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Chronic lymphocytic leukemia - Section 2

Prognostic factors in chronic lymphocytic leukemia: When, which and how?

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Take-home messages

- CLL has a very heterogeneous clinical outcome depending on many factors; the prognostic markers thus play an important role in disease management and assist in the selection of the best treatment option.
- The key prognostic and predictive factors influencing treatment decisions are *TP53* gene aberrations with increasing significance in the era of novel therapies.
- The introduction of high-throughput genomic approaches has led to the identification of novel genetic abnormalities that could contribute to improved risk stratification of CLL patients, while also enable the tracking of leukemic clone(s) evolution.

Introduction

CLL displays very variable clinical behavior distinctly dependent on a variety of biological, biochemical and genetic features of the disease. Classical prognostic factors such as age, gender, clinical stage, concentration of serum β2-microglobulin and serum thymidine kinase, status of IGHV gene somatic hypermutations (SHM) or chromosomal aberrations still hold their prognostic significance and are incorporated into up-to-date scoring systems.[1,2] Recent tremendous developments in genomic approaches, particularly in next-generation sequencing (NGS), have enabled a deeper insight into the molecular background of the disease and to discover novel markers with a potential role in disease prognostication and therapy response prediction.[3,4] Characterization of the CLL genomic landscape and identification of recurrent driver mutations associated with disease development and progression may improve patient stratification and optimize treatment decisions. Nevertheless, only certain novel genomic abnormalities have been proven to display a clear prognostic and predictive significance, and intensive efforts to elucidate the importance of specific biomarkers are ongoing.

Current state of the art

Since many patients suffering from CLL live for years without clinical symptoms while others require early therapeutic intervention and achieve variable treatment response, they apparently differ in a variety of prognostic and/or predictive factors. Numerous prognostic factors providing information on the likely outcome of the disease, and predictive factors providing information on the likely treatment benefit have been described in CLL, but only a few have been validated by multivariate analyses and prospective clinical studies so far.
To define the highly important factors with the greatest prognostic or predictive power, several attempts to develop a new scoring system for CLL patients have been made. Recently, an international group of CLL investigators published a meta-analysis including data from 8 controlled, randomized, prospective clinical trials and identified five independent prognostic factors: *TP53* gene deletion and/or mutation, IGHV gene SHM status, serum β2-microglobulin concentration, clinical stage and age.[2] In addition, many newly identified markers are being assessed for their clinical applicability.

Clinical prognostic factors

Clinical stage (Rai 0–IV, Binet A-B-C) importance arises from its direct impact on treatment decisions. However, clinical staging does not identify patients with an incipient disease and high probability of progression and also does not predict a treatment response. Age (having a borderline at 65 years) showed a significant prognostic impact on overall survival and is also considered as a prognostic factor.[2]

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Serum parameters

From biochemical markers, mainly serum β2-microglobulin concentration is widely used holding its significance in CLL prognostication as an independent biomarker and has become part of the patient risk stratification system.[5]

Genetic markers

Immunoglobulin heavy variable (IGHV) gene somatic hypermutation (SHM) status has been proven in many studies to be a robust prognostic marker associating unmutated/minimally mutated IGHV sequences with unfavorable disease prognosis.[6,7] IGHV gene SHM status is unaffected by disease progression and its analysis can be performed at any stage throughout the disease course, according to the ERIC recommendations.[8,9] B cell receptor (BcR) immunogenetic characteristics beyond IGHV gene SHM status also appear to be prognostically relevant in the era of targeted therapy using BcR signaling inhibitors. Indeed, one-third of CLL patients express stereotyped B-cell receptors[10] which are grouped into distinct subsets displaying consistent biological characteristics and a clinical course ranging from very indolent (subset 4) to aggressive (subsets 1 and 2) disease.[11] Different spectra of recurrent gene mutations in CLL subsets harboring stereotyped B-cell receptors have recently been described showing a subset-biased acquisition of gene mutations.[12] Detection of chromosomal abnormalities using fluorescent *in situ* hybridization (FISH) has an essential role in CLL prognostication. According to the type of genomic aberrations, the Döhner's classification has defined five categories: del(17p), del(11q), 12q trisomy, normal karyotype, and del(13q) as the sole abnormality, with patients carrying del(17p) having the shortest median treatment-free interval. Locus 17p13 encodes the antioncogene *TP53* and its inactivation by deletion is frequently associated with mutation of the second allele; however, *TP53* mutations also occur independently of del(17p). *TP53* gene alterations are the most important genetic prognostic and predictive marker in CLL associated with very poor prognosis and resistance to chemoimmunotherapy, and should always be analyzed before a therapeutic decision is made.[13] Moreover, even low-burden CLL clones carrying *TP53* mutations detected by ultra-deep NGS could predict an inferior outcome.[14-16] Deletion 11q22-23 involving the ataxia-telangiectasia mutated (*ATM*) gene is also known to provide a negative impact on disease prognosis having the importance mainly in elderly patients. CLL patients with biallelic *ATM* defects have even shortened progression-free survival (PFS) and an adverse impact on overall survival (OS) has been documented.[17]

Complex karyotype, defined as the presence of three or more chromosomal abnormalities, has recently been shown to have a prognostic and predictive significance due to its negative influence on TTFT and OS in CLL patients treated with ibrutinib.[18] In addition, many novel genes identified using NGS technologies are potentially applicable for CLL prognostication.[3,4] *NOTCH1* and *SF3B1* gene mutations led to a shorter OS in CLL patients treated within clinical studies.[19] The importance of these alterations, including mutations in *BIRC3* and *MYD88* genes, has been included in the genetic prognostic model.[20,21] Prognostic or predictive significance of some other markers, such as CD38, ZAP70, peripheral lymphocytosis, bone marrow infiltration and serum soluble CD23, has been rather overcome by more robust novel genetic parameters.[1]

Future perspectives

The heterogeneous clinical course of CLL could likely be explained by the differences in underlying immuno-, cyto- and molecular- genetic prognostic factors. Analysis of these molecular factors at diagnosis and/or disease progression (before frontline therapy) and/or relapse (before subsequent

Table 1. Evaluation of genetic prognostic factors in chronic lymphocytic leukemia patients.

	Complex karyotype	Chromosomal aberrations (FISH cytogenetics)				*TP53* mutations	IGVH gene mutation status
		del(11)	trisomy 12	del(13)	del(17)		
Initial diagnosis	Optional	Yes	Yes	Yes	Yes	Yes	Yes
Disease progression / Before frontline therapy	Yes	Optional	Optional	Optional	Yes, unless detected before	Yes, unless detected before	Yes, unless performed before
Relapse / Before subsequent therapies	Yes	Optional	Optional	Optional	Yes, unless detected before	Yes, unless detected before	Yes, unless performed before
Prognostic significance	Yes*	Yes	Yes	Yes	Yes	Yes	Yes*

**Predictive significance for BcR signaling inhibitors.*

therapy) is strongly recommended for proper disease prognostication and assessment of the therapeutic outcome (Table 1). The application of modern genomic technologies, in particular targeted amplicon based NGS, enables us to further decipher the leukemic cells' molecular heterogeneity and clonal evolution[22] and becomes a part of routine CLL prognostication. Increasing whole genome and exome sequencing possibilities would facilitate 'personalized' CLL patient management and the choice of an optimal treatment strategy in the near future.[23]

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