

Chronic Lymphocytic Leukemia: New Choices for an Old Condition

Over the last decade, major advances in chronic lymphocytic leukemia (CLL) have helped us to understand the underlying pathogenesis leading to the discovery of new prognostic factors. Chemoimmunotherapy has emerged as the current standard of care in the treatment of young and fit patients with CLL. Despite very high response rates, chemoimmunotherapy is too toxic for the majority of elderly patients with CLL. The optimal management approach for patients who are older or for those who do not respond to these agents remains unclear. Patients who have relapsed after treatment or those who have high risk factors also present treatment challenges.

In this issue of *Cancer Control*, we review the more important clinical and therapeutic aspects of CLL. Monoclonal B-cell lymphocytosis (MBL) is an asymptomatic precursor condition for CLL. It is defined by the presence of small, aberrant B-cell clones in the peripheral blood, with a total B-cell count below the threshold for diagnosis of CLL ($< 5.0 \times 10^9$ cells/L). Drs Mowrey and Lanasa review this condition that occurs in approximately 4% to 5% of healthy adults. While most cases of CLL are preceded by MBL, only 1% to 2% of individuals with MBL annually progress to CLL that requires treatment. The absolute B-cell count is most strongly associated with progression, and patients with low-count MBL identified in population screening studies rarely develop CLL. The authors also review ongoing studies to not only better define the relationship between MBL and CLL, but also identify prognostic indicators that predict which patients will progress to CLL. In the near future, these studies will likely yield new insights into the biology of CLL, potentially identifying new therapeutic targets for this incurable disease.

It is well known that the clinical course of patients with CLL is heterogeneous, with some experiencing rapid disease progression and others surviving for decades without requiring treatment. Classically, the Rai and Binet clinical staging systems are being used to define disease extent and predict survival. In the next article, Drs Sagatys and Zhang describe the novel biological and cytogenetic features that are now used routinely in many centers to predict overall prognosis and time to therapy at the time of diagnosis. Current prognostic factors are now directly or indirectly influencing the management of patients with CLL and help to predict treatment-free and overall survival.

Historically, alkylator-based therapy has been used to treat patients with CLL. More recently, the use of mono-

clonal antibodies in combination with chemotherapy has been shown to prolong both progression-free survival and overall survival. This modality is now the preferred front-line therapy for young and fit patients with CLL. In this issue, Dr Desai and I discuss this topic in depth. While more aggressive management may be warranted for certain populations, each patient's comorbidities and performance status must be weighed against the benefits, availability, cost, treatment goals, and incidence of adverse effects associated with each therapy. The ultimate therapeutic goals of prolonged survival and improved quality of life will be validated only by ongoing clinical and laboratory research and by continual enrollment of patients in clinical trials.

Although recent advances in first-line therapy of CLL have prolonged the duration of first remission, patients eventually experience disease progression, with limited therapeutic options. Dr Veliz and I discuss the treatment options for patients with relapsed or refractory CLL including those with 17p deletion, TP53 mutation, and fludarabine-refractory CLL. While newer drugs and combination therapies have shown promise as treatment options for CLL, additional studies are needed to determine the immunosuppression, toxicities, and infections associated with their use.

In the same setting, the current role of immunomodulatory drugs (IMiDs) and active immune therapy as treatment options for this select group is reviewed by Dr Carballido and colleagues in the next article. The rationale of using IMiDs is discussed from the perspective of lenalidomide. As a single agent, lenalidomide offers a significant overall response rate in patients with relapsed/refractory disease as well as in treatment-naive patients. Ongoing clinical trials of this drug in combination with other agents have shown encouraging results.

Finally, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only known treatment modality that currently offers a potential cure to patients with CLL. Drs Kharfan-Dabaja and Bazarbachi discuss the published data of reduced-intensity conditioning (RIC) allo-HCT in patients with CLL. RIC allo-HCT has improved the transplant-associated morbidity and mortality of the procedure and has consequently broadened applicability of allo-HCT to patients with CLL who are generally of more advanced age (> 60 years) and who often suffer from associated comorbidities.

Our improved understanding of the biology of CLL has resulted in an explosion of novel agents over the

last decade. Chemoimmunotherapy has had a dramatic impact on the outcome of fit patients with CLL. It has improved CR rates by eradicating minimal residual disease and has resulted in improved survival. Current guidelines are also recommending different therapeutic interventions in patients with specific cytogenetic abnormalities. However, since not all patients can tolerate aggressive chemoimmunotherapy regimens and patients continue to relapse, new drugs are needed for the majority of these patient populations. The exciting display of ongoing clinical trials and investigational drugs, many of which have a novel mechanism of action, will likely transform the CLL scenario in the coming years. These new drugs, used alone or in combination with monoclonal antibodies, will allow less toxic regimens for more patients and will likely transform this leukemia into a truly chronic condition and maybe even open a door to a cure.

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