Chronic Lymphocytic Leukemia: Diagnosis and Treatment

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CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

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Learning Objectives: On completion of this article, you should be able to (1) correctly formulate a diagnosis of chronic lymphocytic leukemia (CLL), (2) evaluate prognostic factors for patients with CLL, and (3) understand the indications for treatment of patients with CLL and identify the most appropriate regimens in the frontline and relapse settings.

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Abstract

The complexity of the treatment of patients with chronic lymphocytic leukemia has increased substantially over the past several years as a consequence of the advent of novel biological agents such as ibrutinib, idelalisib, and venetoclax, as well as increasingly potent anti-CD20 monoclonal antibodies. In addition, the identification of molecular predictive markers and the introduction of more sensitive and sophisticated techniques to assess minimal residual disease have allowed optimization of the use of chemoimmunotherapy and targeted therapies and may become standard of care in the future. This review summarizes the diagnosis, prognostication, and treatment of patients with chronic lymphocytic leukemia with emphasis on new prognostic and predictive factors and novel treatment strategies.

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Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in the Western World. The complexity of the treatment of patients with CLL has increased substantially over the past several years as a consequence of the advent of novel biological agents, the identification of molecular predictive markers, and the

introduction of more sensitive and sophisticated techniques to assess minimal residual disease (MRD). This review summarizes the diagnosis, prognostication, and treatment of patients with CLL with emphasis on new prognostic and predictive factors and novel treatment strategies.

EPIDEMIOLOGY

Chronic lymphocytic leukemia is the most common adult leukemia in the Western World, accounting for nearly 25% of all leukemias and 1.3% of all cancers. Its incidence is substantially lower among Asian individuals and higher among Ashkenazi Jews. Based on 2012-2014 data, approximately 0.6% of US men and women will be diagnosed with CLL at some point during their lifetime.[1] Between 2010 and 2014, the number of new cases of CLL in the United States was 4.7 per 100,000 men and women per year, and in 2017, up to 20,110 new cases are estimated. The incidence and prevalence of CLL are similar in Europe.[1,2] Chronic lymphocytic leukemia predominantly affects older individuals, with more than 70% of patients being older than 65 years; the median age at diagnosis is 72 years.[3] Males and whites are more frequently affected than females (male to female ratio, 1.5-2:1) and other races.[1,4-6]

ETIOLOGY

A genetic predisposition for CLL is suggested by family studies, with a higher prevalence of disease observed among relatives of patients with sporadic CLL,[7] and up to 6 single-nucleotide polymorphisms known to confer an increased risk for development of CLL in large case-control series.[8] Recently a whole-genome sequencing study reported that CLL mutations can be attributed to 3 key mutational processes: 2 types of activation-induced cytidine deaminase signatures and an aging signature, operating at different times throughout CLL evolution.[9,10]

The frequency of CLL progressively increases with age, suggesting that a persistent exposure to a self- or non–self-antigen may also be a predisposing factor.[11-13] Of interest, among patients with hepatitis C, the incidence of CLL is significantly higher than that in the general population[14]; studies to determine whether specific antigenic stimuli can lead to the development of CLL are ongoing and may shed light on its pathogenesis and natural history. Although individuals living on farms or exposed to Agent Orange are at higher risk for development of CLL and sun exposure protects from its onset, a clear association between CLL and exposure to ionizing radiation has never been proven.[15,16]

CLINICAL PRESENTATION

Patients with CLL have varied clinical presentations. Most patients are asymptomatic and CLL is diagnosed only because of an incidental finding of lymphocytosis on a routine complete blood cell count; this symptom can be accompanied to a variable degree with anemia and/or thrombocytopenia.[17] In some cases, patients also can have palpable lymphadenopathy and/or hepatosplenomegaly, which in rare cases can produce symptoms secondary to local compression.[18] Extranodal and/or extramedullary presentations of CLL rare, with the skin and central nervous system being the most frequent sites of involvement.[19,20] A minority of patients will present with constitutional symptoms, defined as persistent fever, night sweats, and/or unintentional weight loss, while fatigue is a common symptom. Finally, CLL can be diagnosed as a consequence of clinical signs and symptoms secondary to its complications rather than to its direct involvement, including autoimmune disease, infections, or second cancers (see "Complications" section).

DIAGNOSIS

The definition of CLL was first established by the National Cancer Institute Working Group in 1996 and was then modified by the International Workshop on CLL (iwCLL) in 2008.[21,22] The latter definition has not been revised substantially in the latest World Health Organization classification of lymphoid neoplasms.[23] The diagnosis of CLL requires the presence of at least 5×10^9/L B lymphocytes in the peripheral blood and of a clonal B-cell population, detected by flow cytometry, positive for light chain restriction (either κ or λ), CD5, CD23, CD79b, and surface immunoglobulin expression, and low levels of CD20; under simple microscopic examination, CLL cells have a typical appearance of smudge cells, which are artifacts from lymphocytes damaged during the slide preparation. Rarely,

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