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Editorial Open Access

Staging and Prognostic Factors in Chronic Lymphocytic Leukemia: Current Status

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Editorial

Chronic Lymphocytic Leukemia (CLL) is a B-cell malignant disease characterized by a progressive accumulation of B cells in the blood, bone marrow and lymphatic tissue, and which follows an extended disease course [1]. The diagnosis of CLL requires the presence in the peripheral blood of ≥ 5,000 monoclonal B-lymphocytes/μL for duration of at least 3 months. It is the most prevalent leukemia in the Western World with an estimated 15,720 new cases in 2014 and almost 4600 attributable deaths per year in the United States [2]. Chronic lymphocytic leukemia is predominantly a disease of the elderly, with a median age of 70 years at diagnosis. It is a slowly progressive disease, with an 82% five-year survival rate [3]. However, several patients have advanced and progressive disease and a poor prognosis at diagnosis. The management of CLL is determined by the stage and activity of the disease, as well as age and comorbidities. Randomized studies and a meta-analysis indicate that early initiation of chemotherapy does not show benefit in CLL and may increase mortality. There is no evidence that cytotoxic therapy based on alkylating agents has beneficial effects in patients with the indolent form of the disease [4]. The strategy of watchful waiting or observation, i.e. closely monitoring patient status without giving any treatment until progression, may be adopted [5]. However, patients with symptomatic and/or progressive disease should be immediately treated. Chronic lymphocytic leukemia displays a high heterogeneity in its clinical course, which makes the onset time and the choice of therapy difficult to determine [6]. For this reason, recent research on this disease focuses simultaneously on understanding its biology, discovering novel prognostic factors and on incorporating new therapeutic agents in the treatment of CLL. There is increasing interest in the use of prognostic markers which may predict survival and guide management in patients diagnosed with the early stages of CLL. These efforts also aim at proposing new prognostic systems which combine clinical and biological aspects of the disease with special consideration of the results of cytogenetic and molecular tests.

Clinical staging systems were proposed in the early 1980s by Binet et al. and Rai et al. [7,8]. Both systems use simple, inexpensive components such as blood counts and physical examination to identify 3 major prognostic subgroups typified by low, intermediate and high risk. These staging systems are still the most common and validated prognostic factors in the patients with CLL. However, these systems do not fully reflect the high variability of CLL and do not predict survival and response to therapy, particularly in low-risk (Binet A) patients [9]. Currently, up to 80% of newly diagnosed patients presenting with Binet stage A comprise both high-risk and low-risk patients [10]. In addition to clinical staging, other clinical patient characteristics such as gender, age and performance status, as well as some laboratory parameters, reflect the tumor burden and such disease activity characteristics as lymphocyte count, bone marrow infiltration pattern, LDH elevation, or lymphocyte doubling time (LDT) [11]. In addition, several serological parameters such as thymidine kinase1 (TK1), β2-microglobulin and soluble CD23 also provide valuable information about disease progression and survival (Table 1). TK1 is a general proliferation marker [12,13]. Elevated serum TK1 level was found in patients with unmutated immunoglobulin heavy chain variable region gene (IgVH), and in those with higher expression levels of ζ-chain-associated protein kinase 70 kDa (Zap70) and CD38, as well as advanced disease stage [14]. In previously treated CLL patients, β2-microglobulin is also an important prognostic indicator for response to therapy, time to treatment failure and overall survival [15,16].

Newer prognostic factors include also immunoglobulin heavy chain variable region genes (IgVH) mutation status, some cytogenetic abnormalities and gene mutations, cell membrane expression of CD38 and intracellular expression of ZAP-70 (Table 1) [17]. About 50 % of patients with CLL present leukemic cells with somatic hypermutation in IgVH genes, and they tend to have a more favorable outcome than the other half who do not [18,19]. A correlation between the immunoglobulin gene mutational status and prognosis has shown that the median survival for Binet stage A patients with unmutated IgVH genes was 8 years, compared with approximately 25 years for patients with mutated IgVH genes. Multivariate analysis indicates that deletion of 11q22-q23 and deletion of 17p13 are independent prognostic factors identifying patients with a rapid disease progression and a short survival time [20]. Deletion of 17p13 is associated with impaired function of TP53, a key tumor suppressor. Such patients respond poorly to chemo-immunotherapy and have significantly shorter survival compared to patients with standard and low-risk cytogenetics [21,22]. In contrast, deletion of chromosome band 13q14 is associated with a favourable outcome. Moreover, patients with trisomy 12 have a shorter survival than those with 13q deletion. Deletion of 17p and deletion of 11q predominate among advanced stages of CLL and among patients with unmutated IgVH genes. Furthermore, ZAP-70 expression and CD38 expression on leukemic lymphocytes have been found to correlate with IgVH mutations and shorter patient survival. Prognostic score constructed using modified Rai stage, cellular CD38 and serum lactate dehydrogenase significantly predict time to treatment failure and survival in patients at the time of diagnosis. The expression of ZAP-70 remains constant over the course of the disease as opposed to CD38. In addition, CD38 combined with Zap70 expression amplified the prognostic power of both markers. Zap70+/CD38+ patients were found to have shorter event-free survival than CD38–/Zap70– patients [23]. ZAP-70 expression can be evaluated using flow cytometric techniques, immunohistochemistry, western blotting or reverse transcriptase-polymerase chain reaction techniques [24]. The cut-off to classify patients as ZAP-70 positive or ZAP-70 negative remains controversial, and arbitrarily varies between 10% and

20%. More recently, recurring gene mutations such as NOTCH1, BIRC3 and SF3B1 have been identified which may have prognostic value [25,26]. Mutations in NOTCH1 have been described in 5-10% of newly-diagnosed CLL patients with increasing frequencies in advanced disease stages. Correlation of NOTCH1 with clinico-biologic features highlighted a significant association with an unmutated IGHV status, CD38 and ZAP-70 expression, trisomy 12 and a shorter treatment free interval (TFI) [27]. NOTCH1 and SF3B1 mutations may be overcome by aggressive regimens, while BIRC3 might influence the outcome also in patients treated with intensive regimens [28].

Although each prognostic factor has been found to be have significant correlations with survival when evaluated individually, there is increasing appreciation that the most complete information may be obtained by using a combination of several factors in prognostic indexes or models. To identify older and new prognostic factors which are independently associated with time to first treatment for CLL patients without any indication for treatment at time of evaluation, Wierda et al. [29] developed a weighted multivariable model using significant prognostic factors as a tool to identify high-risk patients with shorter time to first treatment. In this model, the presence of three involved lymph node sites, increased size of cervical lymph nodes, 17p deletion or 11q deletion by FISH, increased serum lactate dehydrogenase, and unmutated IGHV mutation status were independently associated with shorter time to the start of first treatment for patients who do not have an indication for treatment at time of evaluation.

Factor	Positive	Negative
Binet clinical stage Rai clinical stage	A 0	B. C I, II, III, IV
Bone marrow histology	Nodular	Diffuse
Lymphocytosis x10^9/l	≤ 50 x 10^9/l	>50 x 10^9/l
Prolymphocytes in PB	≤ 10%	>10%
Lymphocyte doubling time	> 12 m	≤ 12 m
Cytogenetics	Normal, del (13q)	del (11q), del (17p)
IgVH	Mutated	Unmutated
CD38 expression	≤ 30%	>30%
ZAP-70 expression	≤ 20%	>20%
Serum markers*	Normal	Elevated
* LDH, β2- microglobulin, Tymidine kinaze; Serum CD23 level		

Table 1: Classical and newer prognostic factors in CLL

Recently, Pflug et al. [30] developed a comprehensive prognostic index that identifies and combines the 23 prognostic markers of independent importance that are already available based on prospectively collected data from 1948 CLL patients participating in phase 3 trials of the German CLL Study Group [30]. Using a multivariable Cox regression model, 8 independent predictors of Overall Survival (OS) were identified, including sex, age, ECOG status, del (17p), del(11q), IgVH mutation status, serum β2-microglobulin, and serum thymidine kinase. Six predictors are widely available, but two, IGHV MS and s-TK, are not routinely used at many centres. On the basis of a weighted grading system, the authors developed a prognostic index that divided CLL patients with 5-year OS ranging from 18.7% to 95.2% into 4 risk categories (Table 2). This prognostic model allows clinicians to interpret and apply the existing prognostic tests for treatment of individual CLL patient enable to develop risk-adapted therapies for clinical trials. The index may have also application in identifying "very-high-risk" patients with a poor projected survival for more aggressive treatment approaches. Importantly, patients with deletion 17p can be stratified into high-risk or very-high-risk groups with different OS, and probably different treatment approach.

Risk categories for OS	Total risk scores*	5-year PFS rates for patients initially managed with W&W	5-year PFS rates for initially treated patients	5-yr OS rates for all patients
Low	0-2	86.20%	62.90%	95.20%
Intermediate	03-May	52.40%	43.60%	86.90%
High	06-Oct	22.10%	25.60%	67.60%
Very high	Nov-14	0.00%	6.40%	18.70%
*Risk scores of independent factors: del (17p) - 6, β2-microglobulin level >1.7 and ≤ 3.5 mg/L - 1, β2-microglobulin level > 3.5 mg/L – 2, serum thymidine kinase >10.0 U/L -2, age >60 years – 1, male sex - 1, ECOG performance status>0 - 1, del (11q) – 1, unmutated IgVH – 1. Abbreviations: OS – overall survival; PFS – progression free survival; W&W – watch and wait				

Table 2: Comprehensive prognostic index for patients with chronic lymphocytic leukemia (according to Pflug et al. [30])

In conclusion, the introduction of new prognostic factors and development of a comprehensive prognostic index should enable physicians and researchers to identify better patients with CLL and poor prognosis and consider earlier optimal therapeutic intervention.

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