Chronic Lymphocytic Leukemia and Other Lymphoproliferative Disorders

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KEYWORDS

• Chronic lymphocytic leukemia • Non-Hodgkin lymphoma • Elderly

KEY POINTS

- Chronic lymphocytic leukemia and other non-Hodgkin lymphomas primarily affect older patients.
- When making treatment decisions for older patients, it is important to consider not only chronologic age but also fitness level and comorbid conditions.
- Clinical trials that recruit and enroll older and/or less fit patients will improve the treatment options available to this important and growing population.
- Therapies targeting the B-cell receptor signaling pathway are changing the treatment paradigms of many B-cell lymphoproliferative disorders.

CHRONIC LYMPHOCYTIC LEUKEMIA

Epidemiology

Chronic lymphocytic leukemia (CLL) is a disease mainly of the elderly, with a median age at diagnosis of 71 years. Although it accounts for less than 1% of all new cancers diagnosed each year, the prevalence has grown because of improvements in therapy and overall survival, and at this time it is the most common adult leukemia. In 2007, the 5-year overall survival had increased to 87.9% from 69% in 1980, and, with the advent of newer targeted therapies, survival is likely even better for patients diagnosed with CLL in 2015. CLL is more common in men than in women by approximately 2:1, more common in white people than in African Americans, and far less common in any other race.[1]

CLL is a chronic and incurable disease outside of allogeneic stem cell transplantation (AlloSCT). Because of the high treatment-related morbidity and mortality of

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AlloSCT, especially in older patients, this is rarely an option for most patients with CLL. Despite the chronicity of disease and indolent nature experienced by many, patients with CLL have a shorter survival than age-matched controls. Importantly, although many patients with CLL have impaired organ function and reduced performance status, these patients are treated at the same frequency as those with adequate organ function and intact performance status, but they have a shorter overall survival.[2] Thus, management strategies focused on older adults and those with impaired organ function and performance status are needed.

Spectrum of Disease and Prognosis

CLL presents as a spectrum of disease that encompasses monoclonal B lymphocytosis (MBL), small lymphocytic lymphoma (SLL), and the more common CLL. CLL is often found incidentally by the presence of lymphocytosis on routine blood work, with most patients asymptomatic at diagnosis. Unexplained lymphocytosis on a complete blood count differential should prompt peripheral blood immunophenotyping to differentiate a reactive lymphocytosis from one that is malignancy associated. The diagnosis of CLL is established by detecting a clonal population of B cells in the peripheral blood and does not require bone marrow biopsy. On immunophenotyping, this B-cell population typically expresses the surface markers CD5, CD19, CD20(dim), and CD23, with dim expression of surface kappa or lambda immunoglobulin.[3] Patients with greater than 5000 of these monoclonal cells per microliter are classified as having CLL. Those with less than this threshold but with enlarged lymph nodes or spleen are classified as having SLL, and those with less than this threshold and no other signs of disease are best categorized as having MBL. SLL and CLL are managed identically, and are referred to as CLL throughout this article.

Recent studies suggest that approximately 4% of the general population more than 40 years of age harbor a population of clonal B cells with the phenotype of either CLL or another low-grade non-Hodgkin lymphoma (NHL).[4] Three subcategories of MBL have been identified according to the immunophenotypic features: CLL-like, CD5+ atypical, and CD5− MBL. CLL-like MBL is the most frequent and best studied and can be further divided into low-count (LC) and high-count (HC) MBL, based on a cutoff value of 500/μL clonal B cells. LC-MBL typically remains stable and likely represents an age-related immune senescence rather than a premalignant state. HC-MBL is associated with an annual risk of progression requiring therapy at a rate of 1.1%.[5] Patients with MBL share a similar risk of infection and development of nonhematologic cancer to those patients with CLL, highlighting the similarity in disease biology and need for aggressive surveillance.[6,7]

CLL follows a very heterogeneous course, ranging from indolent disease that never requires therapy to short time to initial therapy and an aggressive disease course with multiple relapses. Because of this heterogeneity, prognostic factors are of great importance in counseling newly diagnosed patients. The earliest prognostic tools were the 2 widely used staging schema described by Binet and colleagues[8] and Rai and colleagues[9] (**Table 1**). Increasing stage is related to shortened survival; however, the exact survival statistics have improved since the development of the staging systems.

In addition to clinical staging, cytogenetic and molecular markers can add to prognostication. All newly diagnosed patients with CLL should undergo fluorescence in situ hybridization (FISH) testing for common CLL abnormalities as well as stimulated cytogenetics to determine whether the karyotype is complex (≥3 cytogenetic abnormalities). Complex karyotype is associated with an aggressive disease course, and specific cytogenetic abnormalities on FISH are also strong predictors of disease