count must be less than 5 x 10^9/L. MBL clones are classified similarly to CLL clones (i.e., by immunophenotype) into the following 3 subtypes: (1) CLL-like: CD5+/CD23+ (vast majority), (2) atypical CLL: CD5+/CD23−, and (3) non-CLL-like: CD5− (12).

Monoclonal gammopathy of undetermined significance

Essential monoclonal gammopathy was first described by Waldenström in 1960 following his observation of abnormal narrow bands in the serum of apparently healthy individuals tested by serum protein electrophoresis (13). Although this observation was also termed “benign,” Kyle introduced the term “monoclonal gammopathy of undetermined significance (MGUS)” in 1978 after documenting that asymptomatic patients with monoclonal protein are at higher risk of developing a variety of malignant and nonmalignant conditions, including multiple myeloma, Waldenström macroglobulinemia, and...
Monoclonal gammopathy of indeterminate significance

Similar to MBL, MGUS is a common premalignant condition, with overall prevalence rates among adults ranging from 0.05% to 6.1% (35–40). Accurate and generalizable prevalence estimates for MGUS have been elusive because study methodologies vary considerably (41). Although large-scale studies have been conducted in Olmstead County to establish the prevalence of MGUS among adults, many questions remain. Other population-based studies are limited, evolving laboratory methods enable more sensitive detection of monoclonal proteins, and not all studies have stratified data by age, race, gender, or immunoglobulin type; each of these variables is believed to have important implications for prevalence and possibly outcome. Thus, studies that report higher prevalence (35, 38, 42, 43) tend to employ the most sensitive methods in populations enriched for persons aged 50 years and above. Despite these limitations, however, consistent trends have emerged. From studies in
Monoclonal B-cell lymphocytosis

MCL can be stratified by the absolute B-cell count into "low count" (normal ALC) and "clinical" (lymphocytosis present) MBL. The majority of patients identified from the general population have low count MBL. Several studies have conducted follow-up in MBL patients. The actual cut-off to define clinical MBL varies among studies but those with clonal B-cell count >2×10^3/L tend to have increasing B-cell counts over time although the risk of progression to CLL requiring treatment is still low, approximately 1% to 2% per year for those with elevated B-cell counts. One study found that in a clinical MBL population, B-cell count and CD38 status predicted time to treatment (60). In addition, overall survival of MBL patients who were CD38+ was significantly shorter than age- and sex-matched controls (61). This is consistent with CD38 predicting more aggressive CLL. One study reported a higher rate of hospitalization for infections in both MBL and CLL patients than in controls (62). Studies have shown that the risk of progression for low-count MBL is rare. One population study, with an average follow-up time of 34 months, reported that 90% of CLL-like clones, but somewhat lower proportion of atypical and CD5– MBL clones, persisted over time (63). It is unknown whether MBL individuals who are members of high-risk CLL families have a higher chance to progress. Continued follow-up of these individuals is needed. A study by Landgren and colleagues (64) ascertained individuals from a cohort who developed CLL and had available biospecimens preceding their diagnosis. They reported that MBL preceded virtually all cases of CLL. Thus, MBL is likely to be a critical state in the pathway to CLL but only a small proportion of MBL patients will ever progress to CLL.

Monoclonal gammopathy of undetermined significance

Studies in a defined cohort have shown that MGUS consistently precedes the development of multiple myeloma (58, 65). There are different patterns of progression, ranging from a long stable MGUS phase to a rapidly evolving MGUS phase having a relatively short latent period before diagnosis of myeloma. The average risk of progression to malignancy is approximately 1.0% and 1.5% per year for patients with non-IgM (66) and IgM MGUS (66, 67), respectively. Several factors influence the rate of progression, including the level of the monoclonal protein, the immunoglobulin isotype, the percentage of bone marrow plasma cells and the presence of polyclonal hypogammaglobulinemia (68). Serum-free light chain (sFLC) analysis has been proposed as a method to assess malignant clonal expansion, and inclusion of information about the sFLC ratio further improves prognostic models (69). Non-IgM MGUS most frequently progresses to multiple myeloma, but occasionally other lymphoproliferative disorders develop instead. Similarly, Waldenström macroglobulinemia is the most common malignant outcome for IgM MGUS, but patients are also at risk to develop other B-cell neoplasms, such as chronic lymphocytic leukemia or other non-Hodgkin lymphoma (70). However, the majority of MGUS patients never progress and die from unrelated causes (71).

Although MGUS patients are by definition asymptomatic, they may be subject to increased morbidity and mortality (71, 72). Emerging evidence documents increased risk of hypercoagulability/venous thrombotic disease (42, 73–76) and osteoporosis/fractures (72, 77–79) in MGUS patients, and biomarkers associated with these conditions may have prognostic implications for subsequent progression. MGUS patients have also been found to report certain infections more frequently, but it is unclear whether susceptibility to these infections is related to an underlying immune dysfunction or is a consequence of MGUS-induced immune defects.
In contrast to MBL patients who progress to CLL but do not need treatment, MGUS patients who progress to multiple myeloma are more likely to need therapy. Consensus guidelines for the clinical management of MGUS have been proposed (80). Current recommendations suggest dividing patients into low- and high-risk groups based on the isotype and size of the monoclonal protein (low risk: serum IgG < 1.5 g/dL or IgA or IgM < 1.0 g/dL; high-risk: serum IgG ≥ 1.5 g/dL, IgA or IgM ≥ 1.0 g/dL, or IgD or IgE at any level). Low-risk patients can be monitored every 3 to 4 months for the first year then every 6–to 12 months, depending on their clinical course, laboratory results, and comorbidities. High-risk patients should be monitored more frequently, every 3 to 4 months, indefinitely. Laboratory studies that are useful for monitoring include serum protein electrophoresis, quantitative immunoglobulins, sFLC (if available at diagnosis), complete blood count, creatinine, urea, electrolytes, and calcium.

**Future Challenges: Screening, Prognosis, Prevention**

Table 1 compares MBL and MGUS for key features discussed in this review. For both MBL and MGUS, the risk of progression to a disease needing treatment is low and no early intervention is shown to prevent progression for either condition. Thus, there is no benefit for screening of the general population. MGUS patients with less than 10% infiltration of the bone marrow by lymphoplasmacytic cells have an overall survival similar to that of the general population (81), so patients diagnosed with MGUS should be reassured and care should be taken to not misclassify them as having a malignancy. One exception to the general rule not to screen for MBL is in the case of prospective bone marrow donors. It is has been shown that MBL clones can be transmitted through bone marrow transplantation indicating that such individuals should be excluded as donors (82). To date, there has been no discussion of the theoretical risks because of MGUS for candidate marrow donors and recipients.

Accurate risk stratification for both MGUS and MBL is a major goal. For MGUS, the scope of the problem is indicated by the existence of at least 2 major risk stratification models that use different sets of criteria (69, 83). Future research should focus on the identification of (1) biomarkers that will facilitate the development of individualized risk profiles and (2) molecular markers that will provide insights into the biology of progression and potentially provide therapeutic targets. Such studies should be coupled with prospective well-designed epidemiologic investigations to provide additional information about risk factors for MGUS development and progression. Progression does not seem to be a consequence of a discrete molecular event. Many of the somatic events that characterize myeloma and Waldenström macroglobulinemia can be seen in the MGUS phase, suggesting that progression results from the accumulation of sequential, or possibly overlapping, oncogenic events. We need better understanding of the microenvironment, epigenetics, and bone metabolism.

Longitudinal studies with serial follow-up of individuals with these conditions are needed to answer many questions. Among them, do the exposures associated with the malignancies also predict the precursor condition or progression from the precursor to malignancy? Which somatic, germline, and chromosome abnormalities characterize the precursor, and what is the evolution that precedes frank malignancy? To obtain these answers, it is expected that integrated investigations involving genomic (GWAS, expression, chromosome, methylation, etc.), environmental (questionnaire complemented with cytokine and metabolomics characterization), and clinical follow-up will be needed. Because both these

**Table 1. Characteristics of MBL and MGUS**

<table>
<thead>
<tr>
<th>Population prevalence and age</th>
<th>Gender</th>
<th>Risk factors</th>
<th>Ethnic differences</th>
<th>Clinical correlates</th>
<th>Molecular features</th>
<th>Rate of progression</th>
<th>Determinants of progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL</td>
<td></td>
<td>Family history of CLL</td>
<td>Unknown</td>
<td>Increased risk of infections</td>
<td>Similar chromosome findings as in CLL</td>
<td>Clones persist over time</td>
<td>B-ALC &gt; 2000</td>
</tr>
<tr>
<td>3–12% over age 40</td>
<td>Males &gt; Females</td>
<td>Chemical exposures</td>
<td></td>
<td></td>
<td></td>
<td>1–2%/yr requiring treatment (if lymphocytosis present)</td>
<td>CD38+</td>
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<tr>
<td>5%–17% over age 60</td>
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<tr>
<td>MGUS</td>
<td></td>
<td>Obesity, occupation, family history of MGUS, multiple myeloma</td>
<td>Blacks &gt; Caucasians &gt; Asian</td>
<td>Increased risk of fractures, thrombosis</td>
<td>Similar somatic events as multiple myeloma and Waldenström macroglobulinemia</td>
<td>1–2%/yr</td>
<td>Size of monoclonal protein</td>
</tr>
<tr>
<td>3.2% over age 50</td>
<td>Males &gt; Females</td>
<td>Increasing with age</td>
<td></td>
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<td>Type of monoclonal protein</td>
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<td></td>
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<td></td>
<td>Degree of bone marrow infiltration</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>sFLC</td>
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</tbody>
</table>

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malignancies involve B cells, comparisons of "normal" B cells and "premalignant" plasma or CD19/CD20/CD5 cells may offer special opportunities to evaluate serial alterations that may predict progression. As is the case in many complex diseases and the majority of cancer, no single genetic or exposure event fully characterizes cancer, so coordinated and repeated study in defined populations with a rich epidemiologic, clinical, and biospecimen resource will be required to unravel the puzzle. But because progression is uncommon, coordination of efforts in consortia will prove necessary to identify sufficient numbers of patients.

High-risk families with B-cell malignancies provide another powerful opportunity to characterize etiology and progression of MGUS and MBL because close relatives of patients are at substantially increased risk (compared to the population) for developing a precursor condition. Long-term follow-up studies of relatives with MGUS and MBL will help define molecular determinants of progression. In our studies of families ascertained for either multiple cases of CLL or multiple cases of Waldenström macroglobulinemia, we have found that cases of CLL and Waldenström macroglobulinemia (and other lymphomas) often occur among closely related individuals in the same family. One such example is shown in Fig. 1. Studies of both MGUS and MBL in such families provide a unique opportunity to discover and dissect common pathways leading to different B-cell malignancies.

Given that both MBL and MGUS uniformly precede malignancy, chemoprevention strategies are an area of keen interest. Both MGUS and MBL patients have a low probability of progressing to a clinical disease and thus chemoprevention would only be a goal for those who could be determined to be at high risk for developing aggressive disease. The opportunity to prevent or delay the development of the disease outcomes provides a compelling rationale to optimize risk stratification and identify potential therapeutic targets in MBL/MGUS patients. Ideally, chemoprevention trials would employ effective agents with low/no toxicity in high-risk patients. When such agents do become available in the future, these patients should be treated only on clinical trials. In the meantime, efforts should focus on defining high-risk cohorts and standardizing eligibility and response criteria.

In summary, although there are some predictors of progression for MBL and MGUS, there are no reliable markers that predict the risk of progression for individual patients. Molecular studies are underway to be able to better predict who will progress and thus should be followed more closely. Large-scale genomic methods are being applied to CLL, Waldenström macroglobulinemia, multiple myeloma, and many other cancers to discover the somatic changes leading to malignancy. As more of these studies are applied to precursor states, it will be possible to define the critical pathways determining the progression of normal to clonal to malignant B cells.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Acquisition of data (providing animals, acquired and managed patients, provided facilities, etc.): L.R. Goldin, N.E. Caporaso
Analysis and interpretation of data (e.g., statistical analysis, bios-statistics, computational analysis): L.R. Goldin, M.L. McMaster, N.E. Caporaso
Writing, review, and/or revision of the manuscript: L.R. Goldin, M.L. McMaster, N.E. Caporaso
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): L.R. Goldin, N.E. Caporaso
Study supervision: N.E. Caporaso

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References
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46. Iwamoto M, Tagawa M, Tsubakosaki K, Kamihiro S, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance:...


