# Blinatumomab and better BCR::ABL1 inhibition begets better bone marrow transplant outcomes

Marlise R. Luskin[1] and Jessica T. Leonard[2]

[1]Division of Leukemia, Department of Medicine, Dana-Farber Cancer Institute, Boston, MA and [2]Knight Cancer Institute, Department of Medical Oncology, Oregon Health & Science University, Portland, OR, USA

**Correspondence:** M.R. Luskin
marlise_luskin@dfci.harvard.edu

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In this issue of *Haematologica*, Webster and colleagues report the outcomes of two cohorts of patients receiving a first allogeneic bone marrow transplant (alloBMT) with post-transplant cyclophosphamide (PTCy) for acute lymphoblastic leukemia (ALL) in earlier and later eras. They demonstrate improved outcomes in the more recent cohort, which Webster *et al*. attribute to the ability of blinatumomab and potent tyrosine kinase inhibitors (TKI) to more effectively control disease prior to transplantation.[1]

Acute lymphoblastic leukemia in adults has historically been associated with dismal outcomes as the disease is commonly resistant to chemotherapy, and adults, especially older adults, have poor tolerance of conventional treatment intensification.[2] In recent years, novel agents including blinatumomab, inotuzumab, and second- and third-generation TKI for Philadelphia chromosome-positive ($Ph^+$) ALL have allowed more adult patients with $Ph^-$ and $Ph^+$ B-cell ALL to achieve measurable residual disease (MRD)-negative remissions prior to alloBMT, which is associated with better post BMT outcomes.[3-7] AlloBMT continues to represent a valuable treatment option for many patients with high-risk ALL in both first (CR1) and later (CR2+) complete remissions making it essential to understand the outcomes of alloBMT in patients receiving modern pre-transplant therapy.[8]

Webster and colleagues found that more recent "ERA2" (2015-2022) patients had superior outcomes as compared to earlier "ERA1" (2008-2014) patients, an expected but nonetheless heartening finding. This is even though the ERA2 patients were older (median age 50 *vs*. 45.5 years, *P*=0.03), were in poorer medical condition (Hematopoietic Cell Transplantation-specific Comorbidity Index [HCT-CI] ≥4 in 21% *vs*. 9%, *P*=0.01), and almost never received myeloablative conditioning (3% *vs*. 56%, *P*<0.0001). The ERA2 patients had better relapse-free survival (RFS) (Hazard Ratio [HR]: 0.52, *P*=0.001) and overall survival (OS) (HR: 0.54, *P*=0.005); a multivariate analysis confirmed these findings. Improved outcomes were almost entirely due to a decrease in relapse. ERA2 patients had a lower cumulative incidence of relapse (CIR) (HR: 0.45, *P*=0.005) while there was no difference in rates of non-relapse mortality (NRM), grade III-IV acute graft-*versus*-host disease (GvHD), severe chronic GvHD, or graft failure at one year between cohorts.

"The times they are a-changin' ". But why? Webster and colleagues note that ERA2 patients with B-ALL were less likely to have persistent MRD at the time of transplant (17% *vs*. 4.5%, *P*=0.005), which was presumably in large part due to the ability of blinatumomab to 'erase' MRD. (No patients received blinatumomab in ERA1 while in ERA2 approximately one third of B-ALL patients transplanted in CR1 without salvage received blinatumomab) (Figure 1). Impressively, patients with B-ALL transplanted in CR1 (with reduced intensity conditioning and PTCy) after blinatumomab exposure had a 5-year CIR of 9.9% (95% CI: 3-23) and NRM of 6.7% (95% CI: 1-19) compared to 5-year CIR of 26.5% (95% CI: 19-34) and NRM 13.9% (95% CI: 9-20) in those who did not receive blinatumomab. This suggests that blinatumomab prior to transplant may improve both the efficacy and safety of transplant and that myeloablative conditioning may not be essential when disease is optimally controlled.

Patients with $Ph^+$ ALL showed a similar improvement in outcomes in ERA2, with improved OS (*P*=0.01), RFS (*P*=0.001), and CIR (*P*=0.003). When focusing solely on the patients who received TKI but not blinatumomab prior to transplant, patients who received a later generation TKI had improved OS (HR: 0.39, 95% CI: 0.18-0.84), RFS (HR: 0.33, 95% CI: 0.16-0.65), and reduced CIR (SDHR: 0.27, 95% CI: 0.11-0.67). In the recent PhALLCON study, ponatinib improved rates of MRD negativity after induction as compared to imatinib, and thus the improved outcomes post alloBMT seen in $Ph^+$ patients are also likely due to improved disease control pre-transplant.[9]

The T-cell ALL story is less sanguine. These patients did not show an improvement in MRD persistence between ERA1 and ERA2 (41.7% *vs*. 28.0%, *P*=0.47) and there was no difference

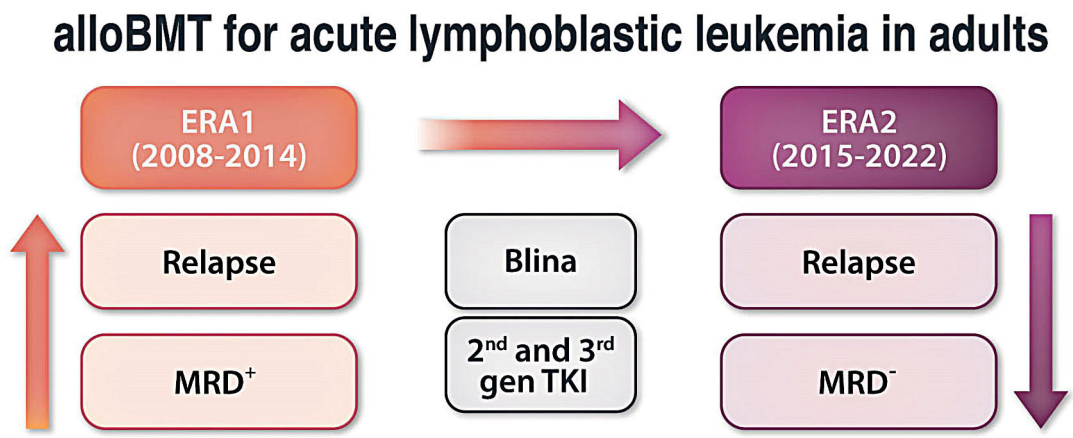


**Figure 1. Decrease in acute lymphoblastic leukemia relapse after allogeneic bone marrow transplant over time due to improvement in disease control as a result of blinatumomab and advanced tyrosine kinase inhibitors.** alloBMT: allogeneic bone marrow transplantation; Blina: blinatumomab; gen: generation; MRD: achieve measurable residual disease; TKI: tyrosine kinase inhibitors.

in CIR, RFS, or OS between eras, further supporting the hypothesis that the deep remissions induced by effective novel therapeutics set patients up for successful alloBMT. In summary, Webster and colleagues demonstrate convincingly that alloBMT outcomes are improving for patients with B-ALL who enter transplant with excellent disease control. For ERA2 B-ALL patients transplanted in CR1, a 5-year CIR of 9.9% and NRM of 6.7% is impressive, particularly given the assumption that higher risk patients had been referred for transplant. This study also highlights the ongoing unmet need for patients with T-ALL. Webster and colleagues do their part to keep alloBMT in the treatment paradigm for ALL. The critical question going forward will be to understand how increasingly effective transplant and non-transplant approaches compare – a welcome challenge for future investigators.

## Disclosures

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## Contributions

*MRL and JTL wrote the editorial.*

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