Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a disorder characterized by a progressive accumulation of mature B lymphocytes which either avoid death because of external survival signals or go into apoptosis to be replenished by proliferating precursors. CLL is the most common type of leukemia of elderly people in the Western countries. Although the median survival is around 10 years, in individual patients the prognosis is extremely variable, ranging from a very short to a normal life span. After decades during which the wait and watch management has been the normal approach to these patients, the attitude of the physicians towards CLL patients has changed remarkably during the last few years. The reasons for this change are manifold and some are discussed below. For many years CLL has been considered a typical disorder of the elderly, with a median age at diagnosis of about 65 years. Nowadays, because of the improvement of the biological age and the increased median life expectancy of populations, CLL can no longer be considered a typical disorder of the elderly. Although the median age of the patients at presentation is about 65 years, in 20% of cases the diagnosis of CLL is in fact made under the age of 55 years.

Moreover, for a long time CLL was considered a pathology with a long natural history and only palliative therapies that rarely achieved complete responses were utilized. Today, the advances in the field of biology and treatment of CLL have significantly contributed to major changes in the overall management of patients. In fact, nowadays we can effectively stratify prognostically CLL patients at presentation on the basis of a number of laboratory and clinical parameters, and identify patients with good and poor likelihood. Furthermore, through the administration of purine analogues and monoclonal antibodies, used alone or in various combinations, and through the use of autologous and allografting procedures, we can offer CLL patients therapies potentially capable of eradicating the leukemic clone. We report below the recent progresses in the prognostic stratification and treatment options of CLL patients, and discuss how these advancements have changed the approach of physicians to this disease.

New prognostic parameters

In the last two decades, numerous papers in which the prognostic value of clinical and laboratory parameters was evaluated have been published. The necessity of identifying new parameters which allow to predict the clinical course of CLL patients is due to the fact that although the classifications of Rai and Binet offer important prognostic clues at the time of diagnosis and are the most useful prognostic parameters in CLL, they fail to provide indications about disease heterogeneity and treatment requirements. During the last few years, the major advancements in the prognostic stratification have originated from a better understanding of the biology of CLL and from the improvement of laboratory methods. In fact, the use of interphase fluorescence in situ hybridization (FISH) has allowed to identify abnormalities in approximately 80% of CLL cases and to document the strong association between cytogenetic aberrations and prognosis: patients with del(13q) have an excellent prognosis, whereas those with del(11q) or del(17p) have a poor survival. Moreover, different groups have reported the prognostic impact of the IgVH mutation status on prognosis. These reports have shown that CLL patients presenting mutated IgVH (>2% difference of nucleotide sequences from germ line cells) have a significantly longer survival than those with a germline status (<2% difference). An association between CD38 expression on CLL lymphocytes and the IgVH mutational status has been reported. Patients whose cells have a mutated Ig gene tend to have low levels of CD38 and unmutated CLL patients have higher levels. Although this association is not strict and the predictive power of CD38...
as a surrogate for the IgVH mutational status has been questioned, recent reports have confirmed the independent prognostic significance of both parameters.\textsuperscript{6,7} Finally, the use of the DNA microarray technology has shown that gene expression profile of patients with different IgVH mutational status has a differential expression of about 100 genes.\textsuperscript{8} Two of these genes are ZAP-70 and LPL that are overexpressed in germline samples. ZAP-70 analysis by flow-cytometry and immunocytochemistry, and the quantification of LPL by quantitative RT-PCR on CLL cells have allowed to document correlation of these parameters with the IgVH mutational status and their strong prognostic value.\textsuperscript{9,10} With the aim of conclusively defining the prognostic power of these biological parameters, our group has taken a different approach and has performed a complete biological work-up in a selected group of patients observed at our Institute with a highly stable and untreated disease over a 10-23 year follow-up period.\textsuperscript{11} This approach allowed to show that highly stable CLL patients have a well defined biological picture characterized by a typical CLL morphologic and immunophenotypic profile, the lack of expression of the CD38 antigen, a mutated IgVH pattern, absence of p53 mutations, a CD4/CD8 T-cell ratio >1, lack of 17p and 11q deletions, as well as of complex karyotypic aberrations, and the frequent presence of the 13q14 deletion or of a normal karyotype. All these data document that today it is possible to perform a biological work-up at the time of diagnosis that allows to predict early stage CLL patients who will rapidly progress and will show a short life span on the one hand, and the group of those who will have a prognostic expectation that parallels that of healthy age-matched individuals on the other hand.

**Modifications of clinical approach based on new prognostic parameters**

The improvement in the autologous and allogeneic transplantation procedures and the availability of newer and potentially more effective therapies such as fludarabine and monoclonal antibodies (rituximab and alemtuzumab) that have allowed to achieve higher response rates, including molecular remissions, and the possibility of indentifying at presentation early stage patients with poor prognosis have cast doubts on the "wait and watch" management that for many years has been the normal approach to CLL patients. At the same time, all these issues have raised new questions about the possibility of impacting on survival of patients with well defined adverse prognostic features through an early and more aggressive treatment intervention and about the possibility of choosing between different therapeutic approaches through the biological characteristics of the neoplastic cells. An objective response to the first question will be possible only when the results of studies, such as the CLL1 and CLL7 trials of GCLLSG in which stage A poor-risk patients are randomized either to receive chemotherapy or to wait and watch modality, will become available. With regard to the correlation between response to therapy and biological features, it has been reported that patients with deletion of 17p and/or abnormalities of p53 show a poor response to alkylating agents, fludarabine and rituximab\textsuperscript{12,13} while a therapeutic success can be achieved with alemtuzumab.\textsuperscript{14} Furthermore, two retrospective studies have recently evaluated the impact of autologous stem cell transplantation on prognosis of patients with a different IgVH mutational status and have shown that the unfavorable prognostic value of germline IgVH status still remains after autologous stem cell transplantation,\textsuperscript{15,16} although this procedure may prolong survival compared to conventional therapy. Better results have been obtained through the use of allogeneic stem cell transplantation. Ritgen et al have, in fact, reported the efficacy of this procedure in eradicating the leukemic clone in germline patients.\textsuperscript{17}

**Conclusions**

In conclusion, in the light of the advances in the understanding of the pathogenesis of the disease - in the field of diagnosis, prognosis and therapy - it is apparent that the overall approach to the management of CLL patients is changing dramatically. In fact, through a broad and integrated laboratory and clinical work-up at presentation, it is now possible to identify patients with a very good prognostic expectation who do not require treatment and patients with a very poor survival likelihood who should be considered for early and aggressive treatment modalities in an attempt to impact on life expectancy. All these issues indicate that in the future we may offer each CLL patients a more targeted algorithm of treatment (or non-treatment) based on his/her clinical and biological characteristics of the disease.
References