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ORIGINAL ARTICLE

Efficacy and safety of blinatumomab treatment in adult Korean patients with relapsed/refractory acute lymphoblastic leukemia on behalf of the Korean Society of Hematology ALL Working Party

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Abstract

Blinatumomab, a bispecific T cell-engaging antibody, has demonstrated efficacy for relapsed or refractory acute lymphoblastic leukemia (ALL). In this study, we evaluated the efficacy and toxicity of blinatumomab in adult Korean patients with relapsed or refractory Philadelphia-negative B cell precursor ALL. A total of 50 patients received blinatumomab treatment between June 2016 and August 2017 in Korea. The median number of prior therapy was one (range, 1–4). Among the 49 evaluable patients, 22 (44.9%) achieved complete response (CR) or CR with incomplete blood count recovery, and 16 of whom subsequently underwent allogenic stem cell transplantation. Although no statistically significant differences were observed, patients with extramedullary disease and poor performance status had lower responses to blinatumomab treatment. In addition, the use of high-dose dexamethasone prior to blinatumomab treatment did not affect the response to blinatumomab. The median event-free survival and overall survival of the responders were 7.5 and 8.1 months, respectively. For non-hematologic toxicities, the most common toxicity was infection. The incidences of severe cytokine release syndrome and neurologic toxicity each was 4%. In conclusion, blinatumomab was an effective and tolerable therapy in adult Korean patients with relapsed or refractory Philadelphia-negative B cell precursor ALL.

Keywords Blinatumomab · Acute lymphoblastic leukemia · Predictor

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Introduction

Over previous decades, modifications of combination chemotherapy have resulted in significant survival improvements for pediatric patients with acute lymphoblastic leukemia (ALL) [4, 14]. However, improvements of survival outcome have been unsatisfactory in adults ALLs. Although the remission rates of adult ALL are > 80% with conventional chemotherapy regimens, most patients eventually experienced relapse. Although various salvage regimens consisted of conventional chemotherapeutic agents have been proposed for adult patients with relapsed or refractory ALL, the results of these regimens have been unsatisfied [3]. Therefore, adult patients with relapsed or refractory ALL have dismal prognoses, with 5-year survival around 7% [6]. In addition, the re-induction with conventional chemotherapy for relapsed or refractory ALL, in the context of previous exposure, generally causes excessive toxicity.

Recently, a bispecific T cell-engaging therapy has been developed to enhance cancer cell-killing efficacy in some types of hematologic malignancies [8, 9]. Blinatumomab is a bispecific T cell-engaging antibody for ALL that has dual specificity for CD19 on lymphoblasts and CD3 on cytotoxic T cells. The binding of blinatumomab to both antigens induces a cytolytic synapse between lymphoblasts and activated cytotoxic T cells and exerts cytotoxic activity on lymphoblasts [13]. Blinatumomab monotherapy has shown promising results in patients with relapsed or refractory ALL and in those who were achieving hematologic responses for persistent minimum residual disease [16, 17]. Recently, a randomized phase III study demonstrated the superiority of blinatumomab monotherapy over conventional chemotherapy in relapsed or refractory adult patients with Philadelphia-negative B cell precursor ALL [10]. Most previous reports of the clinical efficacy and toxicity of blinatumomab for ALL are based on clinical trials, and data from real clinical practices are rare. Since in real practice patients may be frailer and present extramedullary disease, the outcomes of blinatumomab in clinical practice may differ from those of clinical trials. In addition, no study has evaluated the efficacy and safety of blinatumomab for ALL in Asian patients.

Here, we collected data of Korean patients with relapsed or refractory ALL who were treated with blinatumomab monotherapy and analyzed the clinical outcomes and response rates according to patient subgroups.

Patients and methods

We retrospectively collected the data of adult patients (aged > 18 years) with relapsed or refractory ALL who were treated with blinatumomab between June 2016 and August 2017 in Korea. Patients with Burkitt's lymphoma, or Philadelphia-chromosome-positive B cell precursor ALL, were excluded. Complete remission (CR) was defined as < 5% blasts in the bone marrow (BM) aspirates, with full hematologic recovery in the peripheral blood (neutrophil count > 1×10^9/L and platelet count > 100×10^9/L). CR with incomplete blood count recovery (CRi) was defined as < 5% BM blasts with incomplete hematologic recovery (neutrophil count < 1×10^9/L or platelet count < 100×10^9/L). Cytogenetic risk was classified into standard and high risks, based on conventional cytogenetic studies or fluorescent in situ hybridization. Patients who had complex karyotype (five or more chromosomal abnormalities), hypodiploidy (<44 chromosome), or *MLL* gene rearrangements were classified as high risk. Toxicity data was assessed by the National Cancer Institute Common Toxicity Criteria (v4.0) and collected during two cycles of blinatumomab. This study was approved by the Institutional Review Board of each participating hospital, in accordance with the Declaration of Helsinki.

Statistical analysis

The patients and disease characteristics were summarized using frequency tabulations for categorical variables and median (range) for continuous variables. Univariate analysis of the predictors associated with response was performed using the χ^2 test. Event-free survival (EFS) was defined as the time from the first day of blinatumomab treatment to the date of relapse or death from any cause. Overall survival (OS) was defined as the period from the first day of blinatumomab treatment to the date of the last follow-up or death from any cause. EFS and OS were evaluated using Kaplan-Meier estimates and compared using the log-rank test. The estimate of the relative risk of events and its 95% confidence interval (CI) was estimated using the Cox proportional hazard model. All statistical computations were performed using SPSS software (ver. 21; SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant in all analyses.

Results

Patient population

In total, 50 patients with relapsed or refractory ALL from 16 institutions who were treated with blinatumomab between June 2016 and August 2017 were included in this study. All patients had Philadelphia-negative B cell precursor ALL and showed CD19 expression on leukemic cells at diagnosis. Patients' clinical characteristics at the initiation of blinatumomab treatment are summarized in Table 1. At the time of blinatumomab treatment, the median patients' age was 45 years (range, 19–71 years), and 10% were 65 years or older. The

Table 1 Clinical characteristics of all patients at the time of blinatumomab initiation ($n = 50$)

Characteristics	
Median age, years (range)	45 (19–71)
> 65, *n* (%)	5 (10%)
Sex, *n* (%)	
Male	20 (40.0)
Female	30 (60.0)
ECOG performance status, *n* (%)	
0–1	35 (70.0)
≥ 2	15 (30.0)
Salvage treatment phase, *n* (%)	
First	29 (58.0)
Second	12 (24.0)
Third or later	9 (18.0)
Previous allogenic stem cell transplant, *n* (%)	
Yes	27 (54.0)
Relapse site, *n* (%)	
Bone marrow only	39 (78.0)
Extramedullary only	5 (10.0)
Bone marrow + extramedullary	6 (12.0)
BM blast, *n* (%)	
< 50%	8 (18.6)
≥ 50%	35 (81.3)
Cytogenetic risk, *n* (%)	
Standard risk	26 (61.9)
High risk	16 (38.1)
Median time to initiation of blinatumomab, months	13.5 (0.9–160.8)

High risk, MLL, complex, hypodiploidy

n number, *ECOG* Eastern Cooperative Oncology Group, *BM* bone marrow

median proportion of blasts in the BM was 81% (range, 4–99%), the median time to blinatumomab treatment from diagnosis was 13.5 months (range, 0.9–160.8 months), and the median number of prior therapy was one (range, 1–4). Twenty-seven (54.0%) patients underwent allogenic stem cell transplantation (SCT) prior to blinatumomab treatment, 11 (22%) had extramedullary disease at time of blinatumomab treatment, and 5 had extramedullary disease only. The most common site of extramedullary disease was the central nervous system (CNS, 4 cases), and all patients with CNS disease had BM relapse. Other sites of extramedullary disease included the liver, lymph nodes, uterus, bone, and skin. Cytogenetic results were available for 42 patients at time of blinatumomab treatment, and 16 (38.1%) had high-risk cytogenetics.

Response to blinatumomab treatment

In total, 50 patients received blinatumomab treatment as salvage chemotherapy. The treatment schedule of blinatumomab was the same as that in a previous study [16]. During induction cycle 1, patients received blinatumomab for 4 weeks (9 μg/day for 1 week, then 28 μg/day for 3 weeks by continuous infusion). After induction cycle 1, patients were treated with 28 μg/day for 4 weeks followed by a 2-week treatment-free interval. Dexamethasone premedication (20 mg) was administered 1 h before treatment initiation in each cycle and before the dose step-up in one cycle. Prephase treatment was generally performed in patients with BM blasts ≥ 50% or peripheral blood blast ≥ 15,000 cell/μL to reduce severe cytokine release syndrome (CRS), but the regimen for prophase treatment was heterogeneous, including dexamethasone only, hydroxyurea and dexamethasone, cyclophosphamide and dexamethasone, cytarabine, dexamethasone, and hydroxyurea, or etoposide and dexamethasone.

One patient died of infection during the first cycle of blinatumomab, and we evaluated the responses of the remaining 49 patients to blinatumomab treatment. Twenty-two (44.9%) patients achieved remission, including 21 CR and one CRi. The treatment flow and outcomes of all patients are shown in Fig. 1. After the first cycle of blinatumomab, response assessments were performed in 46 patients. Twenty-one (46.9%) patients achieved remission, including 21 CR and 2 CRi. In 17 patients who achieved CR/CRi after the first cycle, 14 maintained remission and three showed disease progression after the second cycle of blinatumomab. In 23 patients with persistent disease after the first cycle, 11 received a second cycle of blinatumomab, and 2 (18.1%) achieved CR. Three patients who did not have response evaluations after the first cycle of blinatumomab showed progressive disease after the second cycle of blinatumomab. Sixteen patients subsequently underwent allogenic SCT, and 13 patients who did not respond to blinatumomab received salvage chemotherapy with various regimens of conventional chemotherapeutic agents. We were able to evaluate response assessments of eight patients, only one (12.5%) of whom had remission.

In this study, we evaluated the response rate to blinatumomab treatment according to patient subgroups (Table 2). Neither age, time from diagnosis to treatment, salvage treatment phase, performance status, cytogenetic risk at diagnosis, high tumor burden, history of allogenic SCT, or dose of dexamethasone prior to blinatumomab predicted patient response to blinatumomab treatment. Patients with extramedullary disease at the time of blinatumomab treatment had lower response rates than patients with BM relapse only, although this difference lacked statistical significance ($P = 0.478$). Two (33.3%) of six patients who had BM relapse with extramedullary disease showed responses, and one (25.0%) of four patients with extramedullary relapse only showed response to blinatumomab treatment. In four patients with CNS disease, one patient received a single dose of intrathecal chemotherapy with methotrexate prior to initiation of

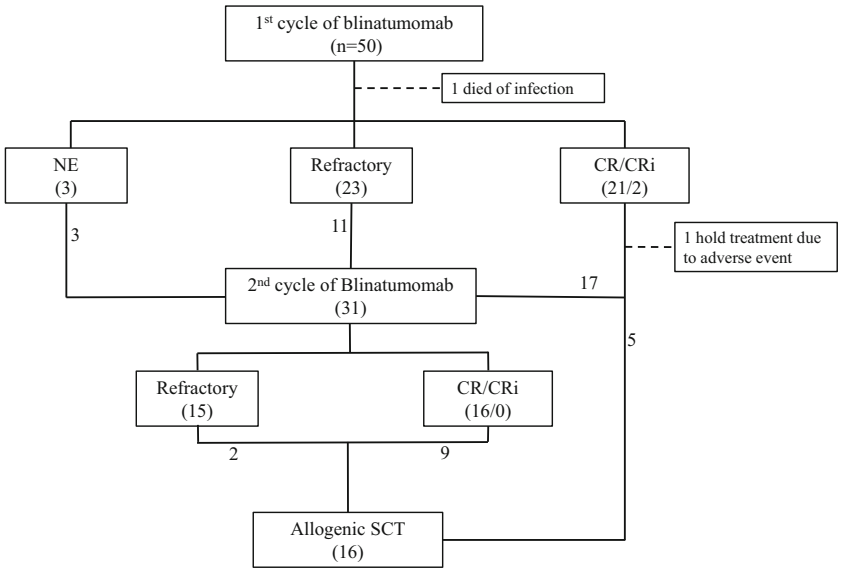

Fig. 1 Treatment flow and outcomes of all patients ($n = 50$)

blinatumomab and achieved CR after the first cycle of blinatumomab therapy, but stopped further treatment due to grade 3 neurotoxicity such as confusion, aphasia, and change in mental status at day 1 of the second cycle. Other patients did not receive intrathecal chemotherapy prior to or during blinatumomab therapy and showed progressive disease after the first cycle of blinatumomab.

Survival outcomes

Over a median follow-up of 4.3 months, 28 patients (56%) had disease progression, and 18 (36%) did by the time of the last follow-up. The median EFS was 3.3 months (range, 2.1–4.6 months), and the median OS was 7.5 months (range, 5.3–9.7 months). Patients who responded to blinatumomab treatment had a longer EFS and OS durations than patients who did not (EFS; 7.5 vs. 2.0 months, $P < 0.001$, OS; 8.1 vs. 5.2 months, $P < 0.001$, Fig. 2a, b). In addition, patients who subsequently underwent allogenic SCT had a longer EFS and OS intervals than patients who did not (EFS; 7.5 vs. 2.4 months, $P < 0.001$, OS; 7.5 vs. 5.2 months, $P = 0.058$, Fig. 2c, d).

Toxicity

The toxicities observed during blinatumomab induction therapy are summarized in Table 3. The most common non-hematologic toxicity was infection, and 25 (50%) patients developed infectious complications within two cycles of blinatumomab and severe infections (≥ grade 3) were observed in 8 (16%) patients. One patient died of pneumonia during the first cycle of blinatumomab, 10 (20%) patients developed CRS of any grade, and CRS of grade 3 developed in two (4.0%). A high dose of dexamethasone (> 80 mg) prior to the initiation of blinatumomab did not decrease the development of CRS of any grade ($P = 1.000$), but severe CRS did not occur in patients who received a high-dose dexamethasone prior to the initiation of blinatumomab treatment. Cardiovascular events, such as arrhythmia or hypotension, developed in 7 (14%) patients, and neurologic adverse events of any grade developed in 18 (36%). Severe neurologic adverse events (grade 3–4) developed in two (4%) patients, one of whom developed the adverse event during the first cycle of blinatumomab and did not receive a second cycle. The other patient developed grade 4 neurologic adverse events during the second cycle of blinatumomab and fully recovered with supportive care including a short course of dexamethasone and treatment interruption. This patient subsequently received allogenic SCT. Two of four patients with CNS relapse at the time of blinatumomab treatment developed neurologic adverse events of grade 1 and grade 3, and one with grade 3 neurotoxicity did not recover with supportive therapy and stopped further treatment.

Discussion

This present study shows that blinatumomab is an effective and tolerable therapy for Korean adult patients with relapsed or refractory Philadelphia-negative B cell precursor ALL in real practice. The remission rates and survival outcomes were comparable to those of previous studies [10, 16], despite that patients with extramedullary disease or poor performance statuses were included in this study. Blinatumomab has shown efficacy in phase II studies for relapsed or refractory ALL, ALL with minimal residual disease, and Philadelphia-positive ALL [7, 12]. Based on the promising results of phase II studies, a randomized phase III confirmatory study was conducted to

Table 2 Response rates after induction therapy with blinatumomab among patient subgroups ($n = 49$)

Variables	Response rates 44.9% (22/49)	RR (95%CI)	*P* value
Age at initiation of treatment			
< 55	46.9% (15/32)		
≥ 55	41.2% (7/17)	1.261 (0.384–4.141)	0.769
Sex			
Male	30.0% (6/20)		
Female	55.2% (16/29)	0.348 (0.104–1.161)	0.143
Salvage treatment phase			
1	51.7% (15/29)		
≥ 2	35.0% (7/20)	1.990 (0.616–6.427)	0.381
Time to treatment from diagnosis			
< 12 months	30.4% (7/23)		
≥ 12 months	57.7% (15/26)	3.117 (0.957–10.151)	0.085
ECOG PS at blinatumomab treatment			
0–1	52.9% (18/34)		
≥ 2	26.7% (4/15)	3.094 (0.820–11.672)	0.123
Cytogenetic risk at diagnosis			
Standard	50.0% (19/38)		
High	37.5% (3/8)	1.667 (0.348–7.981)	0.702
Cytogenetic risk at blinatumomab treatment			
Standard	46.2% (12/26)		
High	50% (8/16)	0..857 (0.246–2.983)	1.000
EMD at blinatumomab treatment			
No	48.7% (19/39)		
Yes	30.0% (3/10)	2.217 (0.499–9.847)	0.478
BM blast at blinatumomab treatment			
≤ 50%	66.7% (6/9)		
> 50%	41.2% (14/34)	2.857 (0.609–13.395)	0.263
Previous allogenic SCT			
No	47.8% (11/23)		
Yes	42.3% (11/26)	1.250 (0.404–3.866)	0.778
Dose of dexamethasone prior treatment			
≤ 80 mg	45.9% (17/37)		
> 80 mg	41.7% (5/12)	1.190 (0.319–4.442)	1.000

n number, *RR* relative risk, *ECOG* Eastern Cooperative Oncology Group, *PS* performance status, *EMD* extramedullary disease, *BM* bone marrow, *SCT* stem cell transplantation

compare blinatumomab monotherapy with conventional chemotherapy for relapsed or refractory Philadelphia-negative ALL [10]. The remission rates were significantly higher in the blinatumomab group than in the chemotherapy group (44 vs. 25%, $P < 0.001$), and the median OS time was significantly higher in the blinatumomab group than in the chemotherapy group (7.7 vs. 4.0 months, $P = 0.01$). However, the previous phase II and III studies of blinatumomab excluded frail patients and those with extramedullary relapse from clinical trial, and the efficacy of blinatumomab for such patient subgroups has been unclear. In long-term follow-up data of patients with ALL with minimal residual disease who were treated with blinatumomab, two patients relapsed with extramedullary disease of the testes and CNS [17]. This finding suggests that extramedullary disease can play a role in resistance and reduce the efficacy of blinatumomab treatment. One retrospective study recently reported that remission rates were significantly lower in patients with extramedullary disease than in those with BM relapse only (20 vs. 56.3%, $P = 0.03$) [1], but this study did not include patients with CNS disease at initiation of blinatumomab therapy. No study has reported on the efficacy of blinatumomab for patients with CNS disease. In our study, remission rates in patients with CNS disease were as low as those in patients with extramedullary disease, and two patients with CNS disease showed neurotoxicity during blinatumomab therapy. The mechanism of neurotoxicity remains unclear, but there is a concern that it might be related to active CNS disease. In our study, one patient developed neurotoxicity after achieving CR, and the other developed grade I neurotoxicity during blinatumomab therapy, which was managed by supportive therapy. Based on these results, the presence of CNS involvement upon initiation of blinatumomab therapy does not seem to be directly related to increased CNS toxicity. In addition, considering that the remission rate with conventional chemotherapy for patients with BM relapse is about 25% and the prognosis of patients with extramedullary disease is generally poor [5], the role of blinatumomab for extramedullary disease, including CNS disease, should be better defined in larger subsequent studies.

Because the mechanism of action for blinatumomab differs from that of conventional chemotherapeutic agents, the predictors that are associated with blinatumomab responses differ from the known predicting factors of ALL. In our study, the cytogenetic risk at diagnosis or relapse, which is a well-known risk factor for ALL, was not associated with blinatumomab treatment response. Immunologic biomarkers that reflect the mechanism of action for blinatumomab, such as the level of regulatory T cells and PD-1 expression at the time of blinatumomab treatment and T cell expansion and B cell depletion after blinatumomab initiation, have been reported as biomarkers that predict patient response to blinatumomab therapy [2, 11, 19]. Although no statistical significance was found in our study, high tumor burden, short time period from diagnosis to blinatumomab treatment, extramedullary disease, and male sex were associated with relatively low remission rates. In addition, patients with poor performance status (≥ 2) at the time of blinatumomab treatment had low remission rates, which is probably because these patients received more prior treatment. The status of CD19 expression on leukemic cells was also a reported clinical predictor for blinatumomab treatment in previous studies [1, 16]. Because blinatumomab treatment is highly expensive, it is important to find optimal candidates for blinatumomab treatment using these inflammatory biomarkers and clinical predictors.

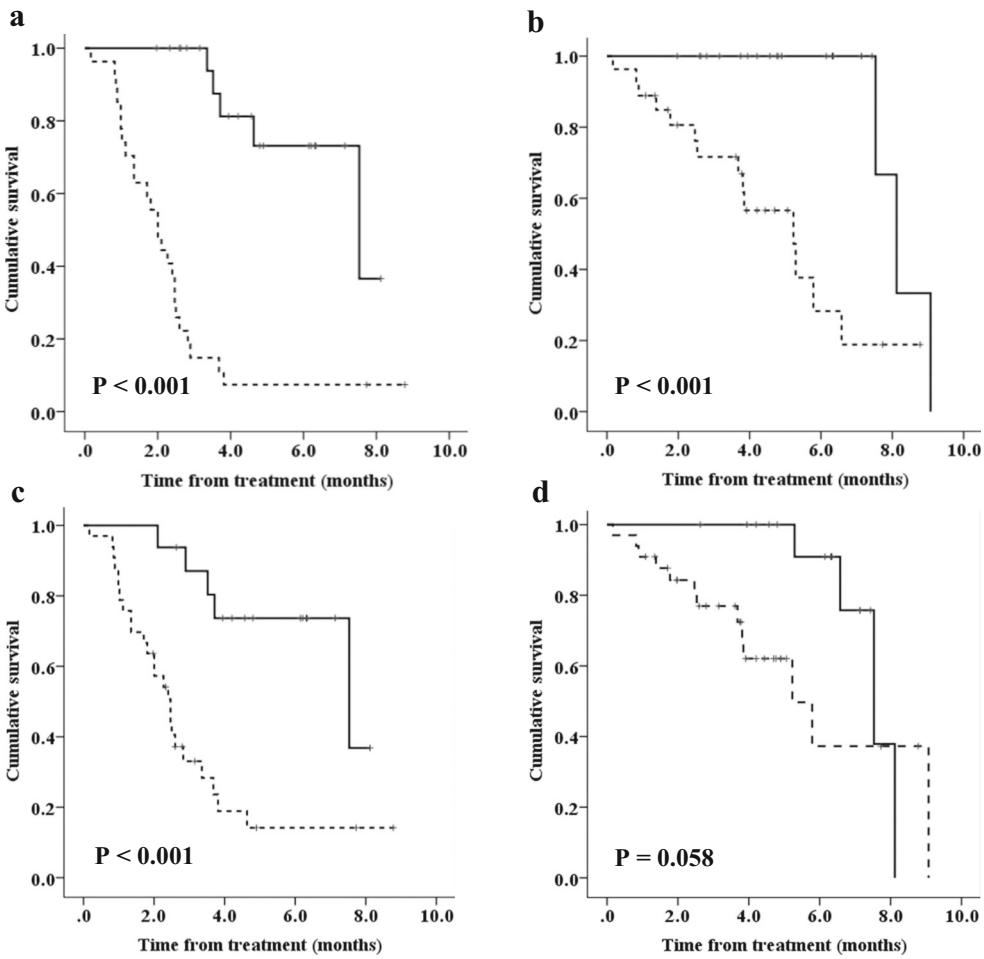

Fig. 2 Kaplan-Meier survival curves for event-free survival and overall survival according to response (**a**, **b**) and performance of allogenic stem cell transplantation (**c**, **d**)

Table 3 Adverse events during induction therapy with blinatumomab ($n = 50$)

	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
Febrile neutropenia	22 (44%)	5 (10%)	15 (30%)	2 (4.0%)	0
Neutropenia	39 (78%)	6 (12%)	10 (20%)	23 (46%)	0
Anemia	37 (74%)	23 (46%)	14 (28%)	0	0
Thrombocytopenia	37 (74%)	6 (12%)	7 (14%)	24 (48%)	0
Infection	25 (50%)	17 (34%)	6 (12%)	1 (2%)	1 (2%)
Cytokine release syndrome	10 (20%)	8 (16%)	2 (4.0%)	0	0
Rash	2 (4%)	2 (4%)	0	0	0
Nausea	1 (2%)	0	1 (2%)	0	0
Jaundice	1 (2%)	0	1 (2%)	0	0
Tumor lysis syndrome	1 (2%)	0	0	1 (2%)	0
Encephalopathy	1 (2%)	0	1 (2%)	0	0
Dizziness	10 (20%)	10 (20%)	0	0	0
Somnolence	8 (16%)	7 (14%)	1 (2%)	0	0
Cardiovascular events	7 (14%)	7 (14%)	0	0	0
Tremor	6 (12%)	6 (12%)	0	0	0
Altered state of consciousness	4 (8%)	2 (4%)	1 (2%)	1 (2%)	0
Confusion	3 (6%)	2 (4%)	1 (2%)	0	0
Ataxia	1 (2%)	1 (2%)	0	0	0
Aphasia	1 (2%)	0	1 (2%)	0	0
Hiccups	1 (2%)	1 (2%)	0	0	0

With regard to toxicity, CRS and neurologic adverse events were the most serious complications associated with blinatumomab therapy, and in our study, severe CRS and neurologic adverse events were the major cause of treatment interruptions. Previous clinical trials have observed a 2–5% incidence of serious CRS (≥ 3). The development of CRS is related to abnormal macrophage activation and is expected in the beginning of the first cycle of blinatumomab [15]. In our study, severe CRS developed in 4% of the patients and treatment interruption was required for recovery; however, patients who received a high dose of dexamethasone prior to blinatumomab did not develop severe CRS. In addition, the use of a high dexamethasone dose did not decrease the response rates to blinatumomab. In a previous study, the use of steroids during the first cycle of blinatumomab did not affect the response or survival outcomes [1]. In addition, since neurologic adverse events may also be related to inflammatory response [18], the application of a high steroid dose may help decrease the development of severe neurologic adverse events. Therefore, the more active use of steroids prior to or during the first cycle of blinatumomab may be required to prevent these severe adverse events. Although infection was common during blinatumomab induction therapy in our study, it is unclear whether blinatumomab is directly related to the development of infectious complications, because various host factors such as duration and degree of neutropenia and lymphopenia, treatment phase, or performance status play an important role in the development of infection.

In this study, patients who subsequently underwent allogenic SCT had longer survival than patients who did not. This difference in survival may have been increased because allogenic SCT was performed mainly in patients who showed response to blinatumomab therapy. If more patients who achieved CR and received maintenance treatment with blinatumomab were included in the non-transplant group, the difference in survival outcome may be less impressive.

In conclusion, 44.9% of relapsed or refractory Philadelphia-negative B cell precursor ALL patients achieved remission after blinatumomab treatment. Although our findings lack statistical significance, patients with extramedullary disease and poor performance status had low responses to blinatumomab treatment. In addition, the administration of a high dose of dexamethasone prior to blinatumomab treatment did not affect the response to blinatumomab. The most common non-hematologic toxicity was infection, and severe CRS and neurologic toxicity developed at a rate of 4% each. Based on these results, blinatumomab was found to be an effective and tolerable therapy in adult Korean patients with relapsed or refractory Philadelphia-negative B cell precursor ALL.

Compliance with ethical standards

This study was approved by the Institutional Review Board of each participating hospital, in accordance with the Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

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