Clinical Cancer Research

FDA Approval: Blinatumomab

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Abstract

On December 3, 2014, the FDA granted accelerated approval of blinatumomab (Blincyto; Amgen, Inc.) for treatment of Philadelphia chromosome–negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia (R/R ALL). Blinatumomab is a recombinant murine protein that acts as a bispecific CD19-directed CD3 T-cell engager. The basis for the approval was a single-arm trial with 185 evaluable adults with R/R ALL. The complete remission (CR) rate was 32% [95% confidence interval (CI), 26%–40%], and the median duration of response was 6.7 months. A minimal residual disease response was achieved by 31% (95% CI, 25%–39%) of all patients. Cytokine release syndrome and neurologic events were serious toxicities that occurred. Other common (>20%) adverse reactions were pyrexia, headache, edema, febrile neutropenia, nausea, tremor, and rash. Neutropenia, thrombocytopenia, and elevated transaminases were the most common (>10%) laboratory abnormalities related to blinatumomab. A randomized trial is required in order to confirm clinical benefit. *Clin Cancer Res; 21(18); 4035–9. ©2015 AACR.*

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No potential conflicts of interest were disclosed.

Editor's Disclosures

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CME Staff Planners' Disclosures

The members of the planning committee have no real or apparent conflict of interest to disclose.

Learning Objectives

Upon completion of this activity, the participant should have a better understanding of the mechanism of action of blinatumomab, how the toxicities of blinatumomab reflect the mechanism of action, and the level of evidence supporting use of blinatumomab for the treatment of Philadelphia chromosome–negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia.

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Introduction

Relapsed and refractory precursor B-cell acute lymphoblastic leukemias (R/R ALL) are potentially fatal disorders. Historically, the response of R/R ALL to single-agent salvage therapy is poor. In two large reviews, single agents induced complete remission (CR) in fewer than 10% of patients with R/R ALL (1, 2). For drugs approved in the current era, CR was reported only for 5% to 12% of patients treated with single agents (3, 4).

Recent publications suggest that the response of R/R ALL to induction can be improved by use of intensified reinduction regimens (5, 6). Using such combination therapies, CR was achieved by 25% to 46% of patients with R/R ALL (7), with older age, short first remission, more prior relapses, and relapse after hematopoietic stem cell transplantation (HSCT) associated with a lower CR rate. A reduction in minimal residual disease (MRD) to $<10^{-4}$ was also associated with improved outcome, but this level of MRD was reportedly achieved by only a small fraction of patients in CR with chemotherapy alone (8). Unfortunately, despite such intensified salvage therapy for patients with R/R ALL, median survival was only 3 to 6 months. Thus, there remains a need for additional effective therapies for R/R ALL.

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Herein, we provide a summary of the FDA review (9) of the marketing application for blinatumomab for the treatment of R/R ALL.

Blinatumomab

Blinatumomab (also known as AMG103, MT103, and MEDI-538) is a bispecific CD19-directed CD3 T-cell engager. It mediates formation of a synapse between the $CD3^+$ T cell and the $CD19^+$ target cell, upregulation of cell adhesion molecules, production of cytolytic proteins, and release of inflammatory cytokines, which together result in redirected lysis of the $CD19^+$ target cell.

Blinatumomab has a molecular weight of approximately 54 kDa. It is produced as a single-chain recombinant protein in Chinese hamster ovary cells from a genetic construct encoding the variable fragments of anti-CD3 and anti-CD19 murine monoclonal antibodies. The murine sequences confer an immunogenic nature to protein. Anti-blinatumomab antibodies were identified in 3 (< 1%) of the 325 treated patients, 2 of whom had neutralizing antibodies.

The commercial product for intravenous use is 35 μg of a lyophilized powder copackaged with a solution stabilizer. It is formulated without preservatives, and the prepared solution supports microbial growth. In order to reduce the risk of infusion-related infections, blinatumomab is prepared for administration under aseptic conditions, it is infused using an in-line 0.2-μm filter, and storage or use at room temperature is limited to 48 hours.

Clinical Pharmacology

Pharmacokinetics

Blinatumomab pharmacokinetics (PK) parameters were linear over the dose range of 5 to 90 $\mu g/m^2$. The volume of distribution was 4.5 L, and the elimination half-life was short at 2.1 hours, but PK was highly variable. Steady-state concentrations during continuous infusion were achieved within one day. Mild and moderate renal impairment was associated with a modest decrease in clearance, but the size of the effect did not warrant modification of the starting dose. The impact of severe renal impairment or dialysis on blinatumomab PK was not assessed. There were too few cases of patients with anti-blinatumomab antibodies to allow conclusions about the impact of immunogenicity on PK.

Pharmacodynamics

The pharmacodynamic (PD) effects observed in the patient population included a rapid redistribution of T cells, NK cells, and monocytes resulting in peripheral cytopenias (with recovery in 2–7 days), and an immediate but transient increase in inflammatory cytokines, the magnitude of which appeared to be dose dependent for the initial dose. Serial measurements of serum cytokine concentrations from 186 patients treated on Protocol MT103-211 showed that, within the first 48 hours of the first infusion of blinatumomab, IL10 was elevated in 98% of patients, IL6 in 88%, IFNγ in 54%, IL2 in 27%, and TNFα in 24%.

Assessment of Efficacy

Clinical trial overview

Protocol MT103-211 was a single-arm, open-label, two-step trial of single-agent blinatumomab for treatment of adults with Philadelphia chromosome–negative relapsed or refractory precursor B-cell ALL (R/R ALL). Eligible patients had >10% blasts in the marrow and early first relapse (first remission ≤ 12 months), second or later relapse, refractory disease, or relapse after HSCT. The primary efficacy endpoint was CR + CRh* (CR but with platelets >50 Gi/L and ANC > 0.5 Gi/L) by two cycles of therapy. The objective was to test the hypothesis that the rate of CR + CRh* was > 30%. With a sample size of 140 patients and a true response rate of 45%, the study had 96% power to exclude a 30% response rate with a one-sided type I error rate of 2.5%. Additional patients beyond the minimum sample size were accrued as prespecified in the protocol in order to allow for a supplementary analysis of clinical comparability using a modified manufacturing process.

Treatment plan

Before start of blinatumomab, cytoreduction with dexamethasone, 10 mg/m^2 (maximum 24 mg), daily for up to 5 days was required for patients with blasts >50% or an absolute blast count >15 Gi/L. Blinatumomab was given by continuous intravenous infusion over 4 weeks of a 6-week cycle. The treatment plan consisted of up to two cycles for induction and three cycles for consolidation. In the first cycle, the initial dose was 9 μg/day for week 1, then 28 μg/day (step dose) for the remaining 3 weeks. A dose of 28 μg/day was administered in cycle 2 and subsequent cycles starting on day 1 of each cycle. Dose adjustment was possible in case of adverse events. Dexamethasone, 20 mg, was given intravenously one hour before each treatment cycle and one hour before the step dose to prevent infusion reactions.

The starting dose of blinatumomab was based on the safety results of two prior studies using BSA-based dosing for patients with R/R ALL (10, 11). In these studies, initiation of treatment with 5 $\mu g/m^2$/day was associated with less cytokine release syndrome, and the 5→15 $\mu g/m^2$/day step-dose regimen was found to be tolerable and active. The 9→28 μg/day step-dose regimen for patients ≥45 kg was based on the PK finding of consistency of exposure when comparing fixed-dose to BSA-based dosing.

Disposition and demographics

Protocol MT103-211 accrued 189 patients internationally. At the time of the efficacy analysis, all patients had completed at least two cycles or discontinued early. Four patients with either no evidence of active ALL at enrollment or who were in late first remission were excluded from the efficacy analysis. The demographics of the remaining 185 study patients are shown in Table 1. Forty-six patients went on to allogeneic stem cell transplantation after treatment with blinatumomab.

Efficacy results

The efficacy results are shown in Table 2. In the analysis of the primary endpoint, the rate of CR + CRh* was 42% with a lower 95% confidence intervals (CI) boundary of 34%. To allow for a better understanding of the result in the context of the heterogeneity of the patient population with regard to prognostic factors, the sponsor provided a weighted analysis of patient-level data for 694 historical controls collected from 13 study groups and clinical centers (9). The analysis showed that the expected rate of CR or CR without complete hematologic recovery in some cases was 24% (95% CI, 20%–27%). This result confirmed that the target lower limit of 30% CR + CRh* in this study was reasonable for the accrued population and that the primary objective was met. The results for the primary endpoint were largely consistent across the subpopulations tested.

Table 1. Characteristics of the patients in protocol MT103-211

Number of patients	185
Median age (range)	39 years (18–79 y)
≥65 years old	25 (14%)
Gender	
Male	116 (63%)
Female	69 (37%)
Race	
Caucasian	142 (77%)
Other	24 (13%)
Not recorded	19 (10%)
Disease status	
≥Second salvage	107 (58%)
Post HSCT relapse	39 (21%)
Early first relapse	23 (12%)
Primary refractory	16 (9%)
Prior relapses	
0	16 (19%)
1	104 (42%)
2	45 (22%)
>2	20 (17%)
Prior HSCT	63 (34%)

Abbreviation: HSCT, hematopoietic stem cell transplantation.

Key secondary and exploratory endpoints were used to inform the regulatory decision-making process (Table 2). CR was achieved by 60 (32%) of the patients. The sponsor developed a model to project CR using a meta-analysis of summary data from multiple publications. Using this model, the projected CR rate for the accrued population treated with existing therapies was 13% (95% CI, 4%–34%), and the OR for CR using blinatumomab over existing therapies by simulation was 3.50 (95% CI, 1.63–8.40; ref. 9). For the patients who achieved CR, the median relapse-free survival (RFS) was 6.7 months, so it was concluded that the responses were reasonably durable (due to the competing risk of death in remission, RFS was used as the measure of duration of response). Finally, patients who achieved CR or CRh* were also tested for MRD using a sensitive molecular method. CR or CRh* with a reduction in MRD to less than 10^{-4} was achieved by 31% of the study population.

Assessment of Safety

Nonclinical toxicology

Blinatumomab bound to human and chimpanzee peripheral blood mononuclear cells. In a nonterminal repeat-dose study of intravenous blinatumomab in chimpanzees and repeat-dose studies of a murine surrogate of blinatumomab in mice, test article–related changes included increased expression of T-cell activation markers and lymphocytopenia. Additional toxicologic findings in chimpanzees included expression of inflammatory cytokines, increases in body temperature and heart rate, and a decrease in blood pressure. These findings were consistent with the cytokine release syndrome observed in clinical studies.

Table 2. Outcomes of the patients in protocol MT103-211

Primary efficacy endpoint	
CR + CRh* *n* (%; 95% CI)	77 (42%; 34%–49%)
Key supporting analyses	
CR *n* (%; 95% CI)	60 (32%; 26%–40%)
Median RFS for CR (range)	6.7 months (0.5–16.5 mo)
Key exploratory analysis	
MRD-negative CR + CRh* *n* (%; 95% CI)	58 (31%; 25%–39%)

Abbreviations: CRh*, CR but with platelets > 50 Gi/L and ANC > 0.5 Gi/L; MRD, (negative is $<10^{-4}$); RFS, relapse-free survival (used as a measure of duration of response).

Safety events in the intended population

Safety was assessed in 212 adults with R/R ALL treated with blinatumomab using the fixed 9→28 μg step-dose regimen or the BSA-based 5→15 μg/m^2 step-dose regimen. A treatment-emergent adverse event (TEAE) was experienced by >99% of patients, and the event was grade ≥3 for 78%. The most common (≥10%) TEAEs that occurred on treatment or within 30 days of the end of infusion are listed in Table 3. The most common grade ≥ 3 nonhematologic TEAEs were febrile neutropenia (23%), pneumonia (8%), pyrexia (7%), sepsis (5%), dyspnea (5%), and hypertension (5%). Four patients (2%) had hypersensitivity reaction events that could not be attributed to a cause other than blinatumomab.

The protocol did not provide specific criteria for diagnosis of cytokine release syndrome or infusion reaction. Events described by the terms "cytokine release syndrome," "infusion reaction," and "capillary leak syndrome" occurred in the same timeframe (median time to onset of 2 days) and with overlapping signs and symptoms, and thus, for the purposes of the safety analysis, these event terms were considered together as a grouped term

Table 3. Treatment-emergent adverse reactions in the safety population[a]

Preferred term[b]	**Any grade**	**Grade ≥ 3**
Pyrexia	131 (62%)	14 (7%)
Headache	77 (36%)	7 (3%)
Edema	63 (30%)	3 (1%)
Febrile neutropenia	53 (25%)	48 (23%)
Nausea	52 (25%)	0
Hypokalemia	48 (23%)	13 (6%)
Rash	45 (21%)	5 (2%)
Constipation	43 (20%)	1 (<1%)
Tremor	42 (20%)	3 (1%)
Diarrhea	42 (20%)	3 (1%)
Neutropenia	40 (19%)	37 (17%)
Abdominal pain	40 (19%)	5 (2%)
Anemia	40 (19%)	28 (13%)
Cough	39 (18%)	0
Fatigue	37 (17%)	2 (1%)
Arrhythmia	37 (17%)	4 (2%)
Hypertransaminasemia	32 (15%)	15 (7%)
Dyspnea	32 (15%)	11 (5%)
Chills	31 (15%)	0
Insomnia	31 (15%)	0
Dizziness	30 (14%)	1 (<1%)
Back pain	29 (14%)	4 (2%0
Thrombocytopenia	29 (14%)	21 (10%)
Vomiting	28 (13%)	0
Immunoglobulins decreased	27 (13%)	3 (1%)
Hypotension	26 (12%)	7 (3%)
Pain in extremity	26 (12%)	2 (1%)
Cytokine release syndrome	26 (12%)	5 (2%)
Hypomagnesemia	25 (12%)	0
Weight increased	23 (11%)	0
Bone pain	23 (11%)	6 (3%)
Chest pain	23 (11%)	2 (1%)
Hyperglycemia	22 (10%)	13 (6%)
Altered state of consciousness	22 (10%)	3 (1%)
Hyperbilirubinemia	22 (10%)	11 (5%)
Arthralgia	21 (10%)	4 (2%)
Decreased appetite	21 (10%)	6 (3%)

[a]*N* = 212 adults with R/R ALL treated with blinatumomab using the fixed 9→28 μg or the BSA-based 5→15 μg/m^2 step-dose regimens.
[b]Grouped terms. See Supplementary Table S1 for further information.

(see Supplementary Table S1). Cytokine release syndrome was reported for 12% of the patients (grade ≥3 cytokine release syndrome in 2%).

A neurologic toxicity occurred in 53% of the patients. The hazard rate for the first neurologic event diminished over time, but new events were reported throughout the period of blinatumomab administration. The nature of the neurologic toxicity was variable; 72 different neurologic or psychiatric adverse event terms were reported. Grade ≥3 neurologic TEAEs that occurred in 2 or more patients were encephalopathy, headache, altered state of consciousness, aphasia, ataxia, confusional state, nervous system disorder, tremor, neurotoxicity, and seizure. Leukoencephalopathy was identified in 7 patients, including one with JC virus in the spinal fluid. Patients ≥65 years old had an increased rate of neurologic events.

Laboratory abnormalities were common, as might be expected in patients with RR ALL, but where shifts could be assessed for a worsening from grade ≤2 at baseline to grade ≥3 after start of therapy, nonhematologic abnormalities that occurred in >10% of patients included increased gamma-glutamyl-transferase, increased alanine aminotransferase, increased aspartate aminotransferase, and hyperbilirubinemia. The elevated transaminases generally occurred in the setting of cytokine release syndrome.

Blinatumomab administration was interrupted in 32% of the patients and discontinued prematurely in 17%. The most common reasons for interruption were neurologic toxicity and cytokine release syndrome. The most common reasons for permanent withdrawal included neurologic toxicity and sepsis.

One hundred and thirty deaths were reported. The majority of the deaths were considered related to active primary malignancy or complications of HSCT. Two deaths were concluded to have potentially resulted from a direct toxicity of blinatumomab, and in both cases, the clinical manifestations were attributed to or were similar to those expected for cytokine release syndrome. The rate of day-30, all-cause mortality was 8% (95% CI, 4%–12%); this was not greater than that expected based on a historical control group [14% (95% CI, 12%–16%)] as calculated by the sponsor (9).

Discussion

Although the current standard of care for treatment of R/R ALL is intensive combination chemotherapy, the results with this approach remain disappointing, and effective new treatments that are not cross-resistant based on mechanism of action could potentially transform the outcomes of these patients. In Protocol MT103-211, using blinatumomab to treat patients with R/R ALL, the CR rate was 32%. This result is better than that for any available single agent, and the mixed effects modeling was consistent with improvement over conventional combination therapy. Moreover, the responses were durable (median RFS, 6.7 months). Finally, an MRD response was noted in 31% of the patients treated. None of these outcomes alone would be viewed as more than encouraging from a regulatory perspective, but when taken together, these outcomes form a strong basis for accelerated approval.

The protocol eligibility criteria allowed accrual of patients in early first relapse, any later relapse, relapse after HSCT, or with refractory disease. All of these disease states have a relatively poor prognosis with conventional therapy, but the remission rates and durations of remission differ substantially, and the point estimate for an outcome would vary by the proportion of patients in each prognostic subgroup actually accrued to the study. For interpretation of the results of Protocol MT103-211, the analysis of patient-level data from the historical controls weighted by prognostic subgroup confirmed that the target lower limit of 30% for the primary endpoint was reasonable. A clear rationale for the sample size, prespecification for the timing of the analysis, and data-based justification of the target for the primary endpoint were critical in minimizing bias in the interpretation of this single-arm trial.

FDA has commonly used durable CR as the endpoint for accelerated approval of new agents for treatment of acute leukemia (12). The primary endpoint in Protocol MT103-211 included CRh* as an additional part of the composite. However, there were no independent data to support the prognostic value of CRh*, and the number of patients with CRh* in the protocol was too small to allow for firm conclusions with statistical rigor about its value in predicting clinical benefit.

MRD has not been used previously to support approval of new therapies for R/R ALL, but an MRD response is expected to be reasonably likely to predict clinical benefit based on available data (8). In Protocol MT103-211, only 59% of the patients with CRh* also had an MRD response, leaving a substantial proportion with questionable benefit. Nonetheless, the overall percentage of patients with an MRD response in addition to a CR or CRh* (31%) was greater than that expected using chemotherapy alone (8), and thus the MRD data added support for the conclusion that blinatumomab provided a meaningful therapeutic benefit over existing treatments.

Blinatumomab is a murine protein that activates T cells and eliminates B cells. On the basis of established class safety effects, such an agent would be expected to cause hypersensitivity reactions (13), cytokine release syndrome (14, 15), neurologic toxicity (16, 17), and prolonged immunoglobulin deficiency (18). The actual safety profile of blinatumomab was largely consistent with the expected class safety effects. Although one might argue that some of the reported adverse reactions, such as neutropenia, might be related to active leukemia, similar findings in patients with ALL in morphologic remission when treated confirmed that these toxicities were in fact related to blinatumomab (9, 19).

Hypersensitivity reactions were reported in less than 2% of the patients with R/R ALL treated with blinatumomab, but the actual incidence was difficult to determine, because cytokine release syndrome occurred in the same acute timeframe. Cytokine release syndrome and neurologic toxicity comprised the majority of the serious noninfectious complications. The risks were moderated in part by close monitoring and dose interruption. To minimize these risks in practice, a Risk Evaluation and Mitigation Strategy communication plan to health care providers and a medication guide for patients were required by FDA.

Overall, the available data indicate that the potential safety concerns are outweighed by the expected clinical benefit for the patients with R/R ALL treated with blinatumomab using the approved fixed 9→28 μg step-dose regimen. How the effects of the development of anti-blinatumomab antibodies during the initial treatment might affect safety and efficacy on retreatment with blinatumomab for subsequent relapses remains to be addressed. It should be noted that the safety of this regimen was established only for patients at least 45 kg in weight. An alternative blinatumomab regimen for smaller patients has been proposed

(10), and studies are ongoing to clarify its safety and activity in children.

Authors' Contributions

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