SPECIAL EDITION

Blinatumomab in the treatment of relapsed/refractory acute lymphoblastic leukemia: updates from quality of life and biomarker studies

T. Feys, MSc, MBA

Over the last three decades, the prognosis for adults with newly diagnosed acute lymphoblastic leukemia (ALL) improved significantly. In fact, with the current intensive chemotherapy regimens complete remission rates of 85 to 90% are achieved with 30 to 50% long-term survivors.[1-4] Despite these improvements, most adults with B-cell precursor ALL will have disease relapse and will ultimately die from complications of resistant disease or associated treatment. The current standard salvage chemotherapy for patients with relapsed, or refractory ALL induce a remission in 18 to 44% of patients, but these remissions are mostly not very durable.[5-8] With the current treatment regimens, the median overall survival (OS) among patients with relapsed or refractory ALL ranges from 2 to 6 months with only 10% of patients or less surviving 3 to 5 years.[8,9] As such, more effective treatment are urgently needed to improve the prognosis of these patients.

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IMPROVED OUTCOMES WITH BLINATUMOMAB COMPARED TO CHEMOTHERAPY IN RELAPSED REFRACTORY ALL

Blinatumomab is a bispecific T-cell engager (BiTE) antibody construct that simultaneously binds to CD3-positive cytotoxic T-cells and to CD19-positive B-cells. In doing so, blinatumomab allows the patient's endogenous T-cells to recognize and eliminate the CD19-positive ALL cells.[10,11] In a phase 2 trial, including 189 patients with relapsed or refractory B-precursor ALL (B-ALL), blinatumomab induced a complete remission with complete or partial hematologic recovery (CR/CRh) in 43% of patients with a median OS of 6.1 months.[12] These promising findings formed the basis for the multinational, randomized, phase 3 TOWER trial comparing blinatumomab with standard chemotherapy in the treatment of patients with relapsed or refractory B-ALL.[13]

In the TOWER study, 405 adult patients with relapsed or refractory, Philadelphia chromosome–negative B-ALL, were randomized to receive blinatumomab (N= 271) or standard chemotherapy (N= 134). The median OS in the study proved to be significantly longer in patients treated with blinatumomab compared to chemotherapy (median OS: 7.7 *vs.* 4.0 months; HR[95%CI]: 0.71[0.55-0.93]; p= 0.01) (*Figure 1*). In addition to this, remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the chemotherapy arm, both with respect to complete remission with full hematologic recovery (34% *vs.* 16%, p< 0.001) and with respect to complete remission with full, partial, or incomplete hematologic recovery (44% *vs.* 25%, p< 0.001). A treatment with blinatumomab also resulted in a higher rate of event-free survival (EFS) than what was seen with chemotherapy (6-month estimates 31% *vs.* 12%; HR[95%CI]: 0.55[0.43 to 0.71]; p< 0.001) and the remissions with blinatumomab also proved to be more durable than the responses to chemotherapy (median duration of remission: 7.3 *vs.* 4.6 months).[13]

Adverse events of grade 3 or higher were reported in 87% of the patients in the blinatumomab group and in 92% of the patients in the chemotherapy arm in the TOWER trial. The incidence of grade ≥3 neutropenia was lower with blinatumomab than with chemotherapy (37.8% *vs.* 57.8%) as was the incidence of grade ≥3 infections (34.1% *vs.* 52.3%). Grade ≥3 cytokine release syndrome (CRS), a known side effect of blinatumomab, was seen in 4.9% of patients in the experimental arm (*vs.* 0% on chemotherapy).[13]

In summary, the TOWER trial clearly established the clinical potential of blinatumomab in the management of relapsed/refractory ALL. During the 2017 annual meeting of the

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Please send all correspondence to: T. Feys, Ariez international, Oude Houtlei 118, 900 Ghent, E-mail: t. feys@ariez.com, Tel: 0479/567890

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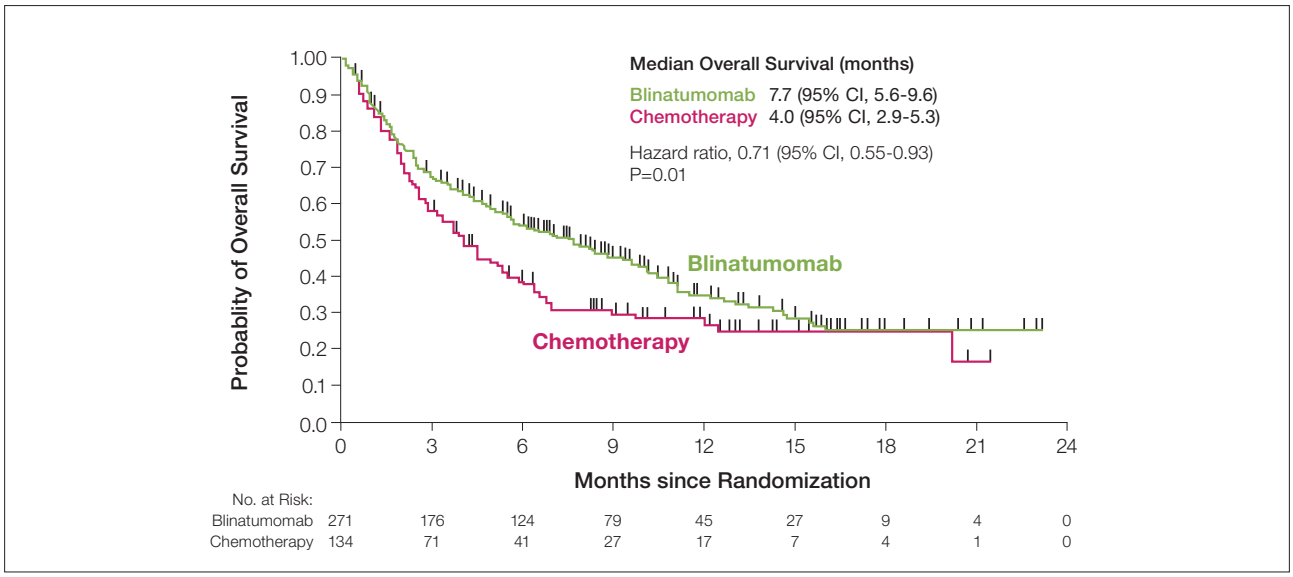

FIGURE 1. Significantly longer OS with blinatumomab than with standard chemotherapy in the phase III TOWER trial.[13]

American Society of Hematology (ASH), updated data were presented on the impact of blinatumomab on the quality of life of patients in the TOWER trial.[14] In addition to this, *Wei et al*. presented results of a study evaluating the impact of baseline biomarkers on the clinical outcome of relapsed/refractory ALL patients treated with blinatumomab.[15] In a third study of interest, *King et al*. looked for biomarkers that could identify patients who were at a higher risk for CRS.[16]

IMPACT OF BLINATUMOMAB ON THE QUALITY OF LIFE OF B-ALL PATIENTS

During the 2016 annual ASH meeting, *Topp et al*. already reported an analysis of the TOWER study, indicating that blinatumomab delayed the time to a clinically meaningful deterioration (TTD) in health-related quality of life (HRQoL) compared to chemotherapy.[17] Moreover, the HRQoL benefits with blinatumomab relative to chemotherapy could be observed as early as 8 days after treatment initiation.[17] The TOWER study also evaluated the impact of blinatumomab and chemotherapy on specific symptoms that are commonly experienced by adult ALL patients. For this analysis, the newly developed Acute Lymphoblastic Leukemia Symptom Scale (ALLSS) is used, assessing typical ALL symptoms such as fatigue, loss of appetite, fever, night sweats, bruising and bleeding, dyspnea, joint or bone pain, lymph node swelling, infections and itching.[14] In the TOWER trial, the HRQoL was assessed using the ALLSS and the EORTC QLQ-C30 questionnaire on day 1 and on days 8, 15 and 29 of each treatment cycle and during the safety follow-up visit.

Baseline and at least 1 post-baseline ALLSS scores were recorded for 309 of the 376 patients who received at least 1 dose of study drug (blinatumomab: N=223/267; chemotherapy: N=86/109). Whereas patients receiving blinatumomab reported minimal or no change in their mean ALLSS total scores during cycle 1, patients under chemotherapy did indicate a worsening in mean overall ALLSS scores. Patients in the blinatumomab arm experienced a clinically significant delay in the TTD in HRQoL. The TTD in HRQoL was longer in the blinatumomab group for all ALLSS items, except for easy bleeding, fever, joint or bone pain, swollen lymph nodes, and night sweats, which were similar in both groups (*Table 1*).[14]

In summary, this ALLSS analysis of the TOWER study further substantiates the HRQoL benefit of blinatumomab over standard of care chemotherapy in patients with relapsed/refractory ALL.

BIOMARKERS FOR RESPONSE AND TOXICITY IN ADULT ALL PATIENTS TREATED WITH BLINATUMOMAB

To identify prognostic (i.e. patient or tumor characteristics that influence patient outcome) and/or predictive (i.e. factors that predict a response to treatment) biomarkers, all patients enrolled in the TOWER study needed to provide a baseline blood sample. During ASH 2017, *Wei et al*. reported the results of this biomarker analysis.[15] The analysis revealed that a higher platelet count, a lower percentage of bone marrow blasts and higher $CD45^+$ $CD3^+$ $CD8^+$ T-cell counts in patients treated with blinatumomab were associated with a higher likelihood of CR/CRh/CRi. In addition to this, several baseline factors were identified that had an influence on the survival of patients. In fact, higher platelet counts and higher granulocyte counts were shown to be prognostic for a longer OS. In addition to this, a lower $CD45^+$ $CD3^-$ $CD19^+$ cell

TABLE 1. Time to deterioration in ALLSS individual item scores or death in the phase III TOWER study.[15]

Scale	Blinatumomab	Chemotherapy	Hazard Ratio (95% CI)	p-value
TTD in HRQL or death, median (95% CI)				
Tiredness	1.4 (1.0, 2.3)	0.5 (0.5, 1.1)	0.61 (0.44, 0.84)	0.002
Weakness	1.1 (1.0, 1.9)	0.5 (0.5, 1.0)	0.55 (0.40, 0.75)	<0.001
Easy bruising	8.1 (4.2, NE)	1.3 (0.9, NE)	0.54 (0.37, 0.77)	<0.001
Easy bleeding	7.1 (3.5, NE)	2.5 (2.0, 5.2)	0.75 (0.50, 1.10)	0.12
Fever	0.5 (0.3, 0.5)	0.5 (0.5, 0.9)	1.04 (0.77, 1.40)	0.80
Joint or bone pain	1.4 (1.1, 2.0)	1.2 (0.9, 1.9)	0.86 (0.61, 1.20)	0.31
Itch	2.0 (1.5, 3.2)	1.9 (0.5, 2.5)	0.68 (0.48, 0.96)	0.025
Swollen lymph nodes	NE (4.4, NE)	3.5 (2.1, 5.2)	0.73 (0.47, 1.13)	0.15
Fighting infection	1.4 (1.0, 1.8)	0.6 (0.5, 1.1)	0.67 (0.49, 0.91)	0.008
Shortness of breath	4.1, (1.9, NE)	1.8 (1.0, 2.3)	0.62 (0.44, 0.89)	0.007
Unable to eat	1.4 (1.0, 1.5)	0.5 (0.5, 1.1)	0.69 (0.50, 0.94)	0.014
Night sweats	1.2 (1.0, 1.7)	1.1 (0.9, 1.9)	0.94 (0.68, 1.31)	0.64

* Stratified log-rank test; study not powered to detect differences in individual items.

count in patients treated with blinatumomab was predictive for a longer OS. With respect to toxicity, this analysis did not show an association between grade ≥3 neurologic events, infections, or CRS and the percentage of bone marrow blasts, or lymphocyte markers ($CD45^+$ $CD3^+$ $CD8^+$).

In another blinatumomab biomarker study presented at ASH 2017, *King et al.* assessed whether there was a relationship between the level of C-reactive protein (CRP) and ferritin and the development of CRS, or neurotoxicity in patients treated with blinatumomab.[16] This single-center, retrospective analysis included data from 25 relapsed/refractory B-ALL patients who were treated with blinatumomab. In total, 14 patients experienced CRS during cycle 1, with ten grade 1 events and four grade 2 events. Among the 11 patients who started cycle 2, two patients experienced CRS (one grade 1 and one grade 2 event). Interestingly, the median peak CRP was significantly increased (p=0.001) in patients with CRS compared to patients without CRS. In addition to this, the median absolute peak ferritin level and the incremental change in ferritin from baseline in cycle 1 was also found to be significantly correlated to CRS. Neurotoxicity was documented in six patients (24%) during cycle 1. The analysis also indicated that patients with neurotoxicity had a significantly shorter time to peak CRP and significantly increased baseline and peak ferritin levels in cycle 1 (p=0.044 and 0.026, respectively). Next to evaluating the relation between CRP and ferritin levels and toxicity, *King et al.* also assessed whether there was an impact on response. In total, 11 patients (44%) achieved a CR and 14 patients (56%) had refractory disease. Responders were found to have significantly lower baseline CRP (p=0.008) and lower baseline ferritin values (p=0.03).[16]

These data suggest that there is an association between changes in biomarkers (CRP and ferritin) and the development of CRS, and suggests that frequent monitoring of these biomarkers may be useful in predicting patients at risk for CRS and neurotoxicity. However, the sample size in this study was limited and validation of these findings is required.

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