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Blinatumomab: Bridging the Gap in Adult Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

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Abstract

Adult patients with acute lymphoblastic leukemia who relapse after frontline therapy have extremely poor outcomes despite advances in chemotherapy and hematopoietic stem cell transplantation. Blinatumomab is a first-in-class bispecific T-cell engager that links T cells to tumor cells leading to T-cell activation and tumor cell lysis. In December 2014, the Food and Drug Administration approved blinatumomab for treatment of relapsed or refractory Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia. In a phase II trial, blinatumomab produced response rates of 43%, and 40% of patients achieving a complete remission proceeded to hematopoietic stem cell transplantation. Early use of blinatumomab was complicated with adverse effects, including cytokine release syndrome and neurotoxicity. Management strategies, including dexamethasone premedication and 2-step dose escalation during the first cycle of blinatumomab, have decreased the incidence and severity of these adverse effects. Blinatumomab currently is being studied for other B-cell malignancies and has the potential to benefit many patients with CD19+ malignancies in the future.

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Introduction

Despite advances in chemotherapy and hematopoietic stem cell transplantation (HSCT), there are limited options for the treatment of relapsed or refractory acute lymphoblastic leukemia (ALL).[1] Adult patients with ALL who relapse after frontline therapy have extremely poor outcomes.[2] The median overall survival (OS) after relapse is less than 5 months, and the 5-year OS is 10%. Approximately 20% to 30% of patients fail to achieve a complete remission (CR) with second-line therapies.[1,3] Current treatment guidelines heavily favor combination regimens for relapsed or refractory disease, which produce CR and CR with partial hematologic recovery (CRh) rates of 30% to 45%. Recommended options for monotherapy include liposomal vincristine, which produces a CR/CRh rate of only 20%, and blinatumomab, a first-in-class bispecific T-cell engager (BiTE) that can increase CR/CRh rates to 43%.[1,3]

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Blinatumomab is an immunotherapeutic agent that links T cells to tumor cells leading to T-cell activation and lysis of tumor cells.[4] In December 2014, the Food and Drug Administration (FDA) approved blinatumomab for treatment of relapsed or refractory Philadelphia chromosome (Ph)-negative precursor B-cell ALL.[5] Because of positive results and ongoing clinical trials, the role of blinatumomab in hematologic malignancies is likely to expand.

Mechanism of Action

BiTEs, including blinatumomab, bind CD19 and CD3 allowing for formation of an immunologic synapse.[6] CD19 is the earliest B-cell lineage–restricted antigen expressed on the surface of B lymphocytes. It is expressed with high frequency on B-cell lineage–derived leukemias and lymphomas, making it an attractive drug target. CD3 is the invariable component of the T-cell receptor complex expressed on the surface of cytotoxic T lymphocytes. Two single-chain variable domains of 2 monoclonal antibodies, one specific for CD19 and the other for CD3, are linked by a single polypeptide to form a BiTE molecule.[4]

First, blinatumomab binds CD19 on the B-cell given its greater affinity for CD19 compared with CD3.[7] The B-cell presents the blinatumomab molecule awaiting CD3 binding. Then, the T cell binds, forming the immunologic synapse. Once bound, the

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cytotoxic T cell becomes active. Because the small size of the BiTE molecule allows for close proximity of the T cell and tumor cell, costimulatory molecules are not required to induce T-cell response. The T-cell releases perforins, creating holes in the tumor cell and allowing granzyme entry into the cell, ultimately resulting in tumor cell apoptosis. Unlike other cytotoxic monoclonal antibodies, blinatumomab directly activates the T cells and does not rely on antibody-dependent cellular toxicity and complement-dependent cytotoxicity. This allows blinatumomab to evade the mechanism of resistance that some malignancies develop against other immunotherapeutic agents. Activation of the T cell by blinatumomab also causes T-cell proliferation.

Clinical Data

Blinatumomab has been shown to be effective against relapsed and refractory B-cell lineage malignancies, including non−Hodgkin lymphoma (NHL) and B-cell ALL.[8,9] The first clinical trial with blinatumomab was in relapsed or refractory NHL, including mantle cell and follicular lymphoma.[7] Subsequent studies included patients with diffuse large B-cell lymphoma.[8] Efficacy of blinatumomab in diffuse large B-cell lymphoma is promising with an overall response rate of approximately 40%.

After the success of blinatumomab in NHL, the German Study Group conducted a Phase II trial in patients with precursor B-cell ALL with minimal residual disease (MRD) after previous treatment (Table 1).[9] MRD refers to the presence of disease below the threshold for conventional methods of detection. The presence of MRD is an indicator of resistance to chemotherapy and translates to a high rate of relapse. More than 90% of patients with MRD after maintenance treatment will have a hematologic relapse.[9] Patients with MRD after frontline therapy often are considered for allogeneic stem cell transplantations.[11] For 4 weeks of a 6-week cycle, 21 patients with precursor B-cell ALL in morphologic remission with MRD received a continuous intravenous (IV) infusion of blinatumomab at 15 μg/m^2/d. The median age of patients was 47 years. All patients had received induction chemotherapy and at least 1 round of consolidation. Only 2 patients had received previous chemotherapy in the relapse setting. The MRD conversion from positive to negative was 80% after 1 cycle of treatment.

The German Study Group conducted another Phase II trial in patients with primary refractory disease or relapse after induction and consolidation chemotherapy or after HSCT.[10] In the study, 42% of patients had relapsed after HSCT and 19% of patients had received at least 1 salvage regimen if they had not received a transplant. To prevent cytokine release syndrome (CRS), a pretreatment prophase with dexamethasone 24 mg/d for up to 5 days or cyclophosphamide 200 mg/m^2/d for up to 4 days was permitted. Thirty-six patients, including 2 with Ph-positive disease, received blinatumomab at 5 μg/m^2/d for 1 week and then 15 μg/m^2/d for the remaining 3 weeks of the first 6-week cycle. For subsequent cycles, blinatumomab was administered at 15 μg/m^2/d for 4 weeks. Standard response criteria were used to define CR and CRh (Table 2). Twenty-five patients (69%) achieved CR or CRh within 2 treatment cycles. Median OS was 9.8 months, and 52% of patients underwent HSCT after achieving CR or CRh. A trend toward shorter OS was observed in patients who relapsed after prior HSCT (median, 8.8 months) compared with those who relapsed without having had prior HSCT (median, 14.1 months).

Table 1 Clinical Efficacy and Safety for Blinatumomab[3,9,10]

Study	Topp et al,[9] 2011	Topp et al,[10] 2014	Topp et al,[3] 2015
Patient population	MRD-positive B-cell ALL n = 20	RR B-cell ALL n = 36	RR Ph-negative B-cell ALL n = 189
Outcomes	MRD conversion 80%	CR/CRh 69%	CR/CRh 43%
	Allogeneic HSCT 40%	Allogeneic HSCT 52%	Allogeneic HSCT 40%
ADRs:			
Fever	NR	81%	60%
Grade 3 or 4 CRS	0%	6%	2%
Grade 3 or 4 neurologic events	19%	22%	13%

Abbreviations: ADR = adverse drug reaction; ALL = acute lymphoblastic leukemia; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRS = cytokine release syndrome; HSCT = hematopoietic stem-cell transplantation; MRD = minimal residual disease; NR = not reported; Ph = Philadelphia chromosome; RR = relapsed or refractory.

In the largest prospective study in relapsed or refractory ALL, 189 heavily pretreated patients with Ph-negative precursor B-cell ALL received blinatumomab.[3] In the study, 80% of patients had received at least 1 previous line of salvage chemotherapy and 34% of patients had received an allogeneic HSCT before blinatumomab. Patients considered high risk for CRS, defined as bone marrow blasts more than 50%, peripheral blasts of 15,000 cells/μL or greater, or elevated lactate dehydrogenase received dexamethasone 10 to 24 mg/m^2/d for up to 5 days. Dexamethasone prophase treatment concluded at least 3 days before blinatumomab administration. Patients received blinatumomab at 9 μg/d for the first 7 days and then 28 μg/d thereafter by continuous infusion for 4 weeks every 6 weeks for up to 5 cycles. Dexamethasone 20 mg was administered as premedication for the first dose of blinatumomab and before the dose increase on day 8 of the first cycle. Within 2 cycles, 43% achieved CR or CRh and median OS was 6.9 months. Patients who achieved an MRD response had increased OS (6.9 months)

Table 2 Definition of End Points Used in Blinatumomab Clinical Trials[3,10]

CR	≤5% blasts in bone marrow No evidence of circulating blasts or extramedullary disease Recovery of peripheral blood counts: Platelets >100,000/μL ANC >1000/μL
CRh	≤5% blasts in bone marrow No evidence of circulating blasts or extramedullary disease Recovery of peripheral blood counts: Platelets >50,000/μL ANC >500/μL

Abbreviations: ANC = absolute neutrophil count; CR = complete remission; CRh = complete remission with partial hematologic recovery.