

Prognostic factors in chronic lymphocytic leukemia

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introduction

There has been tremendous progress in the identification of molecular and cellular markers that may predict the tendency for disease progression in patients with chronic lymphocytic leukemia (CLL) or detect minimal residual disease after therapy. These developments have created some uncertainty for clinicians with regard to the optimal incorporation of these novel markers into the daily management of CLL patients. Therefore, this article will attempt to summarize the current evidence with regard to novel biological markers in CLL. The recommendations of the recently revised National Cancer Institute guidelines for the diagnosis and treatment of CLL as reported by the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) [1] will be incorporated.

staging systems

There are two widely accepted staging methods for use in both patient care and clinical trials: the Rai [2] and the Binet [3] systems. The original Rai classification was modified to reduce the number of prognostic groups from five to three [4]. As such, both systems now describe three major subgroups with discrete clinical outcomes. These two staging systems are simple, inexpensive and can be applied by physicians worldwide. Both rely solely on a physical examination and standard laboratory tests, and do not require ultrasound, computed tomography or magnetic resonance imaging.

biological parameters predicting the prognosis

molecular genetics

Using interphase fluorescence *in situ* hybridization (FISH), cytogenetic lesions can be identified in >80% of all CLL cases [5]. The most common deletions are in the long arm of chromosome 13 [del(13q14.1)]. Additional, frequent chromosomal aberrations comprise deletions and/or trisomy of chromosome 12, deletions in the long arm of chromosomes 11 [del(11q)] and 6 [del(6q)], and in the short arm of chromosome 17 [del(17p)] [5]. When stimulated *in vitro*, CLL cells can have detectable chromosomal translocations, which are of potential prognostic significance [6]. Complex

chromosomal abnormalities and translocations seem to correlate with more advanced stage and an unfavorable prognosis [6, 7]. Moreover, certain translocations can help distinguish other lymphoproliferative diseases from CLL [e.g. t(11;14), which generally is found in mantle cell lymphoma].

There is increasing evidence from prospective clinical trials that detection of certain chromosomal deletions has prognostic significance. Patients with leukemia cells that have del(17p) have an inferior prognosis and appear resistant to standard chemotherapy regimens employing alkylating drugs and/or purine analogs [8, 9]. In a retrospective analysis on several chromosomal aberrations as detected by FISH, patients who had CLL cells with chromosomal aberrations del(11q) and del(17p) had an inferior outcome compared with patients who had leukemia cells with a normal karyotype or del(13q) as the sole genetic abnormality [5]. On the other hand, patients with leukemia cells having del(17p) may respond to therapy with alemtuzumab, either alone or in combination with other anti-leukemia agents [10, 11]. Detection of these cytogenetic abnormalities has apparent prognostic value and may influence therapeutic decisions. Therefore, it is recommended that cytogenetics be performed before treating a patient. Additional genetic defects may be acquired during the course of the disease [12]; therefore, the repetition of FISH analyses seems justified prior to subsequent, second- and third-line treatment.

mutational status of IgVH, VH3.21 usage and expression of ZAP-70 or CD38

Leukemia cells express immunoglobulins that may or may not have incurred somatic mutations in the immunoglobulin heavy chain variable region genes (IgVH genes). The outcome of patients with leukemia cells that use an unmutated IgVH gene is inferior to that of patients with leukemia cells that use a mutated IgVH gene [13, 14]. In addition, VH3.21 gene usage is an unfavorable prognostic marker independent of IgVH mutational status [15]. Leukemia cell expression of ZAP-70 and CD38 was found to correlate with the expression of unmutated IgVH genes and to predict a poor prognosis [16–22]. However, the association between expression of ZAP-70 or CD38 and expression of unmutated IgVH genes is not absolute. It is uncertain whether leukemia cell expression of unmutated IgVH genes or ZAP-70 predicts the response to treatment or overall survival, once therapy is required [9, 23]. Further clinical trials are needed to standardize the assessment of these parameters and to determine whether they should affect the management of patients with CLL.

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serum markers

Several studies have found that serum markers CD23, thymidine kinase and β 2-microglobulin may predict survival or progression-free survival [24–30]. A recent multivariate analysis of the CLL1 protocol of the GCLLSG has confirmed that the serum markers β 2-microglobulin and thymidine kinase are potent predictors of progression-free survival in Binet stage A CLL [31]. These markers should be further investigated in prospective clinical trials.

marrow examination

Characteristically >30% of the nucleated cells in the aspirate are lymphoid. Although the type of marrow infiltration (diffuse versus non-diffuse) reflects the tumor burden and provides some prognostic information, recent studies of the German and Spanish study groups strongly suggest that the prognostic value of bone marrow biopsy may now be superseded by new prognostic markers [31].

kinetic parameters: lymphocyte doubling time

The prognostic relevance of lymphocyte kinetics was first suggested in 1966 by Galton [32]. Lymphocyte doubling time (LDT; defined as the time period needed to double the peripheral blood lymphocyte count) is a simple and valid parameter to assess the pace of the disease, in particular in early disease (Binet stage A, Rai stages I and II). Although this parameter is not available at diagnosis, it can easily be calculated by extrapolation shortly thereafter. A LDT of <12 months predicts an aggressive course and short survival, while patients with a longer LDT or stable lymphocyte counts tend to have an indolent course [33–36]. Some studies found an independent prognostic value of LDT in multivariate analyses [31, 33], while others failed to do so [37, 38]. Many similar parameters assessing the proliferative potential of CLL cells such as [3 H]thymidine uptake of CLL lymphocytes, mitogenic activity after polyclonal lymphocyte stimulation and the percentage of S-phase lymphocytes as determined by cytofluorometry have been shown to be associated with poor prognosis, but none of them has been tested in large studies with multivariate comparison (reviewed in [39]). Taken together, the definitive value of LDT still needs to be confirmed by large prospective studies including all molecular factors, but the simplicity and ease by which LDT can be determined will probably ascertain its use in the future.

conclusion

The prognostic markers described above may help to predict the prognosis or to assess the tumor burden. With the exception of molecular genetics (FISH), the application of these tests should not be used in routine practice to influence therapeutic decisions. However, certain parameters are useful for predicting the clinical course in individual cases. These tests can be recommended for patients who want a better prediction of the rate at which their disease might progress but it should be emphasized that the indication for treatment does not depend on any of these tests but on the clinical stage and the disease activity. Many of the new prognostic markers still need

further evaluation in clinical trials before they can be formally recommended for routine clinical decision making.

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