

ADVANCES IN LLM

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Is Blinatumomab Now Standard of Care Consolidation for Patients With ALL?



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H&O What is blinatumomab and how does it work in treating acute lymphocytic leukemia (ALL)?

SL Blinatumomab (Blincyto, Amgen), which is classified as a bispecific antibody, harnesses the power of a patient's own immune system to fight leukemia. It accomplishes this by having 2 distinct binding sites. One end of the antibody attaches to the patient's T cells, and the other end attaches to a protein called CD19 that is present on lymphoblastic leukemia cells. This mechanism allows blinatumomab to engage and mobilize the patient's own T cells to fight the leukemia cells expressing CD19.

H&O What was the basis for the US Food and Drug Administration (FDA)'s approval of blinatumomab for the treatment of ALL?

SL Blinatumomab was approved initially for the treatment of patients with relapsed disease in ALL. Following an initial efficacy trial, a randomized trial was performed to compare standard chemotherapy with blinatumomab in patients with relapsed ALL. The results demonstrated that blinatumomab was significantly more effective than chemotherapy for patients with relapsed ALL. Patients in the blinatumomab arm vs the standard chemotherapy arm were more likely to achieve remission and had fewer side effects. Blinatumomab was initially approved only for patients with relapsed disease. Subsequently, results from the BLAST study extended blinatumomab's approval to

patients who had achieved a remission by standard tests but who had evidence of measurable residual disease (MRD), meaning that no leukemia can be seen under the microscope but sensitive testing can still find 1 in 1000 to 1 in 10,000 cells that have characteristics of the leukemia cells. Blinatumomab is currently only approved for patients with leukemia that is relapsed or where there is evidence of MRD.

H&O Before the approval of blinatumomab, what was the previous standard of care for patients with ALL?

SL Before the approval of blinatumomab, the previous standard of care for patients with ALL was chemotherapy. For those who are at high risk of relapse (which traditionally includes most adults with this disease), the previous standard of care was allogeneic bone marrow transplant for those well enough to receive one. For patients with disease that has relapsed after initial therapy, additional chemotherapy was typically used, but with low rates of long-term success.

H&O How does blinatumomab consolidation therapy benefit patients with ALL, particularly those without MRD?

SL As mentioned above, blinatumomab was initially approved for patients with relapsed disease. The initial standard therapy for patients with newly diagnosed ALL

is a combination of different chemotherapy drugs. Typically, patients undergo what is called induction therapy to achieve a remission, followed by several additional months of intensive chemotherapy and then maintenance therapy for about 2 years or a transplant for those who are likely to relapse even if they receive all this chemotherapy. Traditionally, this treatment approach applies to patients of every age group. Somewhere along the way, a decision about whether or not a patient needs a transplant is made during their first remission. Because transplants are associated with many complications, we only want to do them in patients who are likely to do poorly without a transplant.

The problem is that although 80% to 85% of patients will achieve remission, particularly in adults, a large proportion of them experience relapse if they do not get a transplant. The goal of treatment is not only to achieve remission but also to prevent disease recurrence, which is more difficult to manage and requires more aggressive treatment.

We used to say that anyone older than 35 or with certain disease features at the time of presentation were at high risk of disease recurrence and should be considered for a transplant. We have developed the capability of doing more sensitive testing of patients in remission in the last decade or so, and we can identify patients who are in a remission by traditional methods but have evidence of MRD by these newer tests. We now say that most patients who do not have evidence of MRD once they are in remission do not need to have a transplant in first remission.

The question that we posed in our trial was whether adding a drug that has been approved for relapsed disease to the initial standard therapy would decrease the likelihood of relapse in patients. Would incorporating blinatumomab into the initial therapy, rather than waiting for disease relapse, result in more patients staying in remission? The E1910 trial was led by the ECOG-ACRIN Cancer Research Group, which is supported by the National Cancer Institute (NCI), and focused on consolidation treatment for patients in remission. We included patients aged 30 to 70 in the trial and gave them the standard therapy I previously discussed. However, half the patients received 4 months of blinatumomab in addition to standard therapy. The aim was to determine if the addition of 4 months of blinatumomab decreased the risk of disease recurrence and improved survival, particularly in those patients who were MRD-negative after they received the initial 2 months of chemotherapy treatment.

The primary question of the study was what happens when blinatumomab is administered to patients who are MRD-negative. These are patients that have already received chemotherapy and are in remission both by standard evaluation under the microscope and by doing a more sensitive test that can identify a cell with characteristics of

a leukemia cell hiding in 10,000 normal cells. If no MRD was found, we sought to evaluate the efficacy of adding blinatumomab.

Blinatumomab's approval is limited to patients with MRD-positive disease or those who have relapsed. However, we are optimistic that the FDA will grant approval for blinatumomab's use in MRD-negative disease.

H&O Can you describe the outcomes of the trial?

SL The E1910 trial showed that adding blinatumomab to standard chemotherapy improves survival in newly diagnosed ALL patients who are in an MRD-negative remission after initial chemotherapy. A total of 700 patients between the ages of 30 and 70 were initially screened for the trial, out of whom 488 were enrolled. The average age was approximately 50. After the first 2.5 months of treatment, 224 patients who were in an MRD-negative remission were randomized to receive either standard therapy alone or standard therapy plus blinatumomab. In all, 112 MRD-negative patients received blinatumomab and the remaining 112 did not. After more than 2 years of follow-up, 56 of the 224 patients had died; 39 in the standard therapy arm and 17 in the blinatumomab arm, with most deaths happening because of relapse of the leukemia. This means there were 22 fewer deaths among the 112 patients who received blinatumomab. It is worth noting that if a patient does not relapse in the first 2 years, it is unlikely that they will. Relapses tend to occur early over the course of treatment. We were able to save an additional 22 lives through this trial, and it is a huge source of pride for all of us who were involved in the design and conduct of the study. We are so grateful to the patients who participated and their families, and all the others who helped to make this trial a success.

H&O With the widespread adoption of blinatumomab consolidation therapy, do you see

any changes in the management of patients with ALL, and if so, what are they?

SL Blinatumomab is not yet approved for the treatment of MRD-negative disease. Its approval is limited to patients with MRD-positive disease or those who have relapsed. However, we are optimistic that the FDA will grant approval for blinatumomab's use in MRD-negative disease as well. In my own practice, many of us have already started using it for many of these patients, as it offers the potential for improved survival, reduced relapse rates, and a decreased need for transplantation.

H&O What are the side effects or potential complications associated with blinatumomab, and how are these addressed in clinical practice?

SL The major complications associated with blinatumomab occur during its administration. Blinatumomab is given continuously for 24 hours a day for 4 weeks in a row for each cycle, requiring patients to carry the infusion device with them. In the first week, individuals may experience reactions that can affect their breathing and neurologic system, so we monitor them closely in the hospital. However, these reactions subside once the drug is discontinued, eliminating the drug quickly from the system. Sometimes the drug makes the blood counts drop; if so, infusion is halted to allow for recovery. Overall, when given to patients in remission, the drug is well tolerated.

H&O Are there any subgroups of patients who may benefit more from other therapies besides blinatumomab?

SL That is a valid question, and the answer is unknown. Out of 448 patients who initially started treatment on the study, only 224 were randomized after 2.5 months. This occurred because they did not achieve a remission, they had complications, or they were not MRD-negative at that time. Furthermore, despite treatment with blinatumomab, some patients relapsed and/or died. We need to determine whether certain characteristics or patient factors contribute to these outcomes, in order to think about treatment options that could optimize outcomes. This may involve exploring the potential benefits of earlier blinatumomab administration or chimeric antigen receptor T-cell therapy for patients in first remission.

H&O Is there anything else you would like to add?

SL E1910 was an intergroup trial, so even though it was

led by ECOG-ACRIN, all NCI-sponsored clinical trial groups participated. This ensured broad participation from many different sites within the country, including both academic and nonacademic medical centers. Given the relative rarity of this disease, conducting a randomized clinical trial is crucial to answer these questions, and is only possible through the cooperative group mechanism.

The cooperative group mechanism is not sponsored by the drug companies. This approach is essential to conduct a truly unbiased trial. It allows us to ask the questions that are important to patients and the medical community rather than focusing solely on the interests of the drug company. Although the drug company is happy with the positive outcome of the trial, the benefit to the drug company was not a primary motivator behind the research question. We pursued this study to gain insight that could possibly improve leukemia treatment and benefit patients in the medical field as a whole.

Disclosures

Dr Luger has received research funding from Onconova, Celgene, Biosight, Hoffman LaRoche, and Kura; and has received honoraria from Marker Therapeutics, AbbVie, Amgen, Bristol Myers Squibb, Pluristem, Syros, and Agios.

Suggested Readings

Burt R, Warcel D, Fielding AK. Blinatumomab, a bispecific B-cell and T-cell engaging antibody, in the treatment of B-cell malignancies. *Hum Vaccin Immunother.* 2019;15(3):594-602.

FDA expands approval of Blincyto for treatment of a type of leukemia in patients who have a certain risk factor for relapse [press release]. <https://www.fda.gov/news-events/press-announcements/fda-expands-approval-blinicyto-treatment-type-leukemia-patients-who-have-certain-risk-factor-relapse>. Updated March 29, 2018. Accessed May 18, 2023.

FDA granted accelerated approval to blinatumomab (Blinicyto, Amgen Inc.) for the treatment of adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia [press release]. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-granted-accelerated-approval-blinatumomab-blinicyto-amgen-inc-treatment-adult-and-pediatric>. Updated March 29, 2018. Accessed May 18, 2023.

Gökbuğet N, Dombret H, Bonifacio M, et al. Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia. *Blood.* 2018;131(14):1522-1531.

Gökbuğet N, Zugmaier G, Dombret H, et al. Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. *Leuk Lymphoma.* 2020;61(11):2665-2673.

Litzow MR, Sun Z, Paietta E, et al. Consolidation therapy with blinatumomab improves overall survival in newly diagnosed adult patients with B-lineage acute lymphoblastic leukemia in measurable residual disease negative remission: results from the ECOG-ACRIN E1910 randomized phase III National Cooperative Clinical Trials Network trial [ASH abstract LBA1]. *Blood.* 2022;140(2)(suppl).

Rowe JM, Buck G, Burnett AK, et al; ECOG; MRC/NCRI Adult Leukemia Working Party. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. *Blood.* 2005;106(12):3760-3767.

Varadarajan I, Pierce E, Scheuing L, Morris A, El Chaer F, Keng M. Post-hematopoietic cell transplantation relapsed acute lymphoblastic leukemia: current challenges and future directions. *OncoTargets Ther.* 2023;16:1-16.