Improved outcomes of acute lymphoblastic leukemia after allogeneic blood or marrow transplantation with high-dose post-transplantation cyclophosphamide in the era of more effective pre-transplant therapy

Jonathan A. Webster,[1] Madison Reed,[2] Hua-Ling Tsai,[3] Philip H. Imus,[1] B. Douglas Smith,[1] Alexander J. Ambinder,[1] Mark J. Levis,[1] Amy E. DeZern,[1] Gabrielle T. Prince,[1] Tania Jain,[1] Javier Bolaños-Meade,[1] Lukasz P. Gondek,[1] Gabriel Ghiaur,[1] William Brian Dalton,[1] Theodoros Karantanos,[1] Suman Paul,[1] Ephraim J. Fuchs,[1] Cole Sterling,[1] Lode J. Swinnen,[1] Nina Wagner-Johnston,[1] Richard F. Ambinder,[1] Christian B. Gocke,[1] Syed Abbas Ali,[1] Carol Ann Huff,[1] Leo Luznik,[1,4] Ravi Varadhan,[3] Richard J. Jones[1] and Ivana Gojo[1]

[1]Division of Hematologic Malignancy, Department of Oncology, Johns Hopkins University, Baltimore, MD; [2]Department of Internal Medicine, Yale University, New Heaven, CT; [3]Division of Biostatistics and Bioinformatics, Department of Oncology, Johns Hopkins University, Baltimore, MD and [4]Section of Hematology/Oncology, Department of Medicine, Baylor College of Medicine, Houston, TX, USA

Correspondence: J.A. Webster
Jwebst17@jhmi.edu

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Abstract

The therapeutic landscape in acute lymphoblastic leukemia (ALL) has changed dramatically over the last decade. Allogeneic blood or marrow transplantation (alloBMT) has also evolved and remains an important option for consolidation. We assessed the interplay between these factors by analyzing the outcomes of 251 adult ALL (214 B- and 37 T-ALL) patients undergoing alloBMT with post-transplantation cyclophosphamide across two eras: 2008-2014 (ERA1) and 2015-2022 (ERA2). ERA1 patients were younger (median age 45.5 years *vs*. 50 years, *P*=0.03), less likely to have a Hematopoietic Stem Cell Transplant-Comorbidity Index score ≥4 (9% *vs*. 21%, *P*=0.01), more likely to have measurable residual disease by flow cytometry (20% *vs*. 9%, *P*=0.01), and receive myeloablative conditioning (56% *vs*. 3%, *P*<0.0001). Overall survival (OS) (Hazard Ratio [HR]: 0.54, *P*=0.005), relapse-free survival (RFS) (HR: 0.52, *P*=0.001), and relapse (HR: 0.45, *P*=0.0005) were improved in ERA2. Non-relapse mortality was similar between eras (HR: 0.88, *P*=0.73). Significant improvements in OS (HR 0.49, *P*=0.004) and RFS (HR: 0.46, *P*=0.0004) in ERA2 due to fewer relapses (HR: 0.38, *P*=0.0003) were restricted to patients with B-ALL. Irrespective of era, B-ALL patients transplanted in first remission (CR1) had improved RFS (HR: 0.40, *P*=0.05) if they received pre-transplant blinatumomab. Similarly, Philadelphia chromosome-positve ALL patients transplanted in CR1 who received 2nd or 3rd generation tyrosine kinase inhibitors at diagnosis had improved RFS (HR: 0.29, *P*=0.0004) and reduced relapse (HR: 0.23, *P*=0.002) compared to those who received imatinib. Improved alloBMT outcomes in ERA2 in spite of older patient age, increased co-morbidities, and less intensive conditioning were due to reductions in relapse likely driven by changes in pre-transplant therapy.

Introduction

Novel therapies for acute lymphoblastic leukemia (ALL) have dramatically improved outcomes. Blinatumomab eradicates measurable residual disease (MRD) in 80% of B-cell ALL, improves survival when added to front-line chemotherapy in Philadelphia chromosome-negative (Ph$^-$) B-ALL, and yields better salvage outcomes than chemotherapy.[1-3] Inotuzumab ozogamicin and brexucabtagene autoleucel yield response rates of 80.7% and 71%, respectively, in relapsed/refractory B-ALL,[4,5] significant improvements over cytotoxic chemotherapy. Beyond antigen-targeted therapies, ponatinib yields higher rates of MRD-negativity than imatinib in Ph$^+$ ALL.[6] As 45% of older B-ALL patients are Ph$^+$, and MRD-negativity is tied to improved survival,[7,8] better targeted therapies may facilitate the elimination of cytotoxic chemotherapy for vulnerable patients.[9] Thus improvements in salvage outcomes allow more patients to receive a curative allogeneic blood or marrow transplant (alloBMT), while deeper MRD responses improve outcomes for patients pursuing both

alloBMT and chemotherapy consolidation.[10]

With novel therapies, the role of alloBMT in ALL is evolving. Early trials in ALL that were randomized by donor availability demonstrated the superiority of consolidation with alloBMT over chemotherapy or autologous transplant for ALL in first remission (CR1),[11,12] although chemotherapy alone yields comparable survival to alloBMT when patients achieve deep, early MRD responses.[13,14] Novel agents yield dramatically more frequent deep MRD responses, raising questions about the benefit of alloBMT after such therapies. The introduction of high-dose post-transplantation cyclophosphamide (PTCy) as a component of graft-*versus*-host disease (GvHD) prophylaxis has expanded donor options and reduced transplant-related toxicities, thereby improving transplant outcomes. PTCy reduces the incidence of GvHD after HLA-matched transplantation without impacting relapse-free survival (RFS) and facilitates HLA-mismatched alloBMT.[15-17] Reduced-intensity conditioning (RIC) reduces non-relapse mortaity (NRM) and produces similar survival to myeloablative conditioning (MAC) in ALL.[18] The wider adoption of RIC and PTCy have led to increases in the age and volume of patients transplanted for ALL.[19]

Retrospective studies that pre-date novel therapies demonstrate modest improvements in alloBMT outcomes in ALL over time, attributable to reductions in NRM and relapse, which largely correlates with the introduction of tyrosine kinase inhibitors (TKI) for Ph$^+$ ALL.[20,21] Overall survival (OS) for ALL patients undergoing alloBMT has improved with novel therapies, but there was a non-significant improvement in RFS, suggesting the improved OS may merely be a consequence of improved salvage therapies for post-transplant relapse.[22] In relapsed/refractory B-ALL, transplant outcomes following blinatumomab, inotuzumab, and chemotherapy are similar, although pre-transplant inotuzumab increases NRM compared to chemotherapy.[23,24] After treatment with blinatumomab for MRD, the incidence of NRM following a consolidative alloBMT was 36.5%.[25] These analyses, which included myriad conditioning and GvHD prophylaxis regimens, demonstrate the efficacy of alloBMT as consolidation after novel therapies but raise concern that such therapies potentiate NRM. Thus, we analyzed alloBMT outcomes in ALL at our institution in patients who uniformly received PTCy over 15 years.

Methods

Patients

The BMT database at Johns Hopkins was screened for adults with ALL receiving a first alloBMT using PTCy from January 2008 to June 2022. Patient demographics, disease characteristics, and pretransplantation treatment were obtained. Patients were separated into two cohorts based on the commercial availability of blinatumomab. ERA1 was defined as 2008-2014, and ERA2 was 2015-2022. This study was deemed exempt from human subjects oversight under Department of Health and Human Services regulations following review by the Johns Hopkins Institutional Review Board.

Donor typing and graft source

HLA data were obtained for BMT recipients and their donors. Donors were categorized as matched, if they were identical to recipients at all typed HLA loci. Donors were classified as matched sibling donors (MSD), matched unrelated donors (MUD), mismatched unrelated (mMUD), or haploidentical. Donor selection and graft source (unmanipulated bone marrow or mobilized peripheral blood) were based on institutional standards that changed over the course of the study.

Conditioning

The choice of preparative regimen (MAC *vs*. RIC) was based on institutional standards that changed over the course of the study. Additional details of the conditioning regimens and definitions are provided in the *Online Supplementary Appendix*.

Prior treatment

Treatment prior to alloBMT was abstracted from patient charts. A patient was considered to have received salvage therapy if their treatment regimen was changed when they had >5% blasts or extramedullary disease. For salvage regimens, patients were considered to have received blinatumomab or inotuzumab when either drug was used as a component of the salvage regimen. If a patient achieved CR1 (i.e., <5% blasts) but subsequently received treatment for MRD, they were considered to have undergone transplant in CR1 without salvage.

Graft-*versus*-host disease prophylaxis and treatment

Graft-*versus*-host disease prophylaxis for all patients included PTCy 50 mg/kg on days 3 and 4. All patients who received RIC and some who received MAC were given MMF 1 g every 8 hours on days 5-35 and either tacrolimus or sirolimus starting on day 5 for a minimum of 55 days, based on institutional guidelines and available clinical trials.[26,27]

Measurable residual disease assessment

Bone marrow biopsies were performed within 45 days before alloBMT and 50-100 days post transplantation. Multiparameter flow cytometry (MFC) was performed on bone marrow aspirates, with a level of sensitivity of 1/10,000 (0.01%) cells to detect MRD.

Outcome definitions

Overall survival was defined as the time from alloBMT to death from any cause or censored at the last follow-up date. RFS was defined as the time from alloBMT to re-

lapse or death, whichever occurred first, or censored at the last follow-up date. Relapse was characterized by the reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after CR. When estimating the cumulative incidence of relapse, NRM was treated as a competing event, and vice versa. GvHD events were graded based on National Institutes of Health Consensus criteria.[28,29] For the cumulative incidence of GvHD, competing events included relapse, graft failure, and death without the occurrence of the corresponding GvHD event.

Statistical analysis

Demographics, disease characteristics, and treatment modalities were summarized by treatment era, and were compared using Fisher exact test for categorical variables and Student *t* test for continuous variables. Estimators of OS and RFS were reported using the Kaplan-Meier method. Differences in time-to-event outcomes were evaluated using Cox proportional hazards models for RFS and OS. The Fine-Gray model was applied for other time-to-event outcomes that account for competing events. Multivariable models were developed to evaluate differences in clinical outcomes between the two eras while accounting for potential confounders. Adjustments were made for clinically meaningful factors with sufficient frequency across groups, including age at transplant (continuous), disease category (Ph^- B-ALL, T-ALL *vs*. Ph^+ B-ALL), MRD status (MRD^+ *vs*. MRD^-), CR status (CR1 without salvage *vs*. after salvage), and Hematopoietic Stem Cell Transplant-Comorbidity Index score (HCT-CI) (0-3 *vs*. 4+). Subgroup analyses were carried out to assess the differential impact of treatment era on clinical outcomes, with predefined subgroups based on demographic, disease, and treatment characteristics. Interaction tests were performed to evaluate potential interactions between these factors and treatment eras.

Given the differences in follow-up duration between the two eras, sensitivity analyses were performed using information up-to five years post transplant. The five-year cutoff was chosen based on the timing of the last events in ERA2 and to align with the follow-up period applicable to most patients in this group.

Analyses were conducted in STATA and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined at $P<0.05$ for all analyses without multiplicity adjustment. All statistical tests were two-sided.

Results

Patient, transplant, and prior treatment characteristics

Two hundred and ninety-four transplants for adult ALL were identified. Forty-three were excluded because the GvHD prophylaxis was not PTCy (N=11) or it was not a first transplant (N=32). Demographics and transplant characteristics are shown in Table 1 by era. Patients transplanted in ERA2 were older (P=0.03), more likely to have a HCT-CI ≥4 (P=0.01),30 and less likely to have Ph^+ ALL (P=0.04) and persistent MRD prior to transplant (P=0.01). alloBMT in ERA2 used almost exclusively RIC, and more frequently used HLA-mismatched donors (both unrelated and haploidentical relatives) (P<0.0001) and peripheral blood grafts (PBSCT) (P=0.0001). Additional demographic and transplant characteristics are provided in *Online Supplementary Tables S1* and *S2*. Characteristics of pre-transplant treatment for B-ALL, including pre-transplant MRD status, are shown in Table 2. No patients received blinatumomab or inotuzumab in ERA1. In ERA2, nearly a third of B-ALL

Table 1. Patient demographics, disease characteristics, and transplant details by era.

	2008-2014 N=102	2015-2022 N=149	*P*
Age at BMT, years, median (range)	45.5 (20-72)	50 (26-74)	0.03
Age at BMT, years, N (%)			0.07
<40	34 (33)	44 (30)	
40-55	43 (42)	50 (34)	
>55	25 (25)	55 (37)	
Male, N (%)	57 (55.9)	78 (52.3)	-
Diagnosis, N (%)			0.04
Ph^+ B-ALL	56 (54.9)	57 (38.3)	
Ph^- B-ALL	34 (33.3)	67 (45.0)	
T-ALL	12 (11.8)	25 (16.8)	
Remission status, N (%)			0.08
CR1	79 (77.5)	107 (71.8)	
CR1 after salvage	2 (2.0)	13 (8.7)	
CR2/CR3+	21 (20.6)	29 (19.5)	
MRD^+, N (%)	20/100 (20)	13 (8.7)	0.01
HCT-CI, N (%)			0.004
0	37 (37.3)	31 (21.1)	
1-3	53 (52)	85 (57)	
4+	9 (9)	31 (21)	
Myeloablative conditioning, N (%)	57 (55.9)	4 (2.7)	<0.0001
PBSCT, N (%)	3 (2.9)	56 (37.6)	0.0001
Donor, N (%)			<0.0001
MSD	28 (27.5)	22 (14.8)	
MUD	25 (24.5)	13 (8.7)	
Haplo	49 (48.0)	101 (67.8)	
mMUD	0	13 (8.7)	

B-ALL: B-cell acute lymphoblastic leukemia; BMT: blood or marrow transplant; CR1: first remission; CR2/3+: second or third remission or beyond; Haplo: haploidentical donor; MRD^+: positive for measurable residual disease; HCT-CI: Hematopoietic Stem Cell Transplant-Comorbidity Index; mMUD: mismatched unrelated donor; MSD: matched sibling donor; MUD: matched unrelated donor; PBSCT: peripheral blood stem cell transplant; Ph^+: Philadelphia chromosome positive; Ph^-: Philadelphia chromosome negative; T-ALL: T-cell acute lymphoblastic leukemia.

patients transplanted in CR1 received blinatumomab, almost all undergoing salvage received blinatumomab +/- inotuzumab, and the vast majority of Ph$^+$ ALL patients transplanted in CR1 received a 2nd or 3rd generation TKI at diagnosis (*P*=0.0001).

Graft-*versus*-host disease and graft failure

The cumulative incidence of grade II-IV and grade III-IV acute GvHD, moderate-to-severe chronic GvHD at two years, and graft failure at one year were 27.1% (95% confidence interval [CI]: 22-33) and 4.8% (95% CI: 3-8), 11.1% (95% CI: 8-15), and 4.0% (95% CI: 2-7), respectively, with no significant difference between the two eras in terms of GvHD frequency or severity (Figure 1), or engraftment outcomes (SDHR: 0.67, 95% CI: 0.20-2.32). Additional details based on transplant-related factors are included in *Online Supplementary Table S3*.

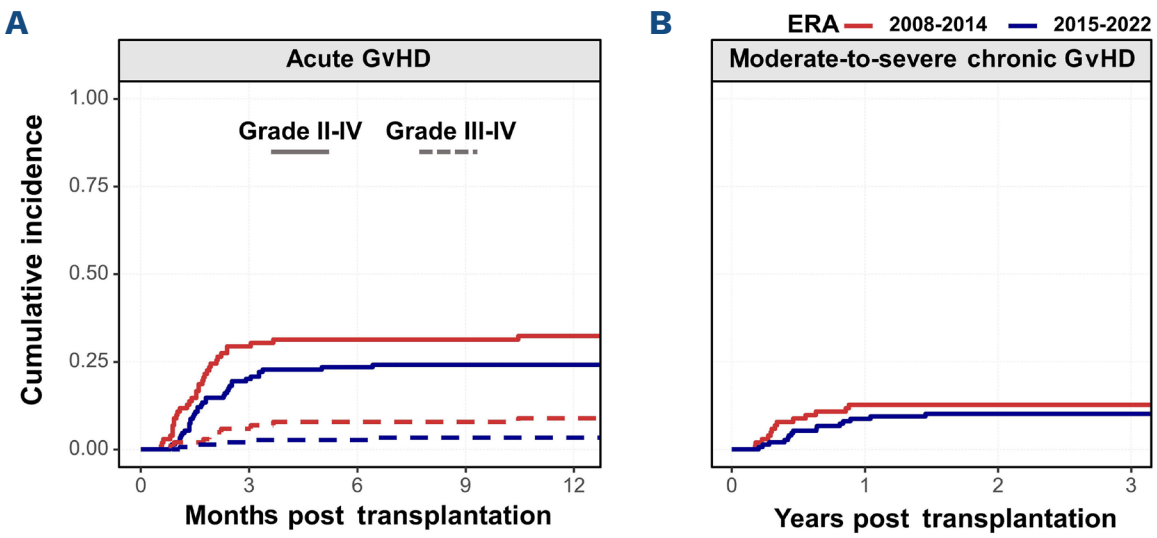
Survival outcomes by era: overall and by subgroups

The median follow-up was 3.50 years and longer in ERA1 (5.77 years) than ERA2 (3.20 years). OS, RFS, cumulative incidence of relapse (CIR), and NRM by era are shown in Figure 2. Patients transplanted in ERA2 had significantly improved OS (HR: 0.54, 95% CI: 0.35-0.83), RFS (HR: 0.52, 95% CI: 0.35-0.76), and CIR (SDHR: 0.45, 95% CI: 0.28-0.70). There was no difference in NRM between eras (SDHR: 0.88, 95% CI: 0.44-1.78). Transplant in ERA2 was also associated with improved OS, RFS, and CIR in multivariate analysis (MVA) (*Online Supplementary Table S4*). Comparisons of OS, RFS, CIR, and NRM between eras by pre-transplant demographics and disease characteristics are present-

Table 2. Pre-transplant treatment characteristics for B-cell acute lymphoblastic leukemia by era including receipt of blinatumomab in first remission, receipt of blinatumomab or inotuzumab for relapsed/refractory patients, and tyrosine kinase inhibitor used at diagnosis for Philadelphia chromosome-positive B-ALL patients transplanted in first remission.

Pre-transplant Rx	2008-2014	2015-2022	*P*
B-ALL in CR1	N=77	N=95	-
Blina, N (%)	0	31 (32.6)	-
No Blina, N (%)	77 (100)	64 (67.4)	-
MRD$^+$, N (%)	9/76 (11.8)	2 (2.1)	0.01
B-ALL salvage	N=13	N=29	-
Blinatumomab, N (%)	0	25 (86.2)	-
Inotuzumab, N (%)	0	9 (31.0)	-
MRD$^+$, N (%)	6/12 (50)	4 (13.8)	0.04
Ph$^+$ B-ALL in CR1	N=50	N=54	-
Imatinib at diagnosis, N (%)	28 (56)	4 (7.4)	0.0001
2nd/3rd gen TKI at diagnosis, N (%)	22 (44)	50 (92.6)	-
MRD$^+$	6/49 (12.2)	2 (3.7)	0.15

Measurable residual disease (MRD) status following receipt of these therapies and prior to transplant is listed for each category by era. B-ALL: B-cell acute lymphoblastic leukemia; Blina: received blinatumomab pre-transplant; CR1: first remission; gen: generation; MRD$^+$: positive for measurable residual disease; Ph$^+$: Philadelphia chromosome positive; Rx: medication; TKI: tyrosine kinase inhibitor.



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GvHD Incidence	2008-2014 (N=102)	2015-2022 (N=149)	Subdistribution HR, 95% CI
G2-4 Acute GvHD at 1 year	31.4% (95% CI 23-40%)	24.2% (95% CI 18-31%)	0.71, 0.44-1.14
G3-4 Acute GvHD at 1 year	7.8% (95% CI 4-14%)	2.7% (95% CI 1-6%)	0.33, 0.10-1.11
Moderate-to-severe chronic GvHD at 2 years	12.8% (95% CI 7-20%)	10.1% (95% CI 6-16%)	0.76, 0.36-1.61

Figure 1. Graft-*versus*-host disease incidence and severity by era. (A) Incidence of acute graft-*versus*-host disease (GvHD) by severity and era. (B) Incidence of moderate-to-severe chronic GvHD by era. (C) Comparison of GvHD incidence by era and severity. CI: confidence interval; HR: hazard ration; N: number.

ed in Table 3, Figure 3, *Online Supplementary Table S5* and *Online Supplementary Figure S1*. When divided by immunophenotype, pre-transplant MRD persistence was significantly less frequent in B-ALL in ERA2 (ERA1 17.0% *vs*. ERA2 4.8%, *P*=0.005) but not in T-ALL (41.7% *vs*. 28.0%, *P*=0.47). OS, RFS, and CIR improved significantly from ERA1 to ERA2 for B-ALL, but not for T-ALL. Notably, the observed improvements in survival outcomes (OS, RFS, and CIR) in ERA2 were restricted to those patient who were MRD^- at the time of transplant, whereas no changes in outcomes were observed in MRD^+ patients. Specific subgroups were then analyzed for the contribution of pre-transplant therapy to the post-transplant survival outcomes.

B-cell acute lymphoblastic leukemia in first remission: contribution of blinatumomab

Among B-ALL patients transplanted in CR1 without salvage therapy, ERA2 patients had improved OS (*P*=0.02), RFS (*P*=0.0004), and CIR (*P*=0.0003) (Table 3). When survival outcomes were analyzed by the receipt of pre-transplant blinatumomab, improvements in OS (*P*=0.23) and RFS (*P*=0.05) were observed in those who received blinatumomab (Figure 4A, B). The 5-year CIR and NRM were 9.9% (95% CI: 3-23) and 6.7% (95% CI: 1-19) among those receiving blinatumomab, and 26.5% (95% CI: 19-34) and 13.9% (95% CI: 9-20) among those who did not. Demographics based on receipt of pre-transplant blinatumomab are presented in *Online Supplementary Table S6*, including indications for blinatumomab. There was improved OS (*P*=0.008), RFS (*P*=0.004), and CIR (*P*=0.01) for the 24 B-ALL patients transplanted in CR1 who received blinatumomab for MRD and achieved MRD negativity, compared to 12 CR1 patients with persistent MRD who did not receive blinatumomab prior to alloBMT (*Online Supplementary Figure S2*).

Philadelphia chromosome-negative B-cell acute lymphoblastic leukemia in first remission: contribution of blinatumomab

For Ph^- B-ALL patients transplanted in CR1 without salvage, the 5-year OS, RFS, CIR, and NRM are shown in Table 3 by era. The presence of pre-transplant MRD declined from 11.1% in ERA1 to 0% in ERA2 (*P*=0.06). Five-year OS and RFS were both 70.6% (95% CI: 43-87) when patients received pre-transplant blinatumomab *versus* 61.0% (95% CI: 46-73) and 51.6% (95% CI: 37-64) without it. The 5-year CIR was 17.7% (95% CI: 4-38) after blinatumomab and 34.3% (95% CI: 21-47) without it.

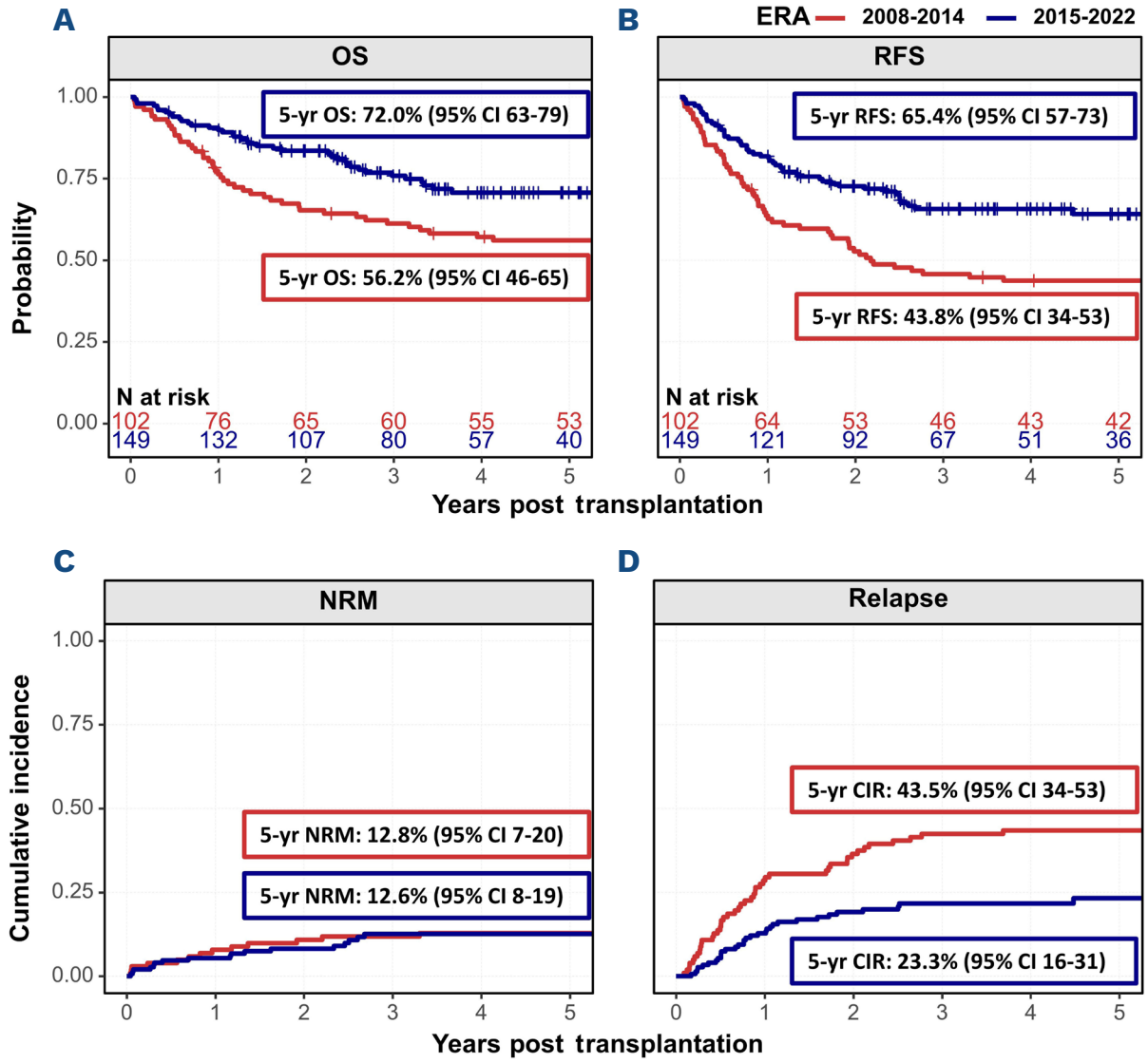

Figure 2. Survival outcomes and relapse by era. (A) Overall survival (OS) by era. (B) Relapse-free survival (RFS) by era. (C) Non-relapse mortality (NRM) by era. (D) Relapse incidence by era. CI: confidence interval; CIR: cumulative incidence of relapse; HR: hazard ration; N: number; yr: year.

Philadelphia chromosome-positive B-cell acute lymphoblastic leukemia in first remission: contribution of front-line tyrosine kinase inhibitors

Among Ph$^+$ B-ALL patients transplanted in CR1 without salvage, ERA2 patients had improved OS (P=0.01), RFS (P=0.001), and CIR (P=0.003) (Table 3). Demographics based on the receipt of imatinib at diagnosis or a 2nd/3rd generation TKI are presented in *Online Supplementary Table S7*. OS and RFS improved significantly among those who received a front-line 2nd/3rd generation TKI *versus* imatinib (Figure 4C, D). The 5-year CIR was higher among imatinib-treated patients (37.9%; 95% CI: 21-54) than those who received a 2nd/3rd generation TKI (10.1%; 95% CI: 4-19). As 14 Ph$^+$ ALL patients received blinatumomab in CR1, an additional analysis excluding those who received blinatumomab compared transplant outcomes by TKI at diagnosis. This comparison similarly demonstrated 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) among those treated with 2nd/3rd generation TKI.

Relapsed/refractory B-cell acute lymphoblastic leukemia: contribution of novel agents

Salvage treatments for B-ALL patients are presented in Table 2. Eight patients received both blinatumomab and inotuzumab for salvage, while one patient received solely inotuzumab. The majority of salvage patients (78.6%) were Ph-negative. OS, RFS, CIR, and NRM for salvage B-ALL patients by era are presented in Table 3. Compared to those who received only chemotherapy, those who received blinatumomab without inotuzumab had improved RFS (HR: 0.32, 95% CI: 0.12-0.84), while those who received inotuzumab and blinatumomab had intermediate outcomes (HR: 0.84, 95% CI: 0.30-2.35) (Figure 5). *Online Supplementary Tables S8* and *S9* show additional data based on patient demographics.

Discussion

Novel therapies have improved outcomes in B-ALL, while PTCy and RIC have expanded access to alloBMT and reduced GvHD. This study examines how the interplay between these developments has influenced alloBMT outcomes in adult ALL. While patients transplanted in ERA2 were older and had more co-morbidities, OS and RFS improved compared to ERA1. Significant improvements in OS and RFS were seen in B-ALL due to reductions in post-transplant relapse that are tied to changes in pre-transplant therapies.

Measurable residual disease detected by MFC pre-transplant led to poorer OS, RFS, and a higher CIR, as previously reported.[31] Significant reductions in pre-transplant MRD from ERA1 to ERA2 were seen exclusively in B-ALL patients, likely attributable to the use of blinatumomab. Strikingly, patients

Table 3. Overall survival, relapse-free survival, cumulative incidence of relapse, and non-relapse mortality by era for the overall population, by immunophenotype (B-cell or T-cell acute lymphoblastic leukemia), and further subdivided by Philadelphia chromosome status and salvage status for B-cell acute lymphoblastic leukemia (first remission without salvage vs. after salvage).

	5-year OS % (95% CI)	5-year RFS % (95% CI)	5-year CIR % (95% CI)	5-year NRM % (95% CI)
2008-2014	56.2 (46-65)	43.8 (34-53)	43.5 (34-53)	12.8 (7-20)
2015-2022	72.0 (63-79)	65.4 (57-73)	23.3 (16-31)	12.6 (8-19)
B-ALL: 2008-2014	56.2 (45-66)	45.2 (35-55)	40.3 (30-50)	14.6 (8-23)
B-ALL: 2015-2022	74.7 (66-82)	69.5 (60-77)	18.5 (12-26)	13.1 (8-20)
T-ALL: 2008-2014	56.3 (24-79)	33.3 (10-59)	66.7 (34-86)	0
T-ALL: 2015-2022	55.9 (31-75)	44.8 (24-64)	47.5 (26-67)	10.9 (2-30)
B-ALL in CR1: 2008-2014	63.3 (51-73)	50.3 (39-61)	36.8 (26-47)	13.1 (7-22)
B-ALL in CR1: 2015-2022	78.2 (68-86)	75.3 (65-83)	13.1 (7-22)	12.7 (7-21)
Ph$^+$ B-ALL in CR1: 2008-2014	65.5 (50-77)	53.4 (39-66)	32.6 (20-46)	14.2 (6-25)
Ph$^+$ B-ALL in CR1: 2015-2022	87.8 (75-94)	83.0 (68-91)	8.5 (2-22)	10.1 (4-20)
Ph$^-$ B-ALL in CR1: 2008-2014	59.2 (38-75)	44.4 (26-62)	44.4 (26-62)	11.1 (3-26)
Ph$^-$ B-ALL in CR1: 2015-2022	65.4 (48-78)	64.1 (47-77)	20.2 (9-34)	15.9 (6-29)
B-ALL after salvage: 2008-2014	15.4 (2-39)	15.4 (2-39)	61.5 (31-82)	23.1 (6-47)
B-ALL after salvage: 2015-2022	63.2 (42-79)	51.7 (33-68)	35.0 (18-52)	13.8 (4-29)

Results are further subdivided by Philadelphia chromosome status and salvage status for B-cell acute lymphoblastic leukemia (first remission) without salvage *versus* after salvage. B-ALL: B-cell acute lymphoblastic leukemia; CI: confidence interval; CIR: cumulative incidence of relapse; CR1: first remission; NRM: non-relapse mortality; OS: overall survival; Ph$^-$: Philadelphia chromosome negative; Ph$^+$: Philadelphia chromosome positive; RFS: relapse-free survival; T-ALL: T-cell acute lymphoblastic leukemia.

treated with blinatumomab for MRD had dramatically improved outcomes compared to patients transplanted with persistent MRD, suggesting that blinatumomab overcomes the poor prognosis of persistent MRD after chemotherapy.[31] Outcomes in MRD-positive patients were similar between eras, whereas outcomes in MRD-negative patients were dramatically better in ERA2. Due to its retrospective nature, we could not explain this difference based on data collected in our study, but a more sensitive MRD test, such as next-generation sequencing (NGS) of the immunoglobulin heavy chain,[32,33] should allow us to examine whether blinatumomab eradicates MRD below the levels detectable by MFC in future studies. While blinatumomab effectively eliminates residual MRD present after chemotherapy, the best long-term outcomes have required consolidation with alloBMT at a cost of significant NRM (36.5%).[25] However, our outcomes using almost exclusively RIC alloBMT with PTCy after blinatumomab for B-ALL in CR1 show almost 6-fold lower rates of NRM, with comparably low rates of relapse. Thus, our data suggest that B-ALL patients should receive blinatumomab to achieve the deepest level of MRD response possible, after which RIC alloBMT with PTCy is effective consolidation.

alloBMT outcomes improved in the front-line and salvage settings in ERA2 for Ph$^-$ B-ALL, but the role of alloBMT for these patients is evolving due to improving outcomes without transplant. The addition of blinatumomab to front-line chemotherapy in Ph$^-$ B-ALL yields 85% 3-year survival largely without alloBMT, but <50% of adult patients tolerated this regimen and achieved a sufficient MRD response to be included.[3] Furthermore, it remains unclear if this front-line blinatumomab approach can consistently reduce the relapse risk and overcome poor outcomes of high-risk genetic subtypes, including Philadelphia chromosome-like, KMT2A-rearranged, low hypodiploidy, and ALL with myeloid mutations, even if they achieve an MRD$^-$ CR1.[3,34] While we demonstrate encouraging alloBMT outcomes following blinatumomab in CR1 for Ph$^-$ B ALL, randomized trials comparing alloBMT with blinatumomab-containing front-line regimens are needed to define the optimal consolidation

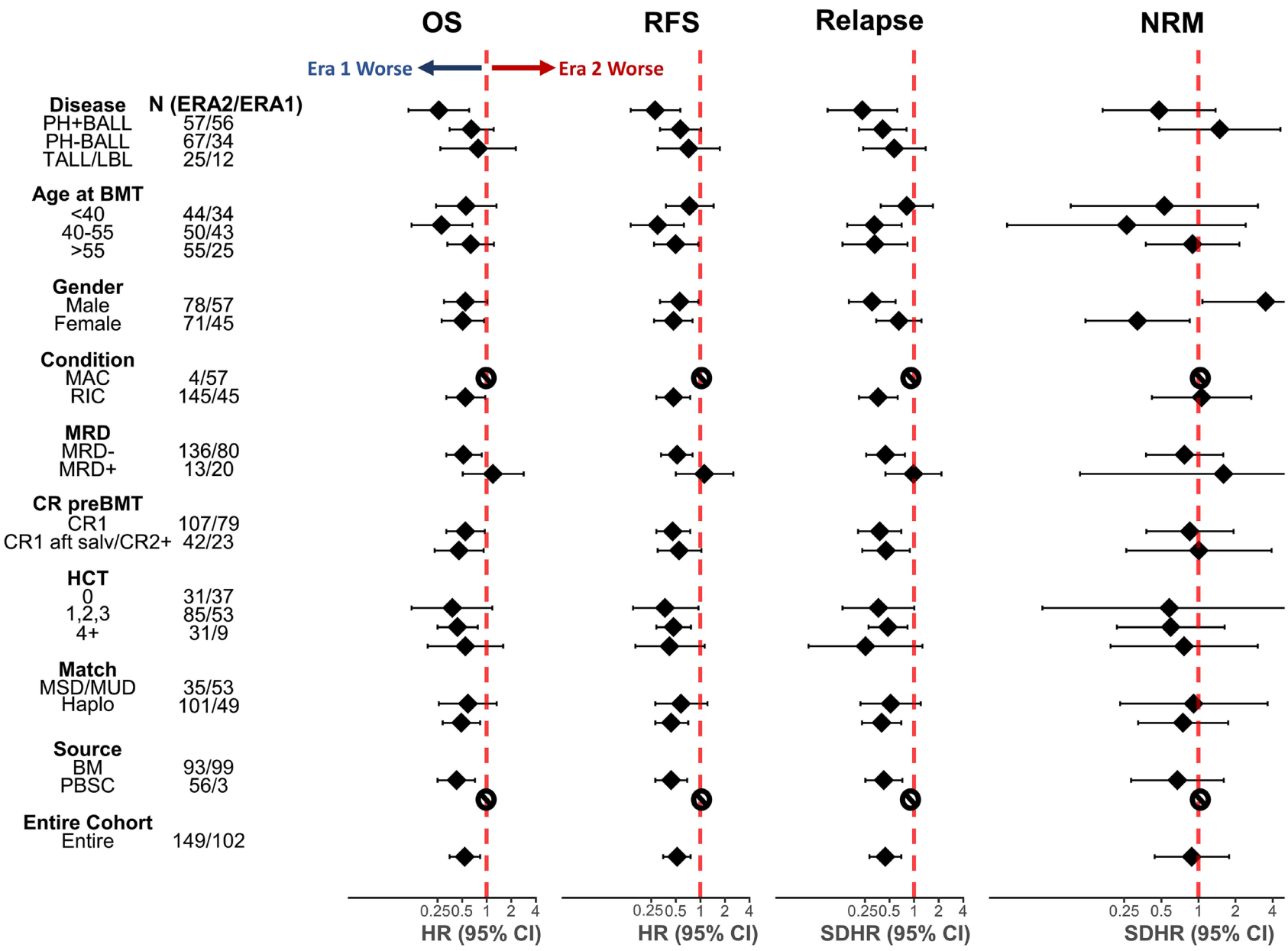

Figure 3. Forest plot comparing overall survival (OS), relapse-free survival (RFS), relapse incidence, and non-relapse mortality (NRM) across eras by subgroup. B-ALL:: B-cell acute lymphoblastic leukemia; CI: confidence interval; HR: hazard ration; LBL: lymphoblastic lymphoma; N: number; Ph$^-$: Philadelphia chromosone-negative; Ph$^+$: Philadelphia chromosone-positive; T-ALL: T-cell acute lymphoblastic leukemia.

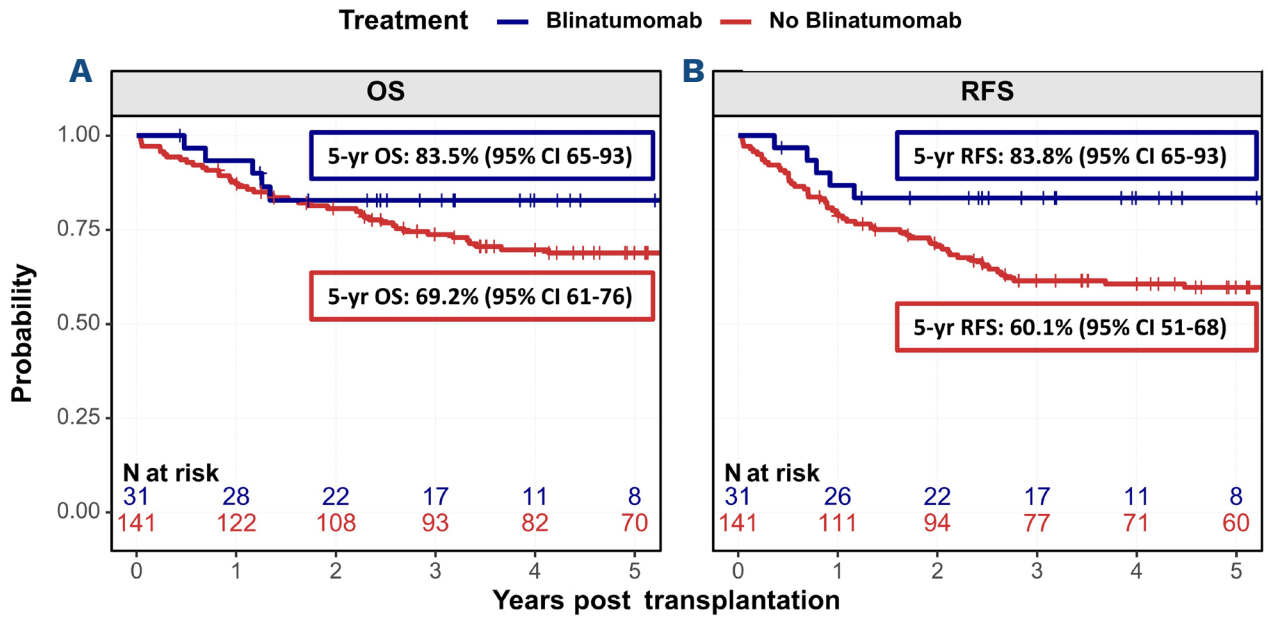

Figure 4. Survival outcomes for B-cell acute lymphoblastic leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia in first remission. (A) Overall survival (OS) for B-cell acute lymphoblastic leukemia (B-ALL) in first remission (CR1) by receipt of blinatumomab. (B) Relapse-free survival (RFS) for B-ALL in CR1 by receipt of blinatumomab. (C) OS for Philadelphia chromosome-positive (Ph^+) ALL in CR1 by tyrosine kinase inhibitor (TKI) at diagnosis. (D) RFS for Ph^+ ALL in CR1 by TKI at diagnosis. N: number; yr; year.

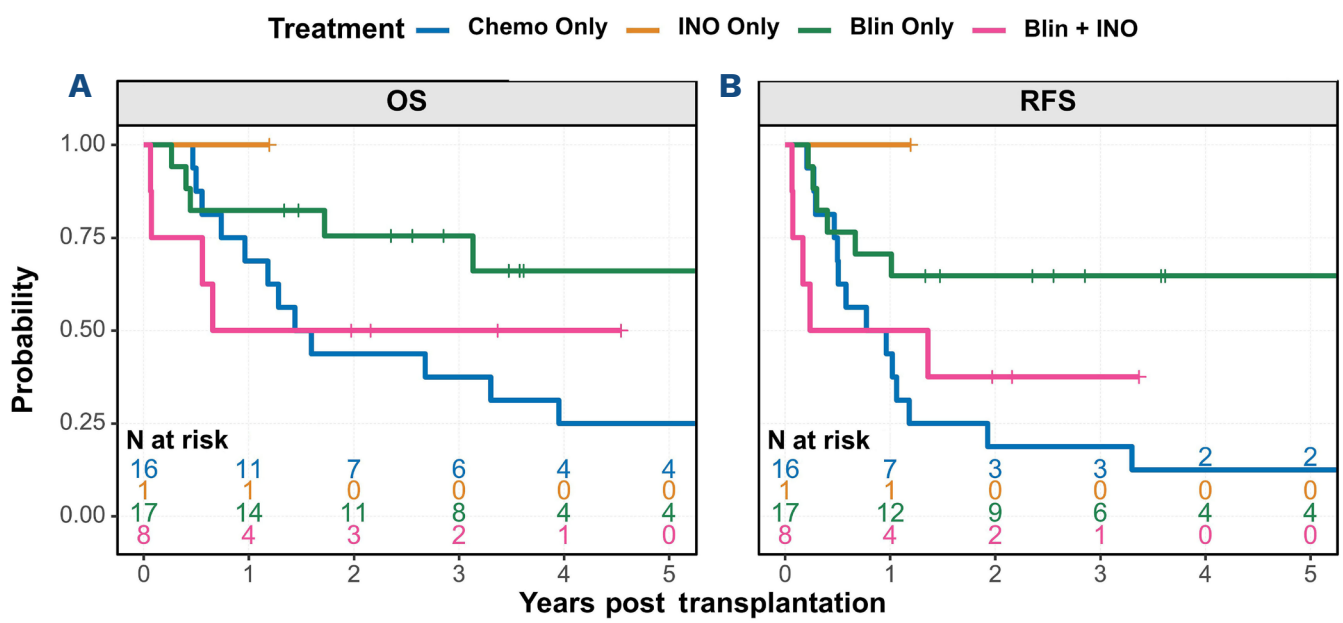

Figure 5. Survival outcomes for salvage patients. (A) Overall survival (OS) by salvage treatment for relapsed/refractory B-cell acute lymphoblastic leukemia (B-ALL). (B) Relapse-free survival (RFS) by salvage treatment for relapsed/refractory B-ALL. Blin Only: treated with blinatumomab without inotuzumab ozogamicin; Blin + INO: treated with blinatumomab and inotuzumab ozogamicin; Chemo Only: treated only with chemotherapy; INO only: treated with inotuzumab ozogamicin without blinatumomab.

based on MRD thresholds, genetic subtypes, age, and tolerance of chemotherapy. A second important consideration is the efficacy of salvage therapy, as deferring transplant in an MRD$^-$ CR1 has been shown to be a viable strategy if consolidation with MAC alloBMT is used in an MRD$^-$ CR2.[35] While our alloBMT outcomes after salvage were dismal in ERA1, they improved dramatically in ERA2 when novel agents were employed for salvage; this suggests that MRD$^-$ patients transplanted in CR2 can be spared the toxicity associated with MAC. Additionally, CD19-targeted chimeric antigen receptor (CAR) T cells with good persistence may obviate the need for alloBMT consolidation in select patients.[36] Given the improved outcomes of alloBMT after novel therapies, future studies comparing outcomes of alloBMT *versus* chemotherapy consolidation must use contemporaneous cohorts, as historical transplant outcomes are an inappropriate comparator.

In Ph$^+$ ALL, alloBMT outcomes improved dramatically in ERA2, but the improving efficacy and reduced toxicity of front-line regimens raises questions about the necessity of transplant. The front-line use of 2nd and 3rd generation TKI instead of imatinib led to fewer relapses, an effect that was independent of blinatumomab. As most patients received dasatinib, our findings contrast with retrospective data showing no benefit of front-line dasatinib over imatinib for patients transplanted in CR1,[37] which may be explained by PTCy preventing the high rates of GvHD previously observed after front-line dasatinib. Recent chemotherapy trials consistently demonstrate better outcomes when Ph$^+$ ALL patients undergo alloBMT in CR1.[38-40] While the benefit of transplant may be mitigated by transplant-related toxicities among deep, early MRD responders to chemotherapy,[13] this analysis notably did not correct for imbalances between those receiving imatinib *versus* dasatinib when comparing alloBMT outcomes to chemotherapy. Studies of front-line blinatumomab with TKI yield 5-year RFS of approximately 75% without transplant, but there remain concerns about CNS relapse and limited follow-up.[41,42] In addition to at least comparable survival and longer follow-up among alloBMT patients receiving a front-line 2nd or 3rd generation TKI, we have previously shown that such patients can discontinue TKI maintenance,[43] which has significant long-term health and cost implications.[44] In contrast to Ph$^-$ ALL, the few available studies of alloBMT for Ph$^+$ ALL in CR2 show poor outcomes,[43,45] but there were too few Ph$^+$ ALL patients undergoing salvage in our study to draw conclusions about the benefit of novel agents. Given the promising outcomes with blinatumomab and TKI, alloBMT in CR1 is likely to be increasingly reserved for Ph$^+$ ALL patients at high risk for relapse based on early MRD response.

Among the 37 T-ALL included in our analysis, we observed no significant improvement in outcomes between eras with poorer RFS and an increased risk of relapse compared to B-ALL. This likely reflects the lack of therapeutic advances for T-ALL during the study period, as nelarabine was approved in 2005,[46] and pre-transplant factors including MRD-positivity and transplant following salvage chemotherapy, which were both more common in T-ALL than B-ALL. Ultimately, T-ALL was not associated with significantly poorer outcomes in MVA, although the number of T-ALL patients was small.

This study demonstrates the benefits of RIC alloBMT with PTCy, which facilitated transplant in older patients with more co-morbidities in ERA2 with low rates of acute and chronic GvHD. Older patients are particularly prone to toxicity with chemotherapy for ALL, with NRM as high as 44%,[47] raising the possibility that a less intense upfront treatment approach that includes blinatumomab followed by alloBMT with PTCy may be a less toxic alternative in selected older patients.[48] Similar to prior studies of PTCy, we observed low rates of grade III-IV acute and chronic GvHD,[15,16,49,50] which can facilitate post-transplant therapies to reduce relapse risk. Nearly all Ph$^+$ ALL patients undergoing alloBMT with PTCy receive post-transplant maintenance,[43] which reduces relapses.[51] Post-transplant blinatumomab has also proven safe as maintenance in Ph-B-ALL but without a clear signal of efficacy compared to historical controls, possibly owing to the concomitant use of immunosuppression.[52] By limiting NRM, GvHD, and the duration of immunosuppression, RIC alloBMT with PTCy, which improves outcomes in acute myeloid leukemia (AML) patients with persistent MRD, is an ideal platform to test post-transplant maintenance approaches.[53]

While the strength of this study is that patients received a universal approach to GvHD prophylaxis, there are a number of limitations, including the use of data from a single center, small numbers of certain subgroups, and varied conditioning regimens, donor types, and cell sources. Given the increasing use of PTCy,[54] a similar study utilizing registry data would be helpful to confirm our findings across multiple centers with larger numbers. Total body irradiation (TBI)-containing MAC is the standard-of-care in pediatric ALL,[55] but TBI-containing RIC regimens yield comparable outcomes in adults,[56] leaving the optimal dose of TBI undefined. Our outcomes using 2 or 4 Gy of TBI were excellent in ERA2, suggesting these TBI doses may be sufficient following novel therapy and PTCy, but there remains a potential role for MAC among patients with persistent MRD that cannot be eradicated by novel agents. Similar to other transplant studies in ALL,[57] there was no significant difference in outcome by donor type, and annual transplant volumes increased with the use of more alternative donors in ERA2. Thus, donor availability should rarely present an obstacle to alloBMT for ALL patients. Finally, PBSCT yield lower relapse rates and higher rates of cGvHD than unmanipulated bone marrow grafts, leading to similar survival.[58,59] While outcomes in our study did not vary by graft source, PBSCT may be preferred in patients at highest risk of relapse due to an increased graft-*versus*-leukemia effect. The choice of conditioning intensity, donor type, and graft source varied

from ERA1 to ERA2, but changes in these variables do not explain the observed improvement in outcomes.

Our data highlight a number of key points regarding the approach to pre-transplant therapy when a RIC alloBMT with PTCy is planned for ALL patients. First, B-ALL patients transplanted in CR1 benefit from pre-transplant blinatumomab through reductions in pre-transplant MRD. Second, Ph^+ ALL patients should receive a front-line 2nd or 3rd generation TKI, and dasatinib yields excellent outcomes. Finally, we recommend caution in comparing novel, transplant-free treatment strategies to historical alloBMT data, as contemporaneous alloBMT patients are also clearly benefitting from novel therapies. This highlights the need for randomized trials in alloBMT to answer disease-specific questions, and the expansion of alternative donor options with PTCy makes it dramatically easier to conduct such trials.

Disclosures

JAW reports research support and consulting fees from Amgen, and consulting fees from Pfizer. ML reports consulting fees from Takeda. IG reports consulting fees from Amgen. All of the other authors have no conflicts of interest to disclose.

Contributions

JAW designed the study, completed data collection, and drafted the manuscript. JAW and H-LT conducted the statistical analysis. H-LT and IJ contributed to the study design and reviewed drafts of the manuscript. PHI and JB-M performed GvHD assessments. MR assisted with data collection. All authors provided clinical care of patients and edited the manuscript.

Data-sharing statement

Deidentified individual participant data collected during the study will be made available indefinitely following publication of this article upon request to the corresponding author by researchers who provide a methodologically sound proposal.

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