Blinatumomab for hard-to-treat form of acute lymphoblastic leukemia

The US Food and Drug Administration (FDA) has granted accelerated approval to blinatumomab for the treatment of adult patients with relapsed/refractory Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (BCP-ALL).[1] Blinatumomab is the first of a novel class of antibodies to receive regulatory approval; a bispecific antibody targeting both CD19, expressed on the surface of B cells, and CD3, on cytotoxic T cells. The approval was based on the findings of a single-arm, multicenter, open-label study in patients at high-risk of poor outcome, which showed a significant improvement of blinatumomab over other available therapies in this setting.[2]

The 189 patients enrolled in the study were aged 18 years or older; were primary refractory after induction chemotherapy; had relapsed within 12 months of first remission, relapsed within 12 months of allo-hematopoietic stem-cell transplantation (allo-HSCT), or were nonresponsive or relapsed after first salvage therapy or beyond; had at least 10% bone marrow blasts; and an Eastern Cooperative Oncology Group Performance Status of ≤2. Patients with active ALL in the central nervous system and clinically relevant CNS pathology, ALL in the testes, Philadelphia chromosome-positive ALL, autoimmune disease, chronic infection, acute graft versus host disease (GVHD), and those who previously received blinatumomab, were among those excluded.

To reduce the risk of severe cytokine release syndrome (CRS), patients with >50% bone marrow blasts, ≥15,000 peripheral blood blasts/μL, or elevated lactase dehydrogenase received pretreatment with dexamethasone (10-24 mg/m^2 a day) for up to 5 days, followed by repeat bone marrow assessment. All patients received pretreatm ent with dexamethasone 20 mg within 1 h before blinatumomab treatment and before each dose step, to reduce the risk of infusion reactions. Blinatumomab was administered as a continuous intravenous infusion with a portable pump at 9 μg/day for days 1-7, stepping up to 28 μg/day for days 8-28 for the first cycle, followed by a dose of 28 μg/day for subsequent cycles, on a 4 weeks on, 2 weeks off schedule. Patients who achieved complete remission (CR) or partial hematological recovery (CRh) in the first 2 cycles could receive up to 3 additional cycles and patients could receive allo-HSCT at the investigator's discretion at any time.

Disease was assessed by bone marrow examination using bone marrow aspirates and core biopsies performed at baseline, the end of each cycle, and at activity follow-up, and by bone marrow blast counts, with minimal residual disease (MRD) negativity defined as <10^{-4} detectable blasts. The primary endpoint was CR (≤5% bone marrow blasts, >100,000 platelets/μL, absolute neutrophil count

What's new, what's important

Refractory adult acute lymphoblastic leukemia (ALL) has extremely poor prognosis. At this point, therapeutic options for these patients are very limited. The US Food and Drug Administration has granted accelerated approval to blinatumomab for the treatment of adult patients with relapsed/refractory Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (BCP-ALL). Blinatumomab is a bispecific antibody targeting both CD19, expressed on the surface of B cells, and CD3, on cytotoxic T cells. It binds to both the pathogenic target cell and T-cells and can recruit and activate T-cells to destroy the target cell without the need for a costimulatory signal.

The approved dose is for blinatumomab via continuous intravenous infusion at a constant flow-rate with an infusion pump using a step-dose of 9 μg/day on days 1-7 of the first cycle, followed by 28 μg/ day on days 8-28 of Cycle 1 and days 1-28 of subsequent cycles for 4 weeks, followed by a 2-week treatment-free period. Patients should receive premedication with dexamethasone 20 mg, 1 h before the first dose, before the step-dose, or when restarting infusion after ≥4 hours. Patients who achieve complete remission or partial hematological recovery in the first 2 cycles could receive up to 3 additional cycles, and patients could receive allo-hematopoietic stem-cell transplantation at the investigator's discretion at any time.

Grade 3 neurologic events were recorded in 11% of patients and; grade 4 neurologic events occurred in 2%, all resolving; and there were no fatal neurologic adverse events. The FDA has placed a black box warning for cytokine release syndrome (grade 3 at a rate of 2%) and for neurological events (grade 3, 11%; grade 4, 2%).

In a value-based environment, it is important to note that although blinatumomab is an important advance in the treatment of this highly refractory patient group, it is one of the most expensive cancer therapies available, costing close to $200,000 for a course of treatment.

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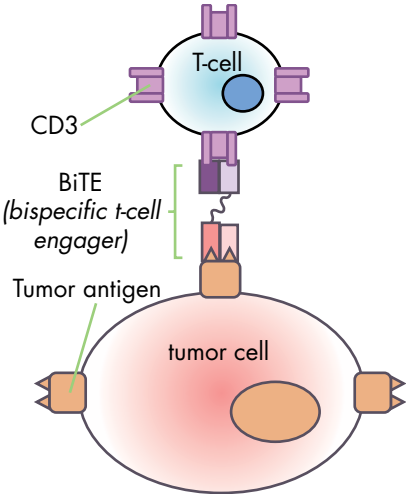
Mechanism of action: blinatumomab

Linking immune cells to cancer cells

B-cell precursor acute lymphoblastic leukemia (BCP-ALL) is a fast growing form of cancer characterized by an overproliferation of B-cell lymphoblasts (a precursor to mature B cells) in the bone marrow and is the most common form of ALL, accounting for about 80% of all cases of the disease. It presents a therapeutic challenge because although most patients respond to initial treatment, only 20%-40% of them remain in remission after 5 years. The persistence of residual disease drives frequent relapse and is the most important negative prognostic factor in this disease setting.

For relapsed/refractory patients, allogeneic hematopoietic stem-cell transplantation (allo-HSCT) is the only curative option, but works best in patients who have achieved complete remission (CR). Therefore, research has focused on finding therapeutic agents that can achieve CR in relapsed/refractory patients so that they can undergo allo-HSCT. Blinatumomab represents an important new therapeutic approach in this setting and a first-in-class approval in two respects; the first CD19-targeting agent and the first bispecific antibody.



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More specifically, blinatumomab is a bispecific T-cell engager (BiTE), an antibody with 2 targets – the cluster of differentiation 19 (CD19) and CD3 proteins. It is an artificial antibody manufactured in Chinese hamster ovary cells, created through fusion of the single-chain variable fragments of 2 different antibodies – one that binds to the CD3 T-cell co-receptor, a protein complex found on the surface of all T cells that is composed of 4 chains that associate with the T-cell receptor and generate an activation signal in T cells, and one that binds to CD19, a tumor-associated antigen expressed on the surface of B-cell malignancies (80% of ALLs).

It is designed to bring the cytotoxic effectors of the immune system, the T cells, in close proximity with tumor cells expressing CD19, to redirect the patient's own immune response to specifically target these malignant cells. In addition to activating both cytotoxic and helper T cells, blinatumomab also increases production of cell adhesion molecules, cytolytic proteins, and inflammatory cytokines.

— Jane de Lartigue, PhD

[ANC] >100,000 cells/μL) or CRh (≤5% bone marrow blasts, >50,000 platelets/μL, ANC >500 cells/μL) within the first 2 treatment cycles. Secondary endpoints included relapse-free survival (RFS), overall survival (OS), proportion of responders undergoing allo-HSCT, and 100-day mortality after allo-HSCT.

Overall, 43% of patients experienced CR (33%) or CRh (10%) within 2 cycles of blinatumomab treatment, with 79% of those patients achieving CR or CRh in Cycle 1. Over a median follow-up of 8.9 months, nearly half of the patients who achieved CR or CRh were alive and in remission. Median RFS was 5.9 months.

CR was 73% among patients with <50% bone marrow blasts at baseline, compared with 29% for those with >50%. Responses were noted in all prespecified subgroups, most notably among patients who were older than 65 years and among those who received prior allo-HSCT, 2 groups for whom current treatment options are particularly limited. MRD negativity was achieved in 82% of CR or CRh responders that were evaluable for MRD response. Median RFS for MRD responders was 6.9 months, and median OS was 11.5 months, compared with 2.3 months and 6.7 months, respectively, for nonresponders. The goal of remission in order to undergo stem-cell transplantation was achieved in 40% of responders, among whom the 100-day mortality rate was 11%.

The prescribing information provides pooled tolerability and safety information from clinical trials in adults who received at least 1 dose of blinotumomab at doses up to 28 μg/m^2/day (n = 212), including those from the pivotal trial.[3] Adverse events (AEs) were consistent with AEs in previous studies of blinatumomab in relapsed/refractory BCP-ALL, with no unexpected toxicities, and treatment-related mortality was low. Almost all patients (99%) experienced AEs, the most common being pyrexia (62%), headache (36%), febrile neutropenia (25%), peripheral edema (25%), nausea (25%), hypokalemia (23%), and constipation (20%). Serious AEs occurred in 65% of patients, most frequently febrile neutropenia, pyrexia, pneumonia, sepsis, neutropenia, device-related infection, tremor, encephalopathy, infection, overdose, confusion, *Staphylococcal* bacteremia, and headache. The rate of fatal AEs was 15%, and the

rate of discontinuation as a result of AEs was 18%.

Among the pivotal trial population (n = 189), neurologic events occurred in 52% of patients and were mostly grade 1 or 2 and easily managed with dexamethasone treatment. Grade 3 neurologic events were recorded in 11% of patients and resolved in 85% of cases; grade 4 neurologic events occurred in 2%, all resolving; and there were no fatal neurologic AEs. CRS was uncommon, with grade 3 CRS reported at a rate of 2%.

According to the prescribing information, for patients who weighed at least 45 kg, blinatumomab should be administered via continuous intravenous infusion at a constant flow-rate with an infusion pump using a step-dose of 9 µg/day on days 1-7 of the first cycle, followed by 28 µg/day on days 8-28 of Cycle 1 and days 1-28 of subsequent cycles for 4 weeks, followed by a 2-week treatment-free period. Patients should receive premedication with dexamethasone 20 mg, 1 h before the first dose, before the step-dose, or when restarting infusion after ≥4 h.

The prescribing information details warnings and precautions on the possibility of infections, CRS, neurological toxicity, and other clinically relevant AEs, as well as effects on the patient's ability to drive and use machinery, and possible preparation and administration errors. In addition to a black box warning on CRS and neurological toxicities, the FDA also approved blinatumomab with a Risk Evaluation and Mitigation Strategy, which consists of a communication plan to inform health care providers about boxed warning risks and the potential for preparation and administration errors.

The single-agent antileukemic activity of blinatumomab in adult patients with relapsed/refractory BCP-ALL and its recent approval by the FDA offer a new therapeutic approach in this setting. Blinatumomab is marketed as Blincyto by Amgen, which is required to conduct a post-marketing study to demonstrate improved survival in this patient population, and several phase 3 studies are ongoing.

References

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