Perspectives on the use of new diagnostic tools in the treatment of chronic lymphocytic leukemia

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Recently, considerable progress has been made 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 uncertainty for clinicians who hope to incorporate the use of these markers and new disease-assessment tools into standard clinical practice. However, clinical trials are required to determine whether poor-prognosis leukemia-cell markers, such as expression of unmutated immunoglobulin genes or the zeta-associated protein of 70 kDa (ZAP-70), can be used as the basis for determining the time or type of therapy. Pending the outcome of such trials, treatment decisions outside the context of a clinical trial still should be based on guidelines established by the most recent National Cancer Institute-sponsored Working Group. (Blood. 2006;107:859-861)

Initial diagnostic work-up of a patient with CLL

The World Health Organization (WHO) classification of hematopoietic malignancies describes CLL (chronic lymphocytic leukemia) as leukemic, lymphocytic lymphoma, being only distinguishable from SLL (small lymphocytic lymphoma) by its leukemic appearance.[1] In the WHO classification CLL is always a disease of neoplastic B cells, whereas the entity formerly called T-CLL is now called T-PLL (T-cell prolymphocytic leukemia).[1]

It is important to verify that the patient has CLL and not some other lymphoproliferative disease that can masquerade as CLL (eg, mantle cell lymphoma, splenic lymphoma with villous lymphocytes, marginal zone lymphoma, or hairy cell leukemia). A minimum of 2 examinations is required to diagnose CLL: (1) evaluation of blood count and blood films and (2) immune phenotype of the leukemia cells in the blood.[2] The cells found in the blood films are characteristically small lymphocytes with a narrow border of cytoplasm and a dense nucleus with partially aggregated chromatin and without recognizable nucleoli. Gumprecht nuclear shadows, or smudge cells, found as cell debris, are characteristic. A minimal panel of cell surface markers to distinguish CLL distinct from other entities includes CD5, CD19, CD20, CD23, and surface immunoglobulin with light chain restriction. Another characteristic of CLL is that the levels of surface immunoglobulin, CD20, and CD79b typically are low relative to that of normal B cells. Although classically an arbitrary threshold of 5000 lymphocytes/μL has been considered as a prerequisite for diagnosis, the diagnosis of CLL now typically relies on the presence of a chronic, absolute increase in blood lymphocytes that have the aforementioned morphologic and immunophenotypic characteristics.

Additional tests at diagnosis

The cytologic and histologic examinations of the marrow are not necessary for diagnosis.[2] However, histologic examination of the marrow can assess the extent and pattern (diffuse, nondiffuse) of the marrow infiltration by CLL and clarify the etiology of cytopenias (eg, leukemic infiltration, autoimmune cytopenia, aplastic marrow). A marrow biopsy is also indicated if there is complete regression of all disease following treatment; a complete remission of CLL implies that the marrow does not show any apparent CLL infiltration.

Other laboratory tests are usually recommended to validate the diagnosis, to assess the extent of the disease, and to avoid complications. These include serum protein electrophoresis to evaluate for paraproteinemia, serum immunoglobulin levels to evaluate for hypogammaglobulinemia, and the Coombs test to detect antierythrocyte autoantibodies. Serum measurements of creatinine, urea, electrolytes, uric acid, bilirubin, and transaminases, as well as of renal status, should be performed before initiating treatment. In addition, before initiating therapies with immunosuppressive agents, patients should be evaluated for evidence of active infection with common viral pathogens (eg, hepatitis virus B and C, cytomegalovirus).

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Staging

The median survival of a patient with CLL from the time of diagnosis varies widely between 2 and more than 10 years, depending on the stage and other patient and disease characteristics. The staging classifications of Rai et al[3] and Binet et al[4] are used to estimate the prognosis based on the extent of lymphadenopathy, splenomegaly, and hepatomegaly measured by palpation and anemia and thrombocytopenia measured by blood cell counts. The Rai staging system is widely used in North America, the Binet staging system throughout Europe. Both systems describe 3 major prognostic subgroups. These 2 staging systems remain the backbone of any clinical decision-making process for patients with CLL. These staging systems have the major advantage of being simple and inexpensive. As such, they can be applied by physicians worldwide. It should be noted that the Rai or Binet staging systems rely solely on a physical examination and standard laboratory tests, whereas the role of various imaging procedures (ultrasound, computed tomographic scan, or magnetic resonance imaging [MRI]) has not been validated.

New prognostic markers

It has been recognized that the Rai or Binet clinical staging systems alone are not sufficient to estimate the individual prognosis reliably, particularly for patients with early-stage disease (eg, Binet stage A, Rai stages 0-II). Therefore, additional parameters have been sought to more accurately assess the prognosis of patients with CLL. This search has provided a steadily increasing number of laboratory tests, which predict the response to treatment, progression-free survival, or overall survival of patients with CLL. In previous, mostly retrospective analyses, the parameters shown in Table 1 have shown promising results, justifying further, systematic investigation in future prospective trials.

The first 4 parameters of Table 1 have proven prognostic value independent of the clinical stage in several studies. However, the methods for measuring some of these parameters (ZAP-70, serum markers, cytogenetics, mutational status of immunoglobulins) have yet to be fully standardized and/or may not be readily feasible in most clinical laboratories. Furthermore, the prognostic value of some of the more easily accessible markers (eg, β-2 microglobulin) has not been as well established as that of immunoglobulin mutation status or certain cytogenetic abnormalities (eg, 17p−). In any case, none of these parameters has yet proven itself useful as the basis for deciding when to initiate therapy in patients with CLL.

Table 1. Leukemia-cell parameters associated with aggressive disease independent of the disease stage

Parameter	Reference
Aberrations in chromosomes 11 (11q-) or 17 (17p-)	Döhner et al[5]
Lack of somatic mutations in the expressed immunoglobulin V_H-genes	Hamblin et al[6]; Damle et al[7]
Expression of cytoplasmic ZAP-70	Rassenti et al[8]; Crespo et al[9]; Orchard et al[10]
Short lymphocyte doubling time (less than 12 months)	Montserrat et al[11]
Elevated serum levels of β_2-microglobulin	Keating et al[12]; Hallek et al[13]
Elevated serum levels of soluble CD23	Reinisch et al[14]; Sarfati et al[15]
Elevated serum thymidine kinase activity	Hallek et al[16]
Leukemia cell-surface expression of CD38	Damle et al[7]; Ibrahim et al[17]

Instead, the relative value to treatment-related decisions of any one or more of these parameters needs to be evaluated in prospective clinical trials.

When to treat

The decision to treat is guided by the stage of the disease, the presence of symptoms, and the disease activity. Evidence that current treatment can affect favorably on survival outcome is only available for patients with Rai III or IV or Binet B or C stage disease or for patients with clear evidence for relatively rapid disease progression. Patients in earlier stages (Rai 0-II, Binet A and B) are generally not treated but monitored with a "watch and wait" strategy. Treatment is necessary in patients with early stage disease (Rai stage I or II, Binet A) only when they have disease-related symptoms, such as decreased performance status, debilitating constitutional symptoms, or threatening complications from spleen, liver, or lymph node enlargement (eg, compression of the large abdominal vessels). Significant disease activity, often defined by a lymphocyte doubling time of less than 12 months, decline in marrow function, or by rapidly growing lymph nodes, is also an indication to treat in the early stages.

Assessment of minimal residual disease

The complete eradication of the leukemia is an obvious desired end point. New detection technologies such as 4-color flow cytometry and real-time quantitative polymerase chain reaction (PCR) have determined that patients who achieve a complete response by NCI-WG guidelines typically have minimal residual disease (MRD). Although eradication of minimal residual disease may improve prognosis, more prospective clinical trials are needed to define the value of MRD assessment as an end point for routine clinical practice. Moreover, the techniques for assessing MRD are currently undergoing a critical evaluation and standardization. Until this process is complete, it is premature to recommend adopting eradication of MRD as a therapeutic end point independent of a clinical trial. Also, future clinical trials that aim toward achieving long-lasting complete remissions should include at least one test to assess MRD, because the lack of leukemia persistence using these sensitive tests seems to have a strong, positive prognostic effect.[18-20]

Conclusion

Most of the new prognostic markers now available for CLL (Table 1) have been investigated either in small patient series or in retrospective analyses. Moreover, they have often not been tested in comparison to all other available parameters. Therefore, the use of these new prognostic markers as the basis for deciding when to initiate therapy appears premature except in the context of prospective clinical trials intended to evaluate the potential value of such markers to treatment-related decisions. Until such evidence is available, the decision to initiate treatment should continue to follow conventional clinical staging and assessment criteria.[2]

Given this situation, clinical trials are required to determine whether patients at high risk for disease progression (ie, with a number of unfavorable prognostic markers) actually benefit from early treatment intervention independent of currently

accepted treatment guidelines. Early identification of such patients could allow for earlier treatment to mitigate the problems associated with symptomatic disease and to avoid exacerbating the cytopenias that characterize patients with advanced-stage disease. Similarly, it remains unclear with currently available data, whether specific risk factors should guide the treatment choice in patients who need treatment. To change this situation, several study groups have initiated clinical trials, in which patients at early stage are examined for the prognostic factors presented in Table 1 and randomly assigned for immediate versus delayed treatment ("watch and wait"), if they show an unfavorable risk factor profile. Furthermore, clinical trials for patients with CLL at advanced stages need to include a complete assessment of these prognostic markers to help determine which patients benefit most from a given treatment. Patients should be enrolled in these clinical trials. It can be anticipated that the educated integration of these novel prognostic and diagnostic tools into the development of rational, risk-adapted treatment strategies will improve the outcome of patients with CLL.

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