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The Kaufman/Rubin/Rai Article Reviewed
Interesting Times in the Diagnosis and Treatment of CLL

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One of the greatest challenges facing the physician caring for patients with chronic lymphocytic leukemia (CLL) is the heterogeneity of this disease. Over the past decade, there have been major advances in understanding the pathophysiology of CLL, and in the identification of biomarkers that are helpful to predict the clinical course for individual patients. Over the same period, the available therapeutic options have developed dramatically, exemplified by the introduction of combination therapy with purine analogs and monoclonal antibodies, resulting in significant opportunities to induce complete remission (CR) in CLL patients.

The alkylating agent chlorambucil (Leukeran) was the mainstay of treatment for CLL until the past decade, and its use was associated with low rates of CR. Instead, the aim was disease control and palliation, and it was repeatedly demonstrated that there was no benefit to initiating treatment in patients with early-stage disease.[1] In contrast, in the recent CLL8 trial, combination therapy with FCR (fludarabine, cyclophosphamide, and rituximab [Rituxan]), has been shown to achieve CR rates of almost 50%, with the benefits being greatest in patients with earlier-stage disease.[2] Thus, the success of these novel therapies raises the question of whether the traditional “watch and wait” approach to patients with early-stage CLL is still valid, or whether an enhanced rate and durability of response could be achieved by more aggressive upfront management. This is especially relevant with CLL being increasingly diagnosed in asymptomatic patients who are found to have a lymphocytosis on a routine blood count.

Prognostic Markers: One of the most important clinical trial questions is whether there

are any clinical or molecular markers that can identify “high-risk” patients, and guide the choice and timing of therapy. In this issue of ONCOLOGY, Kaufman and colleagues explore the range of prognostic markers and treatments currently available, and offer a pragmatic approach to the management of various patient groups.[3] They highlight the fact that the established Rai and Binet clinical staging systems are most useful in predicting outcomes in patients with advanced disease. However, the heterogeneity of CLL is most marked in the low- and intermediate-risk groups, and it is in these patients that there is the greatest requirement for biomarkers that can predict whether the disease will be indolent or aggressive.

Newer markers such as immunoglobulin heavy chain variable-region gene (IgVH) mutation status can provide useful prognostic information, but it has had little impact on determining the choice of therapy, and is not routinely available. Surrogate markers for IgVH mutation status such as ZAP-70 and CD38 expression are more widely available, but do not show an absolute relationship to mutation status, and results can vary over time and between laboratories. Indeed, clinicians may still be better served by established markers such as lactate dehydrogenase and β 2-microglobulin.[4]

Several cytogenetic abnormalities also have prognostic significance, and some of these may affect treatment options. Deletion of 17p13 is associated with rapid disease progression, and by causing loss of p53 often confers resistance to cytotoxic agents: therefore the use of agents that act independently of p53, such as alemtuzumab, should be considered in these individuals. The question of whether patients with poor prognostic features should be treated earlier in their disease course will likely be answered by clinical trials, such as the French/German CLL7 and other ongoing studies.

Treatment Considerations: In addition to the heterogeneity of the disease, the heterogeneity of patients in terms of ability to tolerate potentially toxic therapy, adds further degrees of uncertainty as to the best treatment for an individual. The median age of patients with CLL is between 65 and 68 years old,[5] and by implication, a significant proportion of CLL patients will be elderly with comorbidities. The elderly are generally underrepresented in clinical trials, making it difficult to extrapolate their results. In the German CLL Study Group (GCLLSG)-led CLL8 trial, FCR was noted to cause more neutropenia without a significant increase in severe infections, but the patients were younger (median age: 61 years), fitter, and without any significant renal impairment.[2]

Furthermore, a recent report of the GCLLSG CLL5 study demonstrated that in elderly patients, first-line therapy with fludarabine alone does not result in benefit compared to chlorambucil,[6] in contrast to previous studies in younger patients. There remains a role for chlorambucil in these individuals, potentially in combination with monoclonal antibody immunotherapy and the novel agents described by Kaufman and colleagues.

At the other end of the spectrum, the improvements in outcome that have been seen with immunochemotherapy have consequences for subsequent therapy. There is a need for new agents in CLL and few therapeutic options are available for patients who have relapsed after FCR therapy, particularly for those patients who fail to respond or have short durations of response.

Historically, patients with CLL have not been good candidates for allogeneic hematopoietic stem cell transplantation (SCT), but the use of reduced-intensity conditioning regimens has made this a suitable option for an increased number of CLL patients. Questions remain regarding patient selection and when in the course of their disease allogeneic SCT should be considered. There remains a balance between the potential cure that allogeneic SCT offers, and the increased morbidity and mortality associated with it.

The increased interest in reduced-intensity conditioned allogeneic SCT, along with developments in reducing graft-vs-host disease by newer conditioning regimens, means that this balance is constantly evolving, and the use of SCT can be extended into older populations. At present, allogeneic SCT is considered a reasonable option in “high-risk” patients—those with fludarabine resistance, early relapse, or presence of p53 mutations.[7] It remains unclear whether the developments in immunochemotherapy will decrease the need for allogeneic SCT, and as to what the impact of biomarkers such as IgVH and cytogenetic abnormalities will be on the identification of patients at sufficiently high risk to warrant its use.

Conclusion: These and many other questions about the diagnosis and treatment of CLL remain unanswered in 2009. However, the rapid increase in our understanding of the pathogenesis of this disease, and the similarly rapid increase in the numbers of agents available to treat it, mean that these are interesting times.