

Blinatumomab: A ray of hope for relapsed/refractory adult B-cell acute lymphoblastic leukemia

Sir,

Acute lymphoblastic leukemia (ALL) of B-cell lineage is a relatively infrequent disease in adults that is usually treated with intensive chemotherapy. However, the prognosis for the patients, who are refractory to initial treatment, or relapse (r/r B-ALL), is very poor. A bispecific antibody blinatumomab as a single agent therapy has demonstrated anti-leukemic activity in adult patients with r/r B-ALL, including those who responded poorly to prior therapy. Blinatumomab is the result of translational research project leading to the formation of Bispecific T-cell Engager (BiTE) antibodies. A BiTE monoclonal antibody has two variable regions, one specific to CD3 for T-cell recruitment and activation and the other targeting a different leukemic or neoplastic membrane antigen. With blinatumomab, CD19⁺ blast cells of B-precursor ALL are linked to CD3⁺ T-cells and subject to perforin-mediated cytotoxicity [Figure 1].^[1]

The drug is active at very low concentration, and once cell lysis is completed, the effector-blinatumomab complex is released to start over again. Conceptually, this is immunotherapy at its best because autologous effector cells are brought into direct contact with the target and nothing else. This is a key distinction with the immune effects provided by an allogeneic stem cell transplant, where unrestricted T-cell activation can lead to the serious clinical consequences of graft-versus-host disease.

With single-agent blinatumomab, a complete and durable molecular remission was observed in approximately 70% of adult patients with minimal residual disease (MRD⁺) ALL, and similar activity is also being reported in relapsed ALL.^[2] The goal of the treatment of relapsed patients is to achieve complete remission (CR) and subsequently offer hematopoietic stem cell transplantation (HSCT). MRD can now be detected in over 90% of B-ALL patients with a detection limit of 0.01% compared to 5% using microscopy, allowing a more refined measurement of response. In the first-line treatment of B-ALL, achieving an MRD response in addition to hematologic CR is associated with a better outcome. The results of the largest study so far ($n = 189$) were presented by Nicola Gökbuget during the 19th European Hematology Association congress in Milan.^[3] The clinical study recruited 189 patients ≥ 18 years old who had Ph-negative r/r B-ALL, and poor prognosis. A central reference lab evaluated both the cytologic and MRD response. The primary endpoint was CR or CR with partial hematologic recovery (CRh*) within the first two cycles of treatment. In addition, MRD response within the first two cycles was an exploratory endpoint. The median age of the patients was 39 years (range: 18-79).

The CR/CRh* rate within two cycles was 43% (95% confidence interval [CI]: 36–51%) in all patients and 45% in those who underwent prior HSCT. Among patients who did not receive prior HSCT the rates of CR/CRh* varied, with lower rates observed in patients receiving ≥ 2 prior salvage treatments.

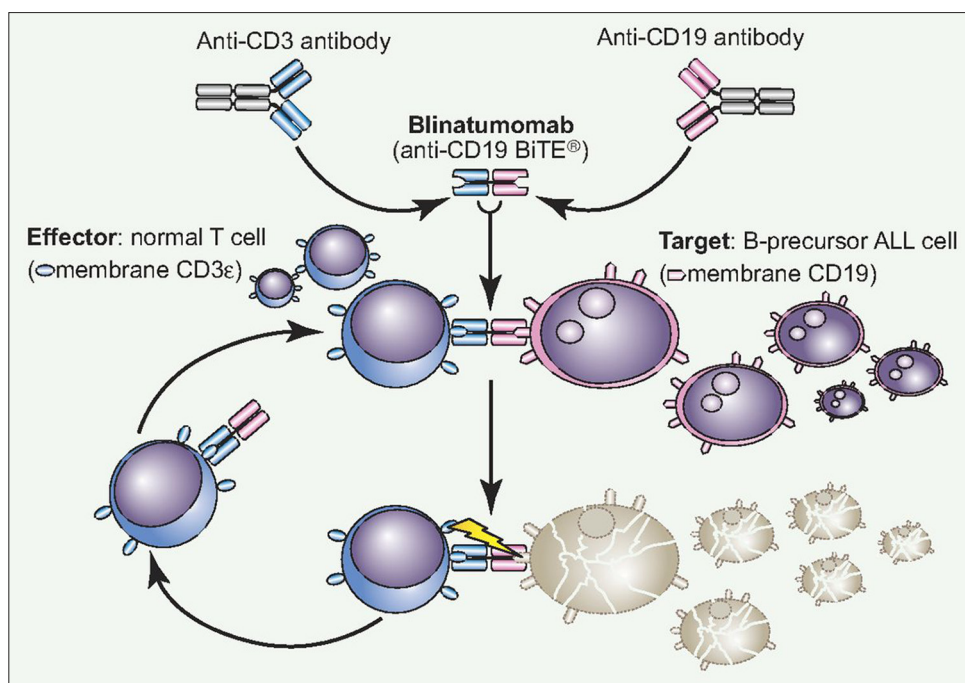


Figure 1: Mechanism of action of the novel bispecific antibody blinatumomab

Median relapse-free survival was 5.9 months (95% CI: 4.8-8.3). The most frequent adverse events were related to cytokine release, that is, febrile neutropenia, fever and headache. Grade 3/4 adverse events included febrile neutropenia, anemia and neutropenia, and nervous system disorders including encephalopathy, headache and ataxia. Most patients had CR with complete recovery of peripheral blood counts (33%), some had incomplete recovery (9%). Among patients who achieved CR/CRh*82% also demonstrated MRD response, indicating that most CRs were deep.

Thus, blinatumomab is a new ray of hope for adult B-ALL patients who have relapsed or refractory to initial treatment and is expected to revolutionize the treatment for them.

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