Assessing prognosis in patients with chronic lymphocytic leukemia a quarter of a century after Rai and Binet staging systems

Chronic lymphocytic leukemia (CLL) has an extremely heterogeneous prognosis. Nowadays, the median survival of patients with this form of leukemia is 8–10 years, compared with 5–6 years in series reported in the 1970s. This is largely due to the higher number of patients who are now being diagnosed in early phase (up to 80%) and, hence, with better prognosis [1, 2]. Individual survival, however, is highly variable.

Classically, clinical stages have been used to predict the behavior of the disease [3, 4]. Although easy to apply and reproducible (a necessary condition for any prognostic factor to be accepted as such), staging systems have some weaknesses. For example, the mechanisms accounting for cytopenias (i.e. bone marrow infiltration, hypersplenism, autoimmune basis) are not taken into consideration. As a result, patients are classified as being in advanced stage independently of the origin of the anemia or thrombocytopenia. Yet there is some indication that the mechanism of the cytopenia is also a factor in prognosis [5]. Even more important is the prognostic heterogeneity within each of the clinical stages. Thus, staging systems do not allow identification of individuals in early stage who are likely to progress and those in whom the disease will have an indolent course. This is important, since patients in early stage who are likely to progress might benefit from being treated immediately after diagnosis, before progression occurs, and also because of the uncertainty of the prognosis in individuals otherwise in good clinical condition in whom the diagnosis has been made on a routine medical examination. Conversely, some patients presenting in advanced stage run an indolent course and for long periods of time may not require therapy; the staging systems do not identify these patients either. All this is essentially due to the fact that clinical stages are a mere reflection of the biological diversity of the disease [6, 7]. Such heterogeneity, fortunately, is rapidly unfolding.

For example, cytogenetic abnormalities, as studied by fluorescence in situ hybridization, can be detected in up to 90% of the patients. Although they are not specific, there are interesting correlates between some cytogenetic aberrations and clinical features. Thus, patients with del(13q) as sole abnormality have good prognosis; in contrast, those with del(11q) or del(17p) tend to have a rapidly evolving disease and do not respond to treatment. Furthermore, trisomy 12 is associated with atypical morphology and immunophenotype, and del(6q) may be observed more frequently in cases with plasmacytoid features [8–11].

On the other hand, CLL has long been considered a homogeneous disease of naïve CD5+ B cells, pre-germinal cells not exposed to antigenic stimulation. In 1999, two different groups made an important breakthrough in the understanding of CLL by showing that, whereas in some cases IgVH genes are unmutated, in others they are [12, 13]. Since somatic mutation takes place in the germinal center of lymphoid follicles, CLL can be a tumor of either pre- or post-germinal-center B cells. These two forms, however, share the same genetic signature as determined by microarrays and, because of this, CLL is considered to be a single disease with two variants (i.e. mutated and unmutated) [14]. The mutational status of IgVH genes separates CLL into two forms with distinct presenting features and outcome. Compared with those with IgVH mutations, patients with unmutated IgVH genes have a more malignant disease, including advanced stage, atypical cell morphology, adverse cytogenetic features and resistance to therapy [12, 13]. Unfortunately, studying IgVH mutations on a routine basis is not yet easy. CD38 expression correlates, although not absolutely, with IgVH mutations; in addition, CD38 expression may vary over time [15]. Recently, it has been demonstrated that ZAP-70 expression, as evaluated by cytofluorometry or PCR, correlates strongly with IgVH mutations and has important prognostic significance by itself [16–19]. Of great importance, these new biological prognostic parameters have independent prognostic value and discriminate, among patients in early clinical stage, those who are likely to progress and those who will remain stable.

As the mysteries of the biology of CLL are revealed, important biological prognostic parameters are claiming a place in the prognostic assessment of the disease. The staging systems developed in the early 1970s have been crucial in the progress of our understanding on CLL. Because of their simplicity and reproducibility they have been widely employed. They have also been critical in conducting randomized treatment studies in comparable series of patients, and in attracting the interest of a new generation of younger physicians and investigators to an old disease. To abandon the clinical staging systems would be not only precipitous, but unwise. Rather than replace clinical stages and other simple prognostic parameters (e.g. degree of bone marrow infiltration, white blood cell count, doubling time), these new factors should currently be employed to refine the prognostic power of classical prognostic factors. Finally, clinical staging systems and other prognostic factors were developed in an era in which no effective therapy existed for CLL. Since prognostic indicators may change as more effective therapies become available, prognosis should be assessed prospectively in patients treated with the newer and more effective therapies. Only in that manner will the most relevant prognostic factors for CLL eventually be identified, a quarter of a century after the introduction of clinical stages.
References