Statement of Editorial Purpose
The Hospital Physician Hematology Board Review Manual is a study guide for fellows and practicing physicians preparing for board examinations in hematology. Each manual reviews a topic essential to the current practice of hematology.

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NOTE FROM THE PUBLISHER:
This publication has been developed without involvement of or review by the American Board of Internal Medicine.
INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common hematologic malignancy in the Western world, representing 30% of leukemias. The median age at diagnosis is 72 years, and fewer than 10% of patients are under 60. CLL occurs more frequently in Caucasians than in other ethnic groups and more often in men than in women. The age-adjusted incidence rate is 4.2 per 100,000 population. Although CLL is generally considered indolent, it is a heterogeneous disease, and while many patients have slowly progressive disease, a proportion of patients have disease that will have a more aggressive course, requiring treatment soon after diagnosis. Over the past 3 decades, increasing knowledge about the mechanism of CLL and the introduction of new chemotherapeutic and biologic agents has led to better treatments, improved risk stratification, and more durable remissions. Despite these advances in treatment, CLL remains incurable outside the setting of hematopoietic stem cell transplant.

DIAGNOSIS AND RISK STRATIFICATION

The diagnosis of CLL requires the presence of at least 5000 B lymphocytes/µL, and peripheral blood immunophenotyping must be performed to confirm their clonality. CLL cells express CD5, CD19, CD20, and CD23, with low expression of surface immunoglobulin, CD20, and CD79b, compared with normal B cells. CLL cells are small, mature-appearing lymphocytes with a dense nucleus, and smudge cells are a characteristic finding on a peripheral blood smear. Monoclonal B lymphocytosis comprises a population of patients who have a clonal B-cell population with fewer than 5000 lymphocytes/µL in the absence of lymphadenopathy or organomegaly. This progresses to CLL at a rate of 1% to 2% per year.

The Rai and Binet systems are the 2 commonly used staging systems in CLL. The Rai system, which originally had 5 subgroups, has been modified to 3, similar to the Binet scheme (Table 1). Genetic risk stratification should be done at diagnosis and prior to each new therapy, and can add important prognostic information to that obtained by traditional staging. Interphase cytogenetics, as determined by fluorescent in-situ hybridization (FISH), not only provides prognostic information, but may also influence therapeutic decisions. Del(13q14) is the most common abnormality and conveys a favorable prognosis when occurring in isolation. In contrast, patients with del(11q23) or del(17p13) abnormalities, resulting in the loss of the tumor suppressor genes ATM and TP53, respectively, frequently have more aggressive disease, progress to requiring treatment faster, and experience inferior progression-free and overall survival with standard therapies. While patients with del(13q14) have a median survival of 133 months beyond diagnosis, patients with del(17p13) have a median survival of only 32 months beyond diagnosis.

In addition to FISH, important prognostic information is conferred by the mutational status of the immunoglobulin heavy chain variable region (IGVH) genes. CLL patients with IGVH genes which have not undergone somatic hypermutation (“unmutated”) have inferior survival compared to those with mutated IGVH genes. Patients with unmutated IGVH are prone to acquiring additional karyotypic abnormalities on metaphase cytogenetics, a process known as “clonal evolution.” IGVH testing is not universally available, so expression of ZAP-70 and/or CD38 as measured by either flow cytometry or immunohistochemistry is often used as a surrogate marker. Serum markers such as CD23, thymidine kinase, and β2-microglobulin may have prognostic value and have been evaluated in several large clinical trials. While bone marrow biopsy is recommended prior to starting therapy, it is typically not done at diagnosis in the absence of cytopenias.

TREATMENT

WHEN TO TREAT

Contrary to other forms of leukemia, many patients with CLL are initially observed following diagnosis.