PROCEEDINGS ARTICLE

Chronic lymphocytic leukemia: treatment of relapse

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Despite significant advances in the frontline treatment of chronic lymphocytic leukemia (CLL), patients eventually experience disease progression. Treatment selection of relapsed disease depends upon a variety of factors, including patient age, performance status, duration of response to initial therapy, type of prior therapy, disease-related manifestations and genetic abnormalities within the CLL cells. This presentation offers synthetic overview of the options in this field.

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Chronic lymphocytic leukemia (CLL), the most common form of adult leukemia, is characterized by a monoclonal proliferation of mature-appearing lymphocytes with distinctive phenotypic features. CLL is a heterogeneous disease with variable prognosis; some patients have an indolent course and a virtually normal life expectancy, whereas others have aggressive disease and a short survival period.¹ A number of prognostic factors (including genomic abnormalities, such as 17p and 11q deletions, unmutated *IgVH* gene, expression of CD38 and ZAP70, and high β_2 -microglobulin levels) have been identified and correlated with resistance to chemotherapy and more aggressive clinical behavior.^{2,3} During the past decade, the treatment approach to CLL has markedly changed from palliative to potentially curative.

Despite these significant advances, patients eventually experience disease progression, after which there are limited therapeutic options available.⁴ In general, patients with asymptomatic relapsed disease should be followed up expectantly, and indications for reinitiation of treatment should follow the same National Cancer Institute and International Workshop on Chronic Lymphocytic Leukemia criteria as in previously untreated patients.^{5,6} Treatment selection of relapsed disease depends upon a variety of factors, including patient age, performance status, duration of response to initial therapy, type of prior therapy, disease-related manifestations and genetic abnormalities within the CLL cells. Treatment decisions are more challenging in patients with therapy-refractory disease or with deletion 17p/TP53 mutation. It is important to mention that fluorescence *in situ* hybridization should be performed in all patients to determine cytogenetic abnormalities before making treatment decisions, as many patients with relapsed CLL will often acquire high-risk chromosomal abnormalities, such as del11(11q12) and del17(17p13), which result in resistance to most conventional chemotherapies used in the treatment of CLL. Among patients with high-risk prognostic factors, a subgroup of ultra-high-risk CLL patients can be identified with a median survival less than 24 to 36 months at the treatment time point. On the basis of this definition, patients with the 17p deletion (5–8%), the TP53 mutation (4–5%) and fludarabine-refractory CLL (5%) belong to this group, as well as patients with suboptimal response to intense treatment. Fludarabine-refractory disease is defined as CLL that does not respond to fludarabine or that recurs within 6 months of treatment with a fludarabine-containing regimen. Resistance to

purine analogs is emerging as a major problem in the management of patients with CLL. Most of these patients have already been exposed to and have become refractory to alkylating agents. Response to fludarabine alone in relapsed CLL ranges from 45 to 65%, and the response rate is even lower in patients refractory to initial therapy (20%).⁷

As a disease of the elderly, treatment strategies in CLL should remain highly individualized. Patients who relapse after a disease-free period of over 1 year (or 2 years after chemoimmunotherapy) are considered to be fludarabine sensitive and may receive the same regimen used for initial treatment.⁸ Those who relapse within 6 months of completing initial fludarabine-containing regimen, or who progress during therapy, are considered to be fludarabine refractory. In addition, more effective regimens tend to be more toxic; therefore, it is important to assess the condition of the patient and define the goals of therapy before making treatment decisions. The goal of therapy may be different in older patients with multiple comorbidities, in whom palliation of symptoms may be more important, compared with fit or younger patients who can handle more intense regimens in a hope to maximize their likelihood of long-term survival with the ultimate goal in high-risk patients to undergo an allogeneic stem cell transplant. Options for refractory patients include alemtuzumab with or without rituximab (not for bulky lymphadenopathy), bendamustine with or without rituximab, high-dose corticosteroids with rituximab, ofatumumab and combination regimens. As CLL itself causes immune dysregulation, serious and life-threatening infections often result after using such immunosuppressive agents. Guidelines for the use of alemtuzumab include mandated weekly cytomegalovirus (CMV) PCR to check for the reactivation of CMV, cotrimoxazole prophylaxis to prevent *Pneumocystis jirovecii* pneumonia and acyclovir prophylaxis against herpes viruses.⁹ If CMV infection is noted, preemptive therapy should be initiated with ganciclovir or foscarnet, and treatment with alemtuzumab should be interrupted.⁹ Finally, the activity of novel targeted agents, although still in early stages of clinical investigation, has been promising and has shown potential to change the future treatment of CLL, for which allogeneic stem cell transplantation remains the only potentially curative therapy. Continued advances in the research of CLL and enrollment of patients in clinical trials will aid in the pursuit of a future cure for CLL.

CONFLICT OF INTEREST

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