Editorial Commentary

Blinatumomab improves outcomes for pediatric patients with low-risk B-cell acute lymphoblastic leukemia in first marrow relapse

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Over the last several decades, advances in treatment approaches have resulted in significant improvements in survival outcomes for children, adolescents, and young adults with newly diagnosed B-cell acute lymphoblastic leukemia (B-ALL). Unfortunately, disease relapse remains the main reason for treatment failure in about 15% of pediatric patients and cure rates following relapse are suboptimal, with high rates of subsequent relapse and death (1-4). Generally, most patients that relapse after completion of primary treatment are able to achieve a second complete remission and cure rates for these patients are around 50%. However, for patients who relapse while on therapy, only 50% to 70% are able to achieve a second remission, with cure rates of only 20% to 30% (1).

Several prognostic factors for survival outcomes have been identified and have been incorporated into risk stratification approaches for first relapse including time from diagnosis to relapse, site of relapse, and minimal residual disease (MRD) after reinduction chemotherapy (2,5,6). While different collaborative groups employ different risk stratification criteria, patients treated on Children's Oncology Group trials have historically been considered low-risk (LR) with more favorable outcomes if they experience bone marrow (BM) relapse [with or without extramedullary disease (BM ± EM)] ≥36 months from initial diagnosis or isolated extramedullary (IEM) relapse ≥18 months from initial diagnosis and have low MRD (<0.1%) at end of reinduction chemotherapy.

The current standard treatment approach for pediatric patients in first relapse includes a 4-week block of intensive reinduction chemotherapy followed by consolidation chemotherapy. For children who have early BM relapse (<36 months from diagnosis) or have late BM relapse (≥36 months after diagnosis) and MRD ≥0.1% after reinduction, consolidation chemotherapy followed by hematopoietic stem cell transplant (HSCT) serve as the best chance of cure for these patients (4). For LR patients with late first relapse and MRD <0.1% following reinduction, survival outcomes are favorable with an approach of chemotherapy alone without HSCT (7-9).

Blinatumomab is a genetically modified antibody and novel immunotherapy that serves as a T cell engager that effectively brings CD3-positive T cells into contact with CD19-expressing B-lineage leukemia cells, inducing T-cell mediated cell death. With its favorable response rate and tolerable safety profile, blinatumomab is approved by the Food and Drug Administration and the European Medicines Agency for the treatment of adult and pediatric relapsed/refractory B-ALL, as well as B-ALL with positive MRD (10). The multicenter, randomized, Phase III Children's

Oncology Group trial AALL1331 was a confirmatory trial to test whether the addition of blinatumomab to standard chemotherapy for the treatment of B-ALL in first relapse would improve disease-free survival (DFS) and reduce rates of subsequent relapse (9-11).

Hogan and colleagues recently reported the findings of LR patients with B-ALL from AALL1331 (11). One of the aims of this study was to compare survival of patients specifically with LR first relapse treated with chemotherapy alone or chemotherapy plus blinatumomab. All patients aged 1–30 years old with B-ALL in first relapse were eligible for AALL1331 and patients were stratified at end-induction to the LR group if they had BM relapse ≥36 months after diagnosis or IEM ≥18 months after diagnosis, and MRD <0.1%. End-induction MRD was chosen as the distinguishing feature to stratify between intermediate risk (≥0.1%) and LR patients (<0.1%). Patients with first marrow relapse ≥36 months after diagnosis and MRD <0.1% after reinduction have outstanding cure rates with chemotherapy alone without HSCT, while relapse ≥36 months after diagnosis and MRD ≥0.1% is associated with significantly worse survival outcomes (7,8). The results for the intermediate and high-risk patients, all of whom underwent HSCT, have previously been published (9).

All patients received 4 weeks of reinduction chemotherapy with dexamethasone, vincristine, pegaspargase, mitoxantrone, and risk-based intrathecal chemotherapy, according to the UKALL R3 regimen (12). Following reinduction, LR patients were randomized to standard chemotherapy versus three 4-week blinatumomab blocks intercalated with the standard chemotherapy blocks, followed by maintenance chemotherapy. Patients with CNS3 disease received intensified intrathecal chemotherapy and cranial radiotherapy. Patients with testicular involvement that persisted after reinduction received testicular radiation.

A total of 255 eligible LR patients after reinduction were randomized with 128 receiving standard chemotherapy alone and 127 receiving chemotherapy plus blinatumomab. Median follow-up was 3.5 years (range, 25 days–6.6 years; interquartile range, 2.5–4.7 years). There was no statistical difference in DFS and overall survival (OS) rates between the blinatumomab and chemotherapy arms with the 4-year DFS (P=0.089) and OS (P=0.11) rates, respectively, 61.2% and 90.4% for blinatumomab versus 49.5% and 79.6% for chemotherapy.

However, DFS and OS differed significantly based on the site of first relapse. Of the two-thirds of patients who had a BM ± EM relapse (n=174), the 4-year DFS (P=0.015) and OS (P=0.02) were 72.7% and 97.1% for blinatumomab versus 53.7% and 84.8% for chemotherapy. For isolated BM relapse (n=142), the 4-year DFS (P=0.031) and OS (P=0.044) were 72.9% and 96.3% for blinatumomab (n=70) versus 57.1% and 84.0% for chemotherapy (n=72). However, for BM + EM relapse (n=32), the 4-year DFS (P=0.30) and OS (P=0.14) were not statistically significantly different at 69.5% and 100% for blinatumomab (n=17) versus 36.1% and 85.7% for chemotherapy (n=15). Nonetheless, while DFS and OS were numerically superior with blinatumomab use in patients with BM + EM relapse, the small number of patients in this subgroup has likely impacted the power to derive a statistically significant difference. One-third of patients (n=81) had a late IEM relapse [25% central nervous system (CNS) and 6.7% testicular] and the 4-year DFS (P=0.62) and OS (P=0.53) were 36.6% and 76.5% for blinatumomab (n=40) versus 38.8% and 68.8% for chemotherapy (n=41). Those with isolated CNS (ICNS) relapse were more likely to have second relapses (66.7%), in which the majority occurred in the CNS (71%).

Importantly, blinatumomab was well tolerated by LR patients with significantly lower toxicities, especially when evaluating hematologic and infectious toxicities, compared with the intensive chemotherapy blocks alone. Additionally, there were overall low rates of cytokine release syndrome and neurotoxicity from blinatumomab, and most were low grade. All adverse events that were attributed to be blinatumomab-related were fully reversible.

The combination of blinatumomab and chemotherapy for LR first relapse B-ALL patients did not improve outcomes for the group as a whole; however, the addition of blinatumomab did significantly improve both DFS and OS for the two thirds of patients who had BM ± EM relapse. Multivariable analysis of DFS for BM ± EM relapse highlighted those younger patients who relapsed later and who had MRD <0.01% had improved outcomes. Of particular interest is that patients with IEM relapse had poor outcomes with both arms. Unfortunately, those with ICNS relapse did the worst with high rates of second relapse and inferior DFS in both arms compared to previous studies. The authors attributed the lower DFS rate for ICNS relapses to reduced intensity of CNS-directed therapy compared to prior trials with fewer intrathecal doses of chemotherapy as well as fewer systemic doses of high-dose cytarabine and methotrexate given on AALL1331, along with different overall approaches to cranial radiation doses and HSCT for these patients. Additionally, given that the majority of second relapses in the ICNS relapse cohort

were in the CNS, this emphasizes that blinatumomab is not particularly effective in treating CNS disease.

Similar experiences and results have been reported in studies of adult relapsed patients with B-ALL. Generally, adult patients with relapsed/refractory (R/R) B-ALL have a dismal prognosis and intensive chemotherapy leads to complete remission in less than 40% of patients (13,14). For these patients, 5-year OS is less than 20%, with some improvement and prolonged OS in patients proceeding to HSCT (14). In the pivotal phase III TOWER study, blinatumomab was found to be superior to conventional chemotherapy for adult patients with R/R B-ALL and a viable bridge to HSCT (15). Dombret *et al.* performed a retrospective analysis on adult patients treated with blinatumomab as first versus later relapse therapy on the pivotal phase III TOWER study (15,16). A total of 104 adult patients in first relapse were compared to 167 patients treated with blinatumomab in second or greater relapse. Median OS was 11.1 months [95% confidence interval (CI): 8.2–not reached] for first salvage versus 5.1 months (95% CI: 3.2–7.1) for those patients treated with blinatumomab in second/later salvage (16). A similar trend was found in a retrospective analysis performed by Topp *et al.* with patients who received blinatumomab as first salvage therapy having longer median OS compared to second/later salvage therapy [10.4 versus 5.7 months; hazard ratio (HR), 1.58; P<0.001] (17). These results confirmed the benefit of blinatumomab is more evident when administered in first relapse compared to second or greater relapse.

Notably, blinatumomab has a more favorable safety profile and superior efficacy when it is administered to patients in remission as opposed to fully relapsed disease, either in the setting of persistent MRD similar to what was done in the AALL1331 study following reinduction chemotherapy or cytoreduction regimen, or in the R/R MRD$^+$ setting as it was applied in the BLAST study (18). Furthermore, survival benefit for even earlier use of blinatumomab as part of the consolidation program was also established among adult patients enrolled in the ECOG 1910 study after achieving MRD-negative CR1 with chemotherapy, and this approach will likely become the new standard of care in adults with newly diagnosed B-ALL (19). Several other studies have demonstrated safety and efficacy of utilizing blinatumomab in combination with chemotherapy early in the course of therapy, with the benefit of blinatumomab extending beyond those in MRD$^+$ CR1 and establishing survival advantage for blinatumomab even in MRD-negative patients (20-23). Therefore, investigating the benefit of integrating blinatumomab during frontline therapy in children with B-ALL may further improve overall outcomes and reduce the risk of relapse.

Given that EM relapse in the CNS is associated with a dismal prognosis and is extremely challenging to treat due to many therapies having decreased permeability and access to the CNS, we sought to better understand extramedullary failure of blinatumomab therapy (24). In this retrospective study, the outcomes of 132 adult patients with either R/R (n=103) or MRD$^+$ (n=29) B-ALL who were treated with blinatumomab were analyzed. Patients with no history of extramedullary disease prior to receiving blinatumomab had improved response to blinatumomab (P=0.019) compared to patients with EM disease. Blinatumomab failure was defined as primary refractory disease to blinatumomab or relapse after an initial response. Of the 89 patients who failed blinatumomab, 38 relapsed with EM disease, including 15 with CNS relapses. This study demonstrated that any prior history of extramedullary disease predicts an inferior response to blinatumomab and is associated with increased risk of subsequent relapse at EM sites, with the CNS as the most common site of extramedullary failure (24). These findings, together with the recent results from AALL1331, confirm decreased efficacy of blinatumomab for the treatment of relapsed EM$^+$ B-ALL when compared to isolated BM involvement. Especially in the setting of CNS involvement prior to blinatumomab, the data suggest limited access of blinatumomab to the CNS with particularly poor responses and increased CNS relapses for patients.

This is contrary to what has been observed for CD19-directed chimeric antigen receptor (CAR) T cell therapy. Many publications report favorable responses to CD19 CAR T cell therapy for patients with EM and CNS disease that are similar to those seen in patients without CNS disease (25-29). Jacoby *et al.* conducted a retrospective analysis of 55 pediatric patients who received CD19-targeted CAR T cell therapy for the treatment of relapsed B-ALL with CNS involvement with 94% of patients achieving a complete remission as a result of this treatment (27). The Pediatric Real World CAR Consortium reported on the outcomes of 184 patients who were treated with CAR therapy and found there was no difference in 12-month relapse-free survival (P=0.92) and 24-month OS (P=0.41) between patients with CNS involvement at time of relapse (n=40), non-CNS extramedullary disease (n=15), and those with BM only relapse (25). In patients with CNS disease, 88% are able to achieve a complete remission in response to CAR T

cell therapy compared to 66% of patients with non-CNS EM relapse (25). Ultimately, CAR T cells are effective at clearing CNS disease and can result in durable remissions for relapsed B-ALL patients with CNS involvement (28).

The recently published results from AALL1331 for children, adolescents, and young adult patients with LR B-ALL with first BM ± EM relapse demonstrated significant improvements in DFS and OS for this cohort. As a result, blinatumomab in combination with chemotherapy for these patients should be considered the new standard of care. Alternatively, those LR patients with IEM relapse, and specifically ICNS relapse, had poor rates of DFS and OS despite the addition of blinatumomab. There is a critical need to improve upon the significantly inferior outcomes of these patients with particular focus on optimizing CNS-directed therapy. Given the promising data on CAR T cell therapy in patients with leukemia with CNS involvement, further clinical trials investigating this treatment approach are of the utmost importance.

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