

A Closer Look at Blinatumomab



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On March 29, 2018, blinatumomab (Blincyto, Amgen) received an accelerated expanded approval for the treatment of adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia (ALL) who are in first or second complete remission (CR) and have minimal residual disease (MRD). Blinatumomab was first approved for use in adult patients (in December 2014) and later in pediatric patients (in September 2016) with relapsed or refractory Philadelphia chromosome (Ph)-negative B-cell precursor ALL; the approval was expanded in July 2017 to include patients with Ph-positive disease. The agent is a bispecific CD19-directed CD3 T-cell engager.

H&O How long have you been using blinatumomab in your practice?

RM We started using blinatumomab in the spring of 2015, so we had some early experience with it. We began using it more often in 2017 with the broader indication, and we will be using it in still more patients now that the indication has been expanded again.

H&O What is the significance of this new indication in MRD?

RM It has long been recognized that MRD in patients with ALL eventually increases the risk for overt hematologic relapse. We also know that after intensive chemotherapy with any of the standard regimens, anywhere from one-third to one-half of patients with ALL are still MRD-positive by either reverse transcription polymerase chain reaction (RT-PCR) or flow cytometry. Finally, we know that allogeneic transplant improves outcomes compared with chemotherapy in patients who have ALL and

remain MRD-positive. The clinical outcomes of transplant are improved if the patients are MRD-negative. This indication gives us a new option for patients who are in hematologic CR after treatment but still have MRD.

H&O Could you talk about the design and results of the trial that served as the basis for this new indication?

RM The BLAST trial (Confirmatory Phase II Study of Blinatumomab in Patients With Minimal Residual Disease of B-Precursor Acute Lymphoblastic Leukemia; NCT01207388), a single-arm phase 2 study led by Gökbuğut and colleagues, included patients from Europe and Russia. The study enrolled 116 patients who were in a hematologic CR but still had MRD. Of note, the threshold for MRD positivity was higher in this than in past studies—it was defined as 10^{-3} or higher. All patients in the study received at least 3 rounds of intensive chemotherapy and were followed for at least 18 months.

The primary endpoint was complete MRD response, which was defined as undetectable disease after a single cycle of blinatumomab with an assay having a sensitivity of 10^{-4} or better. Secondary endpoints included hematologic relapse-free survival (RFS) at 18 months, overall survival (OS), and duration of hematologic remission. Patients were treated with up to 4 cycles of blinatumomab; each cycle lasted 4 weeks and was followed by a 2-week break before the next cycle. Patients could receive a transplant any time after cycle 1 at the discretion of the treating physician. MRD analysis was performed at a central laboratory by either RT-PCR or flow cytometry.

The researchers found that 88 of 113 evaluable patients (78%) were MRD-negative after cycle 1. After cycle 2, an additional 2 patients were MRD-negative. Of interest, MRD negativity was not achieved in any patient after cycle 3 or 4—all responses occurred within 2 cycles of blinatumomab. The RFS rate at 18 months was 54%, and the median RFS was 18.9 months with a median

follow-up of 29.9 months. The median RFS was 24.6 months for those who were in first CR and 11.0 months for those who were in a later CR.

Not surprisingly, patients who had chemotherapy-sensitive disease fared better than those who did not. Of the 110 patients with Ph-negative ALL in hematologic remission who were analyzed, 48 remained in CR, 38 experienced relapse, and 24 died in CR, 20 of whom had received an allogeneic transplant. The median duration of hematologic CR was not reached, and the median OS was 36.5 months. Landmark analysis showed the median RFS to be 23.6 months in patients with MRD negativity and 5.7 months in those without MRD negativity after cycle 1. The median OS was 38.9 months in patients with MRD negativity and 12.5 months in patients without MRD negativity after cycle 1.

Regarding transplant, 67% of the patients underwent an allogeneic transplant. Of these patients, 49% remained in CR, whereas 25% of those who did not undergo transplant or receive further chemotherapy remained in CR.

H&O What is the take-away message from the study?

RM The take-away message is that blinatumomab is very effective at converting patients from MRD-positive to MRD-negative status. Not surprisingly, those who respond to blinatumomab do much better clinically than those who do not. The study also outlines 2 potential roles for blinatumomab. First, it helps us get patients into as deep a remission as possible before they undergo a transplant. Second, it helps us improve the outcomes of patients who are not eligible for transplant, either because they are too sick or because they do not have a donor.

H&O What are the most common adverse events seen with blinatumomab?

RM In the BLAST study, the most common grade 3/4 adverse events included fever (8% of patients), headache (3%), neutropenia (16%), anemia (4%), and transaminitis (5%). A total of 3% of patients had grade 1, 2, or 3 cytokine release syndrome (CRS). Neurotoxicity occurred in 53% of patients, including grade 3/4 neurotoxicity in 13% of patients—the more serious cases were less common. Grade 3/4 neurotoxicities included tremor (5% of patients), aphasia (1%), dizziness (1%), and encephalopathy (5%). Seizure occurred in 2% of patients.

In the randomized trial by Kantarjian and colleagues, which was the basis for the initial approval, the patients tended to have a higher disease burden, but the adverse events were similar. Grade 3/4 neutropenia was reported

in 38% of patients, infection in 34%, transaminitis in 12.7%, neurologic events in 9.4%, and CRS in 4.9%.

H&O Are you finding similar side effects in your practice?

RM Yes, we are. Many of the serious side effects, such as CRS and neurotoxicity, were rare in these larger studies and we have not yet seen them in our practice, although we may over time. In any case, oncologists have become comfortable over the years and decades with managing the side effects of cytotoxic chemotherapy.

Blinatumomab, chimeric antigen receptor (CAR) T cells, and other immunotherapies create a new type of side effect profile, so it is important that our hematology and oncology colleagues and others be able to recognize these toxicities when they occur. We are educating colleagues in critical care, neurology, and emergency medicine to know what to look for and when to call for assistance.

H&O What is your advice regarding preventing or dealing with CRS?

RM The symptoms of CRS include fever, headache, nausea, weakness, hypotension, and transaminitis. Disseminated intravascular coagulation, capillary leak syndrome, and macrophage activation syndrome may also develop.

Blinatumomab can be given in both overt relapse and MRD, so in our practice we first treat patients with multiagent chemotherapy whenever possible to reduce the amount of disease before we use a drug like blinatumomab. That is a good way to reduce the risk for CRS because the risk is higher when the tumor burden is larger.

And of course, oncologists should follow the drug label instructions, which state that patients who are starting therapy should be hospitalized for close observation during the first 9 days of cycle 1 and the first 2 days of any subsequent cycles. If drug administration is interrupted for more than 4 hours in the outpatient setting because of toxicities or technical factors, the patient should be readmitted for close observation while treatment is resumed.

Dexamethasone premedication is also required, with higher doses of dexamethasone given to patients with a larger tumor burden (>50% blasts, or blast count >15,000/mL).

If CRS occurs, the blinatumomab infusion should be discontinued and corticosteroids administered. Close observation and appropriate supportive care of the patient are necessary, and collaboration with the critical care team is essential. In severe cases, use of the interleukin 6 antibody tocilizumab (Actemra, Genentech) may be considered.

An important point is that there is no relationship between the development of CRS and response (or lack of response) to blinatumomab. The development of CRS does not mean that the drug is working or not working; we still must follow the response as we normally do.

H&O What is your advice regarding preventing or dealing with neurotoxicity?

RM As many as 50% of patients experience neurotoxicity with blinatumomab, but most of the side effects are not serious. Serious neurologic events with blinatumomab are rare, with an incidence of 15% or less. When serious neurologic events occur, such as encephalopathy, seizures, speech difficulties, and lethargy, the infusion should be discontinued and dexamethasone administered. A neurologic consult is often necessary as well.

H&O How is blinatumomab administered?

RM Blinatumomab is given as a continuous infusion over the 28 days of each cycle. This is unusual in oncology, so it is important to work with experienced pharmacists and home health agencies. For example, the person administering the infusion needs to know that the infusion line should never be flushed because flushing the line can unintentionally cause an overdose. Experienced centers with 24/7 medical and nursing support are required so that patients can immediately report any side effects and be referred to the emergency department if necessary.

The infusion bag used to require changing every 2 to 3 days, but now the bag can be changed after 7 days. This makes the patient's travel burden somewhat easier.

H&O What else should oncologists know about blinatumomab?

RM The use of blinatumomab needs to be considered thoughtfully as part of a broader strategy for treating a patient. If a patient receives blinatumomab, what is the next step? Will it be allogeneic transplant or CAR T-cell therapy, or is the agent being given with curative intent? Rather than simply deciding to try the medication and see how it works, oncologists should map out these steps beforehand and counsel patients appropriately.

H&O Are any trials on the horizon that might create new indications for the drug?

RM There are 2 ongoing studies with blinatumomab that are especially important and relevant—E1910 (Combination Chemotherapy With or Without Blinatumomab in Treating Patients With Newly Diagnosed BCR-ABL-

Negative B Lineage Acute Lymphoblastic Leukemia; NCT02003222) from the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network (ECOG-ACRIN) and AALL1331 (Blinatumomab in Treating Younger Patients With Relapsed B-cell Acute Lymphoblastic Leukemia; NCT02101853) from the Children's Oncology Group.

E1910 is an ongoing up-front phase 3 randomized trial of multiagent chemotherapy with or without blinatumomab. Its primary endpoint is OS with blinatumomab plus chemotherapy vs OS with chemotherapy alone in 3 groups: (1) patients who are MRD-positive after initial chemotherapy; (2) patients who are MRD-negative after initial chemotherapy; and (3) all patients regardless of MRD status.

AALL1331 is a phase 3 study of patients 1 to 30 years of age with relapsed B-cell ALL. Low-risk patients are randomly assigned to chemotherapy with or without blinatumomab, and intermediate- and high-risk patients are randomly assigned to blinatumomab or chemotherapy followed by allogeneic transplant.

The accelerated US Food and Drug Administration approval decision took into account that these 2 trials are ongoing, and I imagine the results will be considered when the full approval decision is made. In addition, if the E1910 trial shows a benefit to patients regardless of MRD status, blinatumomab may be considered for approval as part of an up-front treatment strategy.

Disclosure

Dr Mattison has served on the advisory boards of Pfizer and Shire and is a co-chair of the ECOG-ACRIN E1910 study.

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