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Biomarkers in chronic lymphocytic leukemia: Clinical applications and prognostic markers

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A B S T R A C T

Chronic lymphocytic leukemia (CLL) is a heterogeneous disease with a variable clinical course. The Rai and Binet staging systems are often used to predict survival. However, they do not take into account other biological characteristics of CLL cells that may influence the disease course and response to treatment. Prognostic factors such as chromosome abnormalities (trisomy 12, 11q deletions and 17p deletions), β2 microglobulin, thymidine kinase, CD38 and ZAP-70 expression, IGHV mutation status, and mutations in genes such as NOTCH1, MYD88, SF3B1, and ATM are also predictors of prognosis. These biological markers have enabled the development of multiparameter risk models to predict overall survival. In addition, these models are useful for treatment decisions, as they can identify patients that could be treated with clinical trials vs. standard of care therapies. This chapter will review the most important prognostic markers that have been described in CLL and their application in clinical practice.

Introduction

Chronic lymphocytic leukemia (CLL) has a variable clinical course [1,2]. Some patients present with an indolent clinical disease that often do not require treatment, while others can experience a very aggressive course. The heterogeneity in the clinical presentation of the disease has made difficult the

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prediction of survival time for CLL patients. Currently, two well-known clinical staging systems are used to stratify patients by risk groups based in clinical and laboratory characteristics [3,4]. The Rai and Binet staging systems are inexpensive and easy to use with a good correlation in terms of survival prediction. However, they do not take into account known biological characteristics of CLL cells that also predict survival and response to treatment [2,5,6]. Additionally, these systems do not fully reflect the high variability of CLL as some patients classified as having early stage disease could rapidly progress [7]. For these reasons, other prognostic factors such as chromosome abnormalities (17p deletion, 11q deletion, trisomy 12), elevated β2 microglobulin (β2M) and thymidine kinase, CD38 expression, unmutated immunoglobulin heavy chain variable gene (IGHV) and ZAP-70 expression, have been investigated and described as good predictors of poor prognosis [8–10].

Different groups have developed multiparameter risk models using these biological markers to predict important clinical end-points, including overall survival (OS) [11,12]. The use of risk models helps physicians in treatment decisions and facilitates counseling to patients. Furthermore, the application of prognostic models is useful in the clinical trials setting as they can help to identify which type of patients should be approached with investigational products in clinical trials vs. standard of care therapies [13].

With the advent of new genetic analysis techniques such as next generation sequencing (NGS) and the study of the CLL genome, the identification of novel genetic mutations in CLL cells, such as notch homolog protein 1 (NOTCH1), myeloid differentiation primary response 88 (MYD88), splicing factor 3b, subunit 1 (SF3B1), and ataxia telangiectasia mutated (ATM), among others, has offered new prognostic information and impacted the future management of patients with CLL [14,15]. This chapter will review the most important prognostic markers that have been described in CLL and their application in clinical practice.

Genomic aberrations in CLL

Interphase fluorescence in situ hybridization (FISH) enables the detection of specific DNA sequences on chromosomes, not only on metaphase chromosomes but also in interphase cell nuclei, and is currently the standard approach for analysis of genomic aberrations in CLL. Furthermore, multivariate analysis revealed that genomic aberrations have an independent prognostic relevance during the course of the disease [8]. At least one cytogenetic abnormality can be detected by FISH in about 80% of patients with CLL [16]. Deletion 13q14 (del(13q)) as a single aberration is associated with long OS, while deletions 11q22-q23 (del(11q)) and 17p13 (del(17p)) are associated with short OS [8]. A hierarchical model for the prognostic impact of genomic aberrations in CLL was developed (in descending order of adversity): del(17p) > del(11q) > trisomy 12 > no aberration > del(13q) [8]. Genomic aberrations are considered a "moving target" since the incidence of a specific genomic aberration can be different in various clinical situations and can change over the disease course. Over time, patients may acquire high-risk aberrations and the acquisition of new aberrations has been associated with a short OS [17,18].

Deletion 13q14

Deletion of band 13q14 is the most common genomic aberration detected in CLL with a prevalence of 40%–60% [8]. It can occur as both monoallelic and biallelic deletion. CLL patients with del(13q), as a sole, have a favorable clinical course with a median survival time longer than even patients with a normal karyotype [8]. It has been demonstrated that the number of malignant cells carrying the del(13q) is strongly correlated with disease outcome [19] and molecular characteristics [20]. Within patients that carry del(13q) there is a variability in their clinical course. Thus, two prognostic groups can be established on the basis of the percentage of cells with del(13q). The patients with a high proportion (>80%) of del(13q) cells had a shorter OS as well as a shorter time to first therapy than patients with <80% cells with del(13q) [8,21–23].

Deletion 11q22-q23

About 20% of CLL patients have deletions of the 11q region. The del(11q) in CLL affects a region that harbors the ATM gene. Patients with ATM have an increased incidence of lymphoma [24,25].