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The impact of diagnosis on the therapeutic management of chronic lymphocytic leukemia

The considerable progress in diagnostic tools, the identification of a number of biological markers improving outcome prediction, and the introduction of new treatment strategies have made the therapeutic management of chronic lymphocytic leukemia (CLL) no longer straightforward. Furthermore, the care of individual patients with CLL has become more demanding, and a comprehensive approach to them should include attention to quality of life (QOL) issues, adherence to supportive care guidelines, consideration of age and comorbidity, recognition of clinical complications such as infection, autoimmune cytopenias, and transformation into a more aggressive disease.[1] In CLL patients, a risk-stratified approach to therapy based on novel prognostic markers is recommended in the context of clinical trials, but not in general routine.[2] How the novel markers could at least complement the traditional prognostic factors in the clinical management of patients with CLL is now discussed.[3]

The diagnosis of CLL essentially relies on the detection of a persistent increase in the absolute number of blood lymphocytes with morphologic and immunophenotypic characteristics.[4] In particular, CLL is defined by the flow cytometry detection of clonal blood B cells $CD5^+$, that also express CD19, CD20, CD23 and surface immunoglobulin (sIg) light chain restriction; the levels of sIg, CD20 and CD79b expression are characteristically low. This minimal panel of cell surface markers allows to distinguish CLL from other chronic leukemic lymphoproliferative disorders (CLD). Although a prerequisite for the diagnosis of CLL is a sustained absolute lymphocytic count higher than 5000/µL, the disease can be also recognized in individuals with fewer than 5000/µl monoclonal B lymphocytes and lymphadenopathy, splenomegaly, hepatomegaly, or cytopenia caused by bone marrow infiltration; in the absence of these features, a monoclonal B lymphocytosis (MBL) is instead categorized.[5] The essential diagnostic work-up of CLL, including the blood count, blood smears and immunophenotyping of leukemic blood cells, can be enriched by additional tests. Among others, the cytologic and histologic examinations of the bone marrow (BM) can be particularly useful to assess the extent and pattern (diffuse, nondiffuse) of leukemic cell infiltration and to evaluate the etiology of cytopenias. Indeed, the cytopenias related to CLL-induced BM failure have to be distinguished from CLL autoimmune complica-

tions, most commonly represented by autoimmune haemolytic anemia (AIHA), immune thrombocytopenia (ITP) or pure red cell aplasia (PRCA). BM biopsy as well as lymph node biopsies can be particularly useful in the presence of atypical morphologic, immunophenotypic and clinical features (or during the follow-up to exclude histological transformation into aggressive non-Hodgkin lymphoma).

Once the diagnosis of CLL is evident, the disease should be staged on the basis of the traditional clinical systems developed by Rai and Binet.[6,7] According to the modified Rai classification, low-risk (Rai 0/Binet A), intermediate risk (Rai I, II/Binet B), and high-risk (Rai III, IV/Binet C) disease categories can be recognized, based on the extent of lymphadenopathy, splenomegaly and hepatomegaly evaluated by physical examination, and anemia and/or thrombocytopenia measured by standard blood cell counts. The role of the various imaging procedures (ultrasound, computed tomography scans, magnetic resonance) has not been validated, although they may provide useful informations in selected patients, such as those with Rai stage 0/Binet stage A and detectable abdominal mass.[8,9] At the present time, the aforementioned staging systems of Rai and Binet remain the basis for assessing prognosis in patients with CLL, being the decision to start treatment guided by the stage of the disease as well as by the presence of symptoms and disease activity.[4] However, 80-90% of patients are now diagnosed while in early-stage of the disease (Rai low or intermediate risk category/Binet A and B), which may have a highly variable clinical course. Since the Rai or Binet staging systems are not sufficient to estimate the individual prognosis reliably, the early-stage patients should be subclassified as being at low, intermediate or high risk for disease progression on cytogenetics and other novel prognostic markers.[10]

In recent years, a wide array of additional parameters with prognostic relevance, such as molecular and cellular features of the leukemic cells, have been proposed. Cytogenetic abnormalities, demonstrated by interphase fluorescence in-situ hybridization (FISH) in about 80% of CLL cases, mostly consist of deletions (del) 13q, 11q, or 17p, and trisomy 12. The detection of these abnormalities can influence therapeutic decisions prior to first treatment as well as to subsequent line treatment, predict the overall response rate and the response duration, or help to distinguish other CLD from CLL, such as t(11:14) generally found in the leukemic phase of mantle cell lymphoma (MCL). Del 11q and particularly del 17p are associated with rapid disease progression or inferior survival, and with distinct clinical pictures such as marked lymphadenopathy (del 11q) or resistance to treatment with conventional chemotherapy (del 17p). Furthermore in patients with disease progression, del 11q, overexpression of c-myc, deletions of the Rb1 gene and mutations of the p53 tumor-suppressor gene have been reported.[5] Other novel factors related to the biology of the disease, such as mutational status of the immunoglobulin heavy-chain variable region genes (IgVH), VH3.21 gene usage, expression of cytoplasmic ZAP-70, cell-surface expression of CD38, and serum markers (levels of soluble CD23, and thymidine kinase activity) have been identified for predicting the clinical course of patients with CLL. Their use, however, should not obviate clinical monitoring for other features traditionally associated with disease progression, such as lymphocyte doubling time, progressive lymphadenopathy, measurement of β_2-microglobulin levels or development of disease-related symptoms or disease-associated cytopenias. Patients with a poor outcome frequently have aberrations in chromosomes 11 (del 11q) or 17 (del 17p), lack of somatic

mutations in the expressed IgVH genes, show expression of cytoplasmic ZAP-70, short lymphocyte doubling time, elevated serum levels of β_2-microglobulin, elevated serum levels of soluble CD23, elevated serum thymidine kinase activity, leukemia cell-surface expression of CD38.[2]

The methods for measuring some of the novel parameters (ZAP-70, serum markers, cytogenetics, mutational status of IgVH) have yet to be fully standardized and/or may not be readly feasible in most clinical laboratories.[8] IgVH mutational status and genomic aberrations have been recognized to be among the strongest factors with an independent prognostic value;[11] when in combinations, they seem to be the most powerful predictors in selecting the patients with the higher risk for disease progression.[10] Indeed, unfavourable aberrations (del 11q, del 17p) occur more frequently in IgVH unmutated, and favourable aberrations (del 13q) more frequently in IgVH mutated subgroups.[11] As it is known, patients with unmutated CLL mostly have a poor clinical outcome with evidence of advanced, progressive disease, atypical peripheral blood cell morphology, adverse cytogenetic features, clonal evolution, and resistance to therapy.[5] The prognostic value of IgVH mutations is independent from that of clinical stage and cytogenetic abnormalities, particularly in patients with early-stage disease. The expression of V3-21 is instead associated with a poor outcome, independently of the mutational status of IgVH.[5,12,13]

ZAP-70 and CD38, identified as surrogate markers of IgVH mutational status, are currently considered as independent prognostic markers.[14] Their combined analysis however seems to reveal complementary prognostic informations, allowing to stratify CLL patients into three subgroups with good, intermediate and poor prognosis;[5,15] in concordant cases, ZAP-70/CD38 could increase the ability to predict mutation of IgVH genes. Furthermore, the simultaneous analysis of IgVH mutational status, ZAP-70 and CD38 have revealed a more refined prognostic value than any factor alone. IgVH mutational status can further stratify discordant ZAP-70/CD38 cases, or change the subgroup stratification in concordant good risk ZAP-70$^-$/CD38$^-$ cases.[16]

In conclusion, the reliable informations from the novel prognostic markers allow a better approach to the risk assessment of CLL patients. Although it remains unclear whether specific risk factors should guide the treatment choice in patients who need therapy.

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