ADVANCES IN LLM

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

Section Editor: Susan O'Brien, MD

Blinatumomab: A Novel Agent to Treat Minimal Residual Disease in Patients With Acute Lymphoblastic Leukemia

Anjali S. Advani, MD
Director, Inpatient Leukemia Unit
Cleveland Clinic Lerner College of Medicine
Department of Hematologic Oncology and Blood Disorders
The Cleveland Clinic
Cleveland, Ohio

H&O What is minimal residual disease (MRD) in acute lymphoblastic leukemia (ALL)?

AA MRD is defined as evidence of disease at the molecular level. In patients with ALL, monitoring of MRD can accurately assess early treatment response and detect relapse. Flow cytometric detection of abnormal immunophenotypes, polymerase chain reaction (PCR) amplification of antigen-receptor genes, and PCR amplification of fusion transcripts are methods with which to analyze MRD. Results of MRD studies can be used to better determine the duration and intensity of treatment, and also to estimate an optimal time frame for hematopoietic stem cell transplantation. Utilizing MRD assays in clinical studies remains somewhat problematic, because determining the best time to study MRD and the levels of MRD that will trigger changes in treatment intensity have yet to be established. Nevertheless, identifying new leukemia markers and continuing to refine these assays should further enable routine monitoring of MRD and shed light on the cellular and biologic features of leukemic cells that resist chemotherapy in vivo.

H&O What is the prognosis of ALL patients with MRD, and what are the current treatment options?

AA The prognosis of patients with MRD following chemotherapy is poor. Unfortunately, no standard treatment algorithm for these patients currently exists. Consideration of allogeneic hematopoietic stem cell transplant remains a reasonable option for these patients; however, whether this approach improves outcome has not been established. The goal of novel therapies has been to eradicate MRD. Treatment with blinatumomab (MT103, Micromet) represents a promising option for these patients.

H&O What is blinatumomab, and what is its mode of action?

AA Blinatumomab is a bispecific T-cell engaging (BiTE) antibody. One arm of the drug has an anti-CD3 antibody, which attaches to T-cells. The other arm has an anti-CD19 antibody, which attaches to cells—such as B lymphoblasts—expressing CD19. Attachment of blinatumomab to the B lymphoblast leads to activation and proliferation of cytotoxic T cells, redirected cell lysis, and apoptosis of the leukemia cell.

H&O Who is the ideal candidate for blinatumomab treatment?

AA Currently, the best data for blinatumomab treatment are in patients with B-cell ALL expressing CD19 and evidence of MRD. However, the drug has potential efficacy in any disease expressing CD19 (ie, B-cell lymphoproliferative disorders). Blinatumomab is likely to have the best activity as a single agent in the setting of MRD. However, future studies are expected to evaluate the drug in combination with chemotherapy for patients with newly

diagnosed or relapsed/refractory disease. Because blinatumomab is well tolerated, it also represents a promising treatment for elderly patients or those patients who are not good candidates for chemotherapy.

H&O What research has demonstrated blinatumomab's efficacy in ALL patients with MRD?

AA The German Multicenter Study Group for Adult Lymphoblastic Leukemia conducted a phase II study of blinatumomab in patients with precursor B-cell ALL and positive MRD. A total of 20 patients with persistent or relapsed MRD after consolidation I of upfront therapy received 1 cycle of treatment continuously by intravenous infusion for 4 weeks. Subsequent consolidation therapy could be administered on a 2-weeks-on, 2-weeks-off schedule. The primary endpoint of the study was the elimination of these leukemia cells to an undetectable level in at least 22% of patients. Within the first treatment cycle, 80% of patients had no evidence of MRD. At a median follow-up of 405 days, the probability for relapse-free survival was 78%. Fever, headache, and chills were the most common adverse events of any grade, and were completely reversible. The most common grade 3/4 adverse event was lymphopenia, which was also reversible. Overall, blinatumomab was well tolerated, and responses were rapid; these results are encouraging.

The phase II European pivotal trial known as BLAST (Blinatumomab Adult ALL MRD Study of T-cell Engagement) plans to enroll up to 130 adult patients who have B-precursor ALL with MRD after treatment with frontline chemotherapy. Patients will receive blinatumomab 15 µg/m² daily for 28 days, followed by 2 weeks off therapy. There will be up to four 6-week treatment cycles. The primary endpoint of this study is molecular complete response. Secondary endpoints include relapse-free survival rate at 18 months (for nontransplant patients), and the mortality rate within 100 days after stem cell transplant. Enrollment is expected to be completed by 2012.

H&O In what other settings is blinatumomab showing promise?

AA Blinatumomab targets CD19, and thus has excellent potential in the treatment of other lymphoproliferative disorders expressing CD19. Updated phase I results from a study of blinatumomab in patients with relapsed non-Hodgkin lymphoma (NHL) were presented in 2010 at the Annual Congress of the European Hematology Association (EHA) in Barcelona, Spain. Blinatumomab had an impressive objective response rate in heavily pretreated NHL patients.

H&O What role do you think novel agents like blinatumomab will play in the future?

AA Blinatumomab is likely to play a role in the treatment of newly diagnosed and relapsed/refractory ALL in combination with chemotherapy. Because the drug works through a different mechanism of action than chemotherapy, it is likely to help eradicate those cells that are resistant to chemotherapy and lead to relapse. The hope is that such an approach will improve the outcomes of patients.

Suggested Readings

Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. *J Clin Oncol*. 2011;29:2493-2498.

Topp MS, Zugmaier G, Gokbuget N, et al. Report of a phase II trial of single-agent BiTE antibody blinatumomab in patients with minimal residual disease (MRD) positive B-precursor acute lymphoblastic leukemia (ALL). *Blood* (ASH Annual Meeting Abstracts). 2009;114:Abstract 840.

ClinicalTrials.gov. An open-label, multi-center phase I study to investigate the tolerability and safety of a continuous infusion of the bispecific T-cell engager MT103 in patients with relapsed non-Hodgkin's lymphoma (NHL). Identifier: NCT00274742. http://clinicaltrials.gov/ct2/show/NCT00274742.

ClinicalTrials.gov. Confirmatory phase II study of blinatumomab (MT103) in patients with minimal residual disease of B-precursor ALL (BLAST). Identifier: NCT01207388. http://clinicaltrials.gov/ct2/show/NCT01207388.