

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Advances in the Use of Alemtuzumab in CLL

Stephan Stilgenbauer, MD
Associate Professor
Department of Haematology, Oncology,
Rheumatology, and Infectious Diseases
University of Ulm
Germany

H&O How does a clinician evaluate whether a patient is a good candidate to receive alemtuzumab?

SS B-cell chronic lymphocytic leukemia (CLL) is the most common leukemia, and it follows a highly variable clinical course. Alemtuzumab (Campath, Genzyme/Bayer), a humanized monoclonal antibody that binds to CD52, is one treatment option. The best candidates for treatment with alemtuzumab—and the drug's primary indication—are patients who are refractory to chemotherapy. In this subgroup, alemtuzumab has demonstrated remarkable clinical activity. Treatment has been trending toward earlier stages of disease, including to first-line treatment. In the first-line setting, alemtuzumab is likely most appropriate for consideration in high-risk patients. In CLL, risk can be defined clinically: patients who do not respond to chemotherapy have a very poor clinical prognosis and are candidates for novel therapies. Risk can also be defined biologically, by genetic markers such as chromosomal abnormalities or immunoglobulin mutation status.

H&O What are the response rates seen with alemtuzumab?

SS Alemtuzumab is approved by the US Food and Drug Administration as monotherapy, and remission rates in chemotherapy-refractory patients are between 30% and 40%, which is higher than the remission rates seen with other salvage chemotherapeutic regimens available. Response rates to single-agent alemtuzumab in the

first-line setting are in the range of 80–90%, indicating that alemtuzumab is likely the most active single agent available for patients with CLL. Dr. Peter Hillmen and colleagues recently published findings on the comparison of alemtuzumab to chlorambucil in the first-line setting. This trial was a randomized, two-arm study. The results have been quite encouraging, as alemtuzumab showed a higher remission rate and longer progression-free survival as compared to chlorambucil. A 42% reduction in risk of progression or death (hazard ratio=0.58; $P=.0001$) was reported for patients who received alemtuzumab. However, I do not think these results will cause a change in the way all patients are treated in the first-line setting. Biologically high-risk patients (eg, 17p deletion) are good candidates for treatment with alemtuzumab, based on these results and others showing that classic chemotherapeutic regimens are not as active in this subgroup.

Also under investigation are combinations of alemtuzumab and chemotherapy. For instance, researchers are combining it with fludarabine and cyclophosphamide; preliminary data from this research indicate that remission rates are higher than 90%. Researchers from The University of Texas M. D. Anderson Cancer Center are combining alemtuzumab with fludarabine, cyclophosphamide, and rituximab (Rituxan, Genentech/Biogen Idec), and this regimen has demonstrated activity in heavily pretreated and relapsed/refractory patients with CLL.

H&O What is the rationale for combining alemtuzumab with rituximab?

SS There is a rationale to combine alemtuzumab with rituximab because both are monoclonal antibodies that target different epitopes on CLL cells, CD52 in the case of alemtuzumab and CD20 in the case of rituximab. Therefore, the combination may have additive or even synergistic activity. Combining these antibodies with chemotherapy, which has a completely different mechanism of action, also has a strong rationale.

H&O How is alemtuzumab administered?

SS Alemtuzumab can be administered intravenously or subcutaneously. The approved route of administration is intravenous. However, alemtuzumab is given three times a week, requiring three infusions lasting 2–3 hours in the clinic or the in-patient ward. This schedule can thus be quite burdensome to the patient. Furthermore, the intravenous route has been shown, particularly at the beginning of treatment, to be associated with serious side effects, including fever, shakes, chills, rigors, and sometimes hypotension or bronchospasm. In comparison, the subcutaneous route has many advantages, including its short and simple administration, which can have less impact on a patient's quality of life. Side effects such as fever, shakes, chills, rigors, and hypotension occur much less frequently with subcutaneous administration. The overall tolerability and feasibility of the subcutaneous route is therefore superior. There has been no formal trial showing that subcutaneous administration is as effective as intravenous administration, but there are data from a single-arm noncomparative trial indicating that remission rates with subcutaneous administration are as good as those seen with intravenous administration. In many centers in Europe, subcutaneous administration is preferred. Although there are comparative trials ongoing, I believe many clinicians worldwide already are administering alemtuzumab subcutaneously in most patients.

H&O How is alemtuzumab used in the consolidation setting?

SS There have been several trials in the United States and Europe providing data on the use of alemtuzumab in the consolidation setting. Initial results were very promising with regard to efficacy, but some toxicity, particularly infections, was observed. This toxicity was likely due to the high doses of alemtuzumab that were given and a relatively short time interval after induction chemotherapy. At the 2007 annual meeting of the American Society of Hematology, Dr. Vicki A. Morrison and colleagues reported the rates of infectious complications seen in three trials of fludarabine-based regimens given to patients with previously untreated CLL; they found that the trials using fludarabine alone or fludarabine plus rituximab had significantly lower rates of infectious complications than the trial using fludarabine plus alemtuzumab. The researchers concluded that consolidation therapy with alemtuzumab following fludarabine increases the overall risk of serious infectious complications, especially cytomegalovirus; prophylactic antimicrobial therapy is thus recommended. Currently under investigation are lower doses for consolidation and longer rest periods after the initial chemotherapy.

One approach in the setting of stem-cell transplantation administers alemtuzumab in the conditioning regimen for the purpose of in vivo T-cell depletion. This approach results in less graft-versus-host disease, but in some trials it has also been associated with higher relapse rates. The other approach, which is completely different, is to use alemtuzumab first, to induce remission, then wait and submit the patient to transplantation after a few weeks or months. In this approach, there is no T-cell depletion, and if the patient, particularly one with high-risk disease, achieves remission, stem-cell transplantation can be used as consolidation therapy.

H&O What are the main avenues of research with alemtuzumab still open?

SS There are several avenues to further evaluate alemtuzumab. First, one of the prime interests is to evaluate the biologic background of alemtuzumab treatment. On the one hand, we are in need of insights into alemtuzumab's mechanism of action and the mechanisms of its lack of activity in some patients. On the other hand, we need to understand the biologics of high-risk patients, such as those with 17p deletions, who should be treated on clinical trials with alemtuzumab, possibly in combination with other agents that have been shown to work independently of p53. A second avenue of further development is combination therapies of alemtuzumab with chemotherapy (eg, fludarabine, cyclophosphamide, or both) or with other biologically active agents. A third, very promising but still underdeveloped avenue, is consolidation treatment. In this setting, alemtuzumab has been shown to have marked efficacy but also considerable toxicity at high doses. There is thus room for further evaluation of this agent as consolidation therapy.

Suggested Readings

- Faderl S, Coutré S, Byrd JC, et al. The evolving role of alemtuzumab in management of patients with CLL. *Leukemia*. 2005;19:2147-2152.
- Faderl S, Thomas DA, O'Brien S, et al. Experience with alemtuzumab plus rituximab in patients with relapsed and refractory lymphoid malignancies. *Blood*. 2003;101:3413-3415.
- Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. *J Clin Oncol*. 2007;25:5616-5623.
- Kay NE, Rai KR, O'Brien S. Chronic lymphocytic leukemia: current and emerging treatment approaches. *Clin Adv Hematol Oncol*. 2006;4(11 suppl 22):1-10.
- Kay NE, O'Brien SM, Pettitt AR, Stilgenbauer S. The role of prognostic factors in assessing 'high-risk' subgroups of patients with chronic lymphocytic leukemia. *Leukemia*. 2007;21:1885-1891.
- Morrison VA, Peterson BL, Rai KR, Byrd JC, Larson RA. Alemtuzumab increases serious infections in patients with previously untreated chronic lymphocytic leukemia (CLL) receiving fludarabine-based therapy: a comparative analysis of 3 Cancer and Leukemia Group B studies (CALGB 9011, 9712, 19901). *Blood*. 2007;110(11): Abstract 756.