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Prognostic factors and risk stratification in chronic lymphocytic leukemia

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ABSTRACT

There is considerable heterogeneity in the clinical outcome of patients with chronic lymphocytic leukemia (CLL). While some patients live for decades without any therapy, others die within years of diagnosis despite multiple treatments. To better counsel newly diagnosed CLL patients about their disease course, the Rai and Binet staging systems were developed four decades ago. A deeper understanding of the biologic and molecular aberrations contributing to the pathogenesis of CLL led to identification of novel prognostic markers such as immunoglobulin heavy-chain variable gene (*IGHV*) mutation status, leukemia-cell expression of CD38, ZAP-70, and CD49d, and cytogenetic abnormalities detected by fluorescent in situ hybridization (FISH). The advent of next-generation sequencing has provided unprecedented insights into the subclonal architecture of CLL and its impact on disease progression and survival. More recently, integrated prognostic scoring systems that incorporate clinical, biologic and genetic characteristics into a single risk score have been developed and appear to improve the accuracy of prognostication for individual patients. This review summarizes the state-of-the-art prognostic factors and will guide the practicing clinician in their care of patients with CLL.

1. Introduction

Chronic lymphocytic leukemia (CLL) is a low-grade B-cell lymphoproliferative disorder, with approximately 16,000 new cases diagnosed in the United States in 2014 [1]. There is considerable heterogeneity in the disease course of CLL – some patients live for decades without therapy, whereas others die due to disease progression within a few years from diagnosis despite treatment [2]. Given the chronic and incurable nature of CLL, it is important to develop effective tools that accurately define prognosis for each individual patient at the time of diagnosis. Such knowledge will allow the practicing clinician to develop effective strategies for (1) patient counseling; (2) determine the frequency of follow-up; (3) identify those most appropriate for early intervention trials; and (4) inform therapy selection.

2. Traditional prognostic factors

The Rai [3] and Binet [4] staging systems, developed in the 1970s, represent one of the initial efforts in segregating CLL patients into distinct prognostic groups. Both systems use simple and readily available clinical and laboratory parameters that classify patients into three major prognostic groups. The characteristics used to classify patient stage by the Rai classification, the expected survival in the original publication [3], and a large recent cohort seen at Mayo Clinic are shown in Table 1. While these prognostic tools have proven incredibly useful over the last 40 years, there remains significant clinical heterogeneity among patients within each Rai and Binet stage category. Additionally, approximately three quarters of all newly diagnosed CLL patients are now diagnosed at the Rai 0/Binet A stage, where these traditional staging systems are unable to accurately stratify risk of progression. Between 1975 and 1995, a number of other prognostic parameters such as lymphocyte doubling time (LDT) [5], pattern of bone marrow involvement (diffuse *v* non-diffuse) [6], and absolute lymphocyte count (ALC) [7,8] were reported to be associated with outcomes. Unfortunately, these markers do not provide significant insights into the biological characteristics of the CLL clone and are therefore unable to fully account for the heterogeneity in clinical outcomes.

3. Newer prognostic factors

3.1. Serum-based markers

Serum parameters such as beta-2 microglobulin (β2M, a component of the HLA class I complex on nucleated cells) and thymidine kinase (TK, an intracellular protein involved in DNA

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