Superior survival with allogeneic hematopoietic stem cell transplantation *versus* chemotherapy for high-risk adult acute lymphoblastic leukemia in a PDT-ALL-2016 pediatric-inspired cohort

The role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) has undergone gradual changes in adult acute lymphoblastic leukemia (ALL). In the era of conventional adult chemotherapy regimen, the MRC UKALLXII/E2993 study has demonstrated that allo-HSCT is superior to consolidation chemotherapy in adult ALL patients in first complete remission (CR1).[1] This supports the critical role of allo-HSCT as a post-remission treatment for adult ALL, including standard-risk (SR) and high-risk (HR) ALL. While a pediatric-inspired regimen remarkably improved the survival of adolescent and young adult ALL (AYA ALL),[2] allo-HSCT was less convincing as post-remission therapy. Several studies compared outcomes from a pediatric-like regimen and from allo-HSCT in adult ALL, revealing that allo-HSCT does not exhibit superiority over a pediatric-inspired regimen.[3,4] However, these studies did not provide a clear conclusion regarding the benefit of allo-HSCT in HR-ALL. The PETHEMA ALL-HR-11 study showed that avoiding allo-HSCT did not compromise the outcomes of HR-ALL patients.[5] The GRAALL 2003/2005 study found that allo-HSCT could improve survival in the minimal residual disease (MRD)-positive subgroup, but not in the MRD-negative population.[6]

In this present study, we designed a PDT-ALL-2016 pediatric-inspired protocol, in which allo-HSCT was assigned post consolidation, instead of post remission, as a total-therapy regimen. Herein, we demonstrate that allo-HSCT post consolidation exhibited superior survival *versus* chemotherapy for HR-ALL, regardless of MRD status, in the PDT-ALL-2016 pediatric-inspired cohort.

We analyzed 245 consecutive adults with HR-ALL diagnosed at Nanfang Hospital from January 2016 to December 2021, with outcomes updated in January 2023. Patients in this study were enrolled from a PDT-ALL-2016 pediatric-inspired cohort, a GRAALL-2003 backbone, PEG-asparaginase-intensified, pediatric-inspired regimen.[7,8] The study was approved by the Institutional Review Board of the Nanfang Hospital. Inclusion criteria for this study were patients with any high-risk features, all of whom achieved complete remission (CR) and received allo-HSCT at CR1.[6,9] High-risk features included: 1) white blood cell (WBC) count ≥30x10^9/L for B-cell ALL or 100x10^9/L for T-cell ALL; 2) presence of t(9;22), t(1;19), t(4;11) or any other 11q23 rearrangements; 3) complex karyotype, hypodiploid, or near-triploid; 4) pro-B or early T-cell precursor (ETP) immunophenotype; 5) Philadelphia chromosome-like (Ph-like) or IKZF1-deleted (IKZF1del) subtype.

Patients were assigned to either the chemotherapy cohort or the transplant cohort after consolidation therapy, according to donor availability and their individual preferences and decisions[10-12] (haploidentical related donor [HID] <45 years of age). MRD evaluation took place after induction (day 45), and the methods and definition of MRD response were reported previously.[8] For patients in allo-HSCT cohorts, 4 cycles of consolidation chemotherapy before transplantation was mandatory. These patients received allo-HSCT from human leukocyte antigen (HLA)-matched sibling donor (MSD), unrelated-donor (MUD), or HID. Donor selection was based on patients' biological characteristics and patients' or guardians' consent. Conditioning regimens consisted of BuCy (busulfan and cyclophosphamide) and TBI/Cy (total body irradiation, cyclophosphamide).

Overall survival (OS) was measured from the date of diagnosis to the date of death or last follow-up. Event-free survival (EFS) was measured from the date of CR1 to the date of any event or at last follow-up. Relapse or death by any cause were considered events in the EFS analysis. Cumulative incidence of relapse (CIR) was calculated from the date of CR1 to the date of relapse, considering non-relapse mortality (NRM) as a competing event. This analysis aimed to compare the outcomes between transplantation and chemotherapy; to avoid bias from other therapies, patients who received immunotherapy when they relapsed, such as chimeric antigen receptor T-cell (CAR-T) therapy or CD3/CD19 bispecific T-cell engager (Blinatumomab), were censored at the time of starting immunotherapy. The left-truncated Kaplan-Meier method was used to compare survival between the allo-HSCT and chemotherapy cohorts, as previously reported.[4] Probabilities of NRM and CIR were generated using cumulative incidence estimates to account for competing risks, and compared by Gray's test. To adjust for differences in baseline characteristics, left-truncated Cox proportional hazards regression was used to compare the 2 cohorts.

A total of 245 patients were enrolled in this analysis. Characteristics of patients in the allo-HSCT cohort and patients in the chemotherapy cohort are summarized in Table 1, which shows comparable baseline characteristics. With a median follow-up of 43.6 (range, 3.5-82.5) months, the 3-year OS and EFS were significantly superior in the allo-HSCT cohort compared to the chemotherapy cohort. The estimated 3-year OS was 77.4% (range, 71.0-84.5%) and 53.3% (range, 43.4-65.5%) in the allo-HSCT and chemotherapy cohorts

Table 1. Patients' characteristics.

Total=245	Allo-HSCT N=159	Chemotherapy N=86	*P*
Age in years , median (range)	29.1 (18.0-60.2)	28.1 (18.0-68.7)	0.435
Sex, N (%)			
Male	68 (42.8)	37 (43)	0.999
Female	91 (57.2)	49 (57)	
Immuno-type, N (%)			
T-ALL	41 (25.8)	20 (23.3)	0.967
ETP	30 (18.1)	14 (16.2)	0.546
B-ALL	118 (74.2)	66 (76.7)	0.845
Pro-B	24 (15.0)	14 (116.2)	0.540
Clinical features, N (%)			
CNSL at presentation	8 (5.0)	7 (8.1)	0.491
High WBC[a]	62 (39.0)	41 (47.7)	0.239
>30x10^9/L for B-ALL	53 (33.3)	33 (38.3)	
>100x10^9/L for T-ALL	9 (5.7)	8 (9.4)	
Cytogenetic features, N (%)			
Non/other	66 (41.5)	41 (47.6)	0.888
*MLL*r	7 (4.4)	3 (3.4)	-
*E2A*r	3 (1.8)	4 (4.6)	-
*IGH*del	9 (5.6)	5 (5.8)	-
Ph$^+$	44 (27.6)	26 (30.2)	-
CK	20 (12.5)	4 (4.6)	-
Missing	10 (6.2)	3 (3.4)	-
Ph-like, N (%)			
No	137 (86.2)	75 (87.2)	0.974
Yes	22 (13.8)	11 (12.8)	
IKZF1 deletion, N (%)			
No	132 (83)	73 (84.9)	0.845
Yes	27 (17)	13 (15.1)	
MRD at day 45, N (%)			
Negative	94 (59.1)	50 (58.1)	0.990
Positive	65 (40.9)	36 (41.9)	
Donor type, N (%)			
HID	93 (58.49)	-	-
MSD/MUD	66 (41.51)	-	-
Reconstitution in days, median ± SD			
Neutrophils	12.54 ± 2.25	-	-
Platelets	14.29 ± 4.28	-	-
GvHD prophylaxis, N (%)			
CSA+MTX	93 (58.49)	-	-
CSA+MMF+MTX+ATG	12 (7.55)	-	-
CSA+MMF+MTX+ATG+PT-CY	54 (33.96)	-	-
Donor sex, N (%)			
F-M	23 (14.47)	-	-
Other	136 (85.53)	-	-
Stem cell source, N (%)			
PB	87 (54.7)	-	-
PB+BM	72 (45.3)	-	-
Conditioning regimen, N (%)			
Non-TBI based	66 (41.51)	-	-
TBI based	93 (58.49)	-	-

(Figure 1A), respectively. The 3-year EFS in the allo-HSCT cohort (71.0%; range, 64.1-78.7%) was also superior to the chemotherapy cohort (38.0%; range, 28.8-50.1%) (Figure 1B). The 3-year CIR was 13.0% (range, 8.2-18.8%) in the allo-HSCT cohort and 54.2% (range, 42.6-64.3%) in the chemotherapy cohort. Meanwhile, the 3-year NRM in the allo-HSCT cohort was 11.1% (range, 6.7-16.6%).

To further address the role of transplantation according to different MRD status, particularly for the MRD-negative subset, subgroup analyses were conducted. In the post-induction MRD-positive subset (allo-HSCT, N=65; chemotherapy, N=36), patients who received allo-HSCT exhibited longer EFS and OS along with lower CIR, compared to the chemotherapy cohort (3-year OS 70.0% *vs*. 36.6%, *P*<0.001; 3-year EFS 63.7% *vs*. 18.9%, *P*<0.001; 3-year CIR 15.7% *vs*. 72.4%, *P*<0.001) (Figure 2A). Notably, patients who achieved MRD negativity also benefited from transplantation. In the post-induction MRD-negative subset (allo-HSCT, N=94; chemotherapy, N=50), the allo-HSCT cohort exhibited longer EFS, OS, and lower CIR than the chemotherapy cohort (3-year OS, 82.5% *vs*. 65.6%, *P*=0.030; 3-year EFS, 76.1% *vs*. 51.1%, *P*=0.010; 3-year CIR, 11.1% *vs*. 42.6%, *P*<0.001) (Figure 2B). Furthermore, for patients with positive post-induction MRD and becoming negative after consolidation therapy, allo-HSCT showed a tendency for better survival (Figure 2C).

In multivariate analysis for the entire cohort (*Online Supplementary Table S1*), allo-HSCT was a protective factor for OS (HR=0.31, 0.19-0.51, *P*<0.001), EFS (HR=0.32, 0.20-0.50, *P*<0.001), and CIR (HR=0.12, 0.07-0.22, *P*<0.001), and negatively affected NRM (HR=4.04, 1.23-13.3, *P*<0.001). Meanwhile, in MRD-negative or positive subsets, allo-HSCT also led to superior OS and EFS in the multivariate analysis (*Online Supplementary Table S2*).

As the HR features included Ph-positive ALL in the PDT-ALL-2016 protocol, we repeated our analysis in Ph-negative HR-ALL (N=175). For these patients, allo-HSCT showed better survival compared with chemotherapy in both the entire cohort, and the MRD positive and the MRD negative cohorts (*Online Supplementary Figure S1*).

Emerging evidence indicates that survival of HR-ALL patients may not be further improved by allo-HSCT when receiving a pediatric-inspired chemotherapy, particularly in the MRD-negative subset. In the present study, our data showed that post-consolidation transplantation exhibited

Allo-HSCT: allogeneic hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; ETP: early T-cell precursor; CNSL: central nervous system leukemia; WBC: white blood cell; Ph$^+$: Philadelphia chromosome positive; *MLL*r: *MLL* rearrangement; *E2A*r: *E2A* rearrangement; CK: complex karyotype; MRD: minimal residual disease; HID: haploidentical related donor; MSD: HLA-matched sibling donor; MUD: HLA-matched unrelated-donor; SD: standard deviation; GvHD: graft-*versus*-host disease; CSA: cyclosporine; MTX: methotrexate; MMF: mycophenolate mofetil; ATG: anti-thymocyte globulin; PT-CY: post-transplantation cyclophosphamide; F-M: female to male; P: peripheral blood stem cells; M: marrow stem cells; TBI: total body irradiation. [a]For B-ALL, WBC>30x10^9/L; for T-ALL, WBC>100x10^9/L.

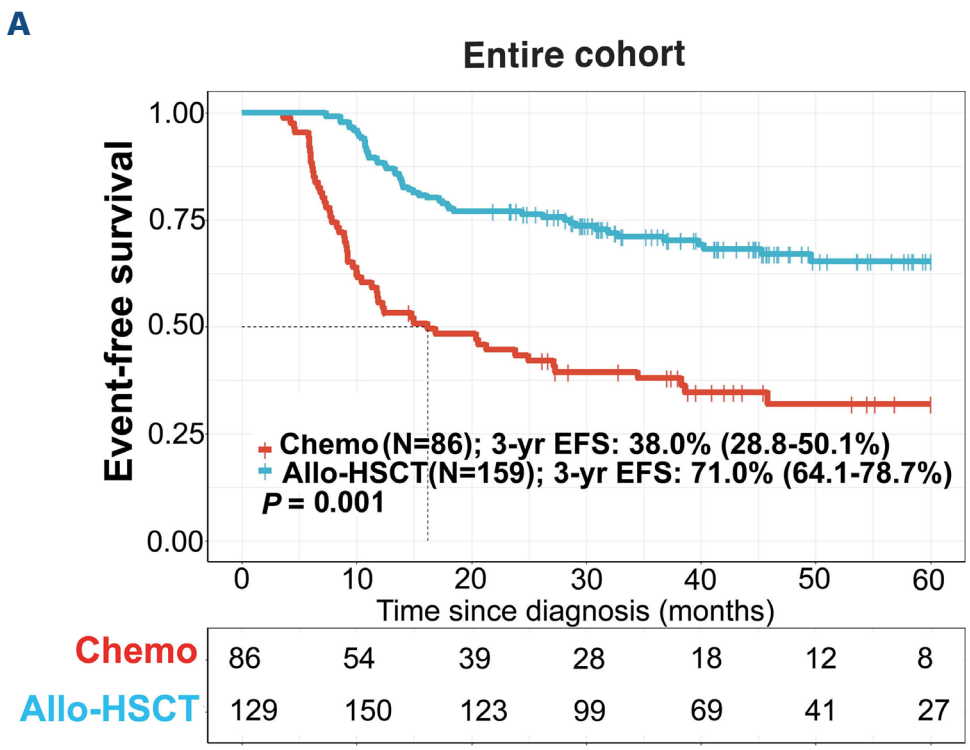
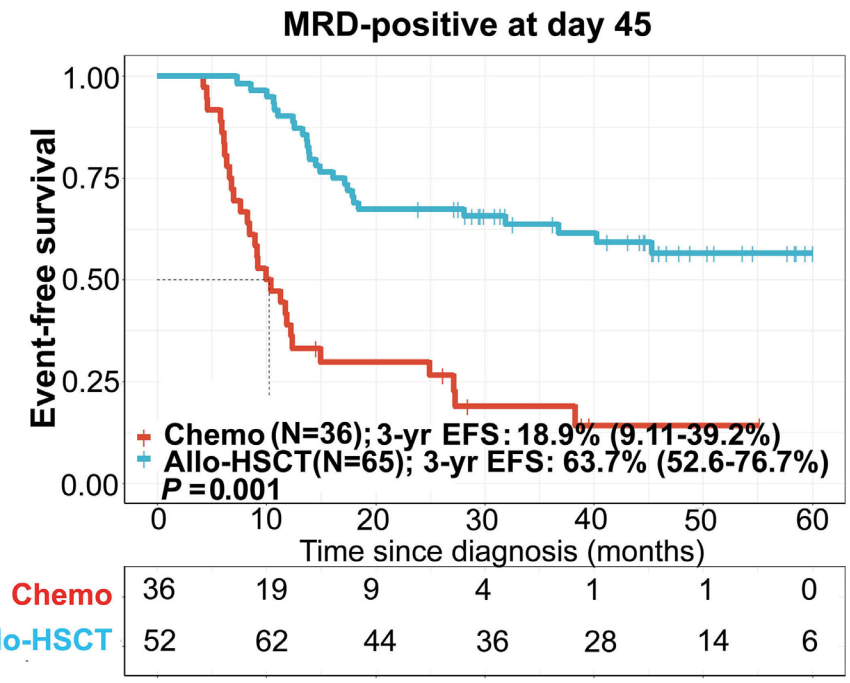


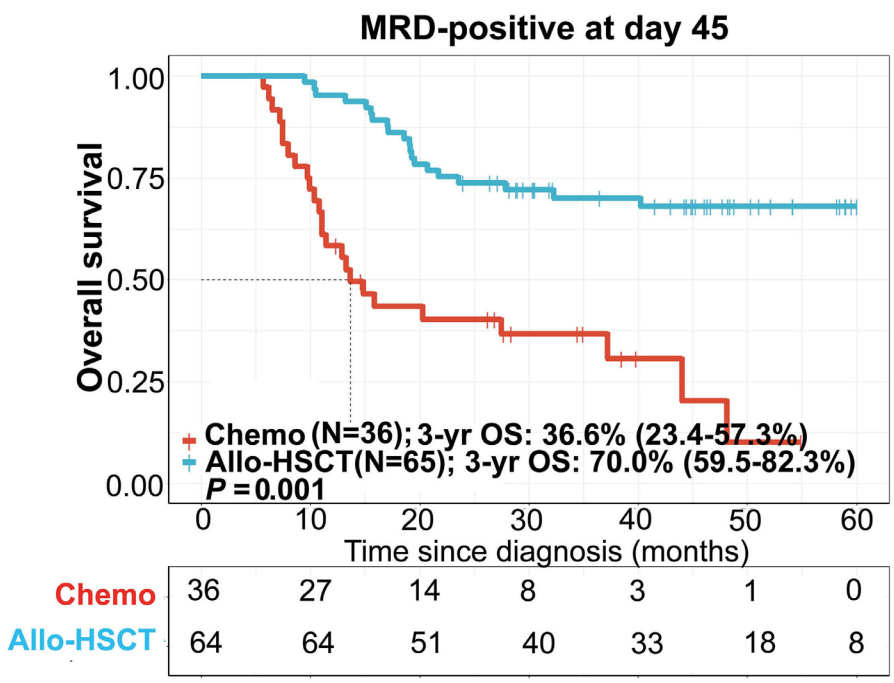
Figure 1. Survival outcomes. (A) Event-free survival (EFS) for entire cohort according to allogeneic hematopoietic stem cell transplantation (allo-HSCT) *versus* chemotherapy (chemo) by left-truncated Kaplan-Meier method. (B) Overall survival (OS) for entire cohort according to allo-HSCT *versus* chemotherapy by left-truncated Kaplan-Meier method. N: number; yr: year.

superior survival compared to chemotherapy for HR-ALL in the PDT-ALL-2016 pediatric-inspired cohort. In this study, we included very high-risk subtypes, such as IKZF1 deletion and Ph-like ALL, and more patients had MRD detected at 45 days, even though the survival of the entire cohort and of the chemotherapy cohort was comparable with other reports.[5,6] These findings suggest that the integrated pediatric-inspired chemotherapy and post-consolidation allo-HSCT may be the optimal therapy for adult HR-ALL. Of note, this study showed the advantage of post-consolidation allo-HSCT for HR-ALL patients in the context of a pediatric-inspired regimen, even for patients achieving MRD negativity.

The efficacy of allo-HSCT has continued to be a subject of debate for as long as a pediatric-inspired regimen has been used in adult ALL. This controversy arises for several reasons. Firstly, the survival rate of AYA ALL patients has been significantly improved by pediatric-inspired regimens. Secondly, it is well-established that there is a weaker graft-*versus*-leukemia (GvL) effect post allo-HSCT in ALL than in myeloid neoplasms. Another unresolved question concerns bridging the gap between the time required for immune reconstitution for GvL and early relapse after allo-HSCT. In the present protocol, we speculated that treatment with a pediatric-inspired regimen could induce durable remission to avoid early relapse, and subsequently provide sufficient time to reconstitute the immune system to exert the GvL effect. Our previous study (PASS-ALL) had shown that this integrated total-therapy yielded durable or deeper MRD response in HR-ALL. We found that, as pre-transplantation chemotherapy, a pediatric-inspired regimen resulted in significantly longer time-to-positive MRD than an adult protocol.[8]

A





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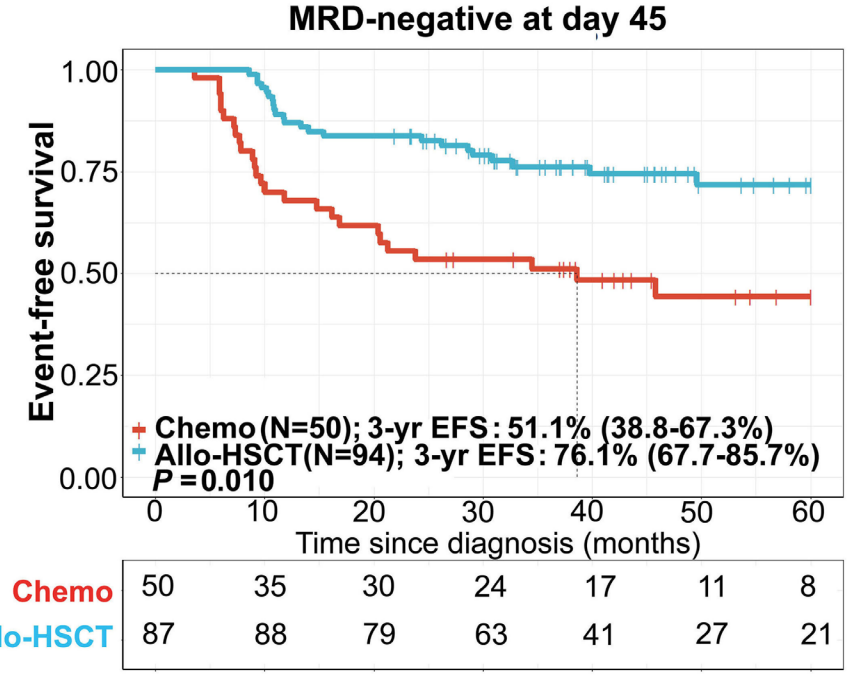

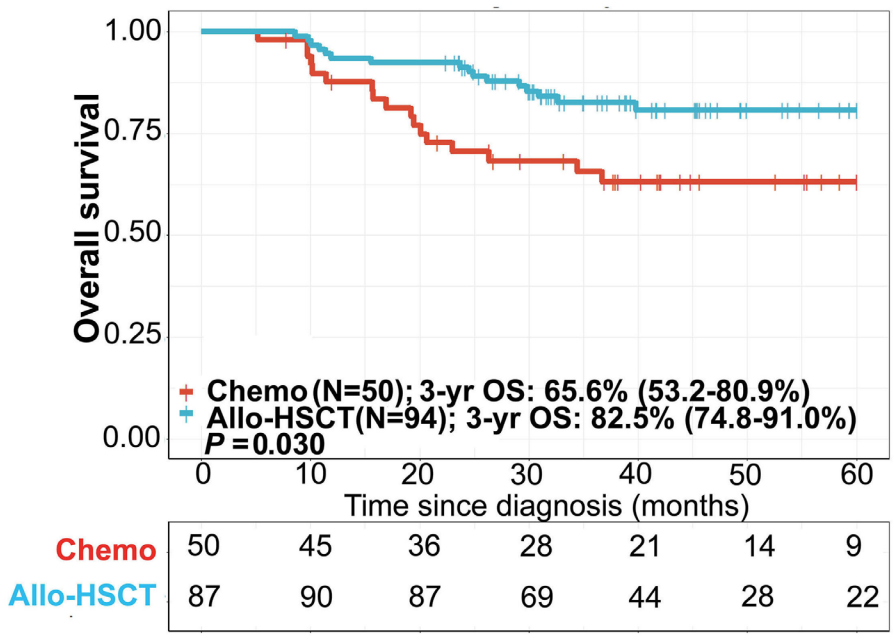

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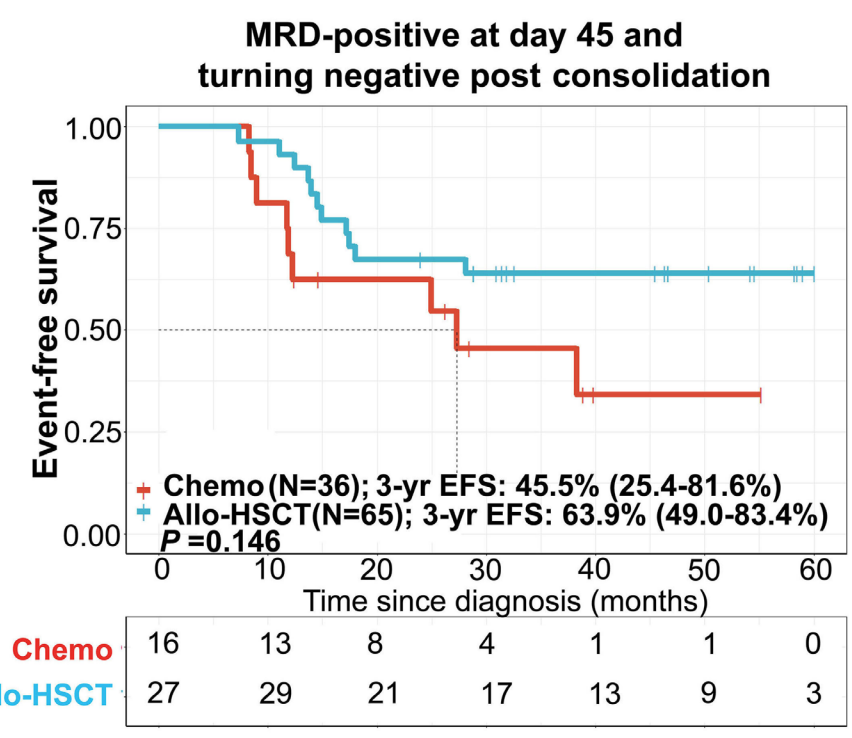

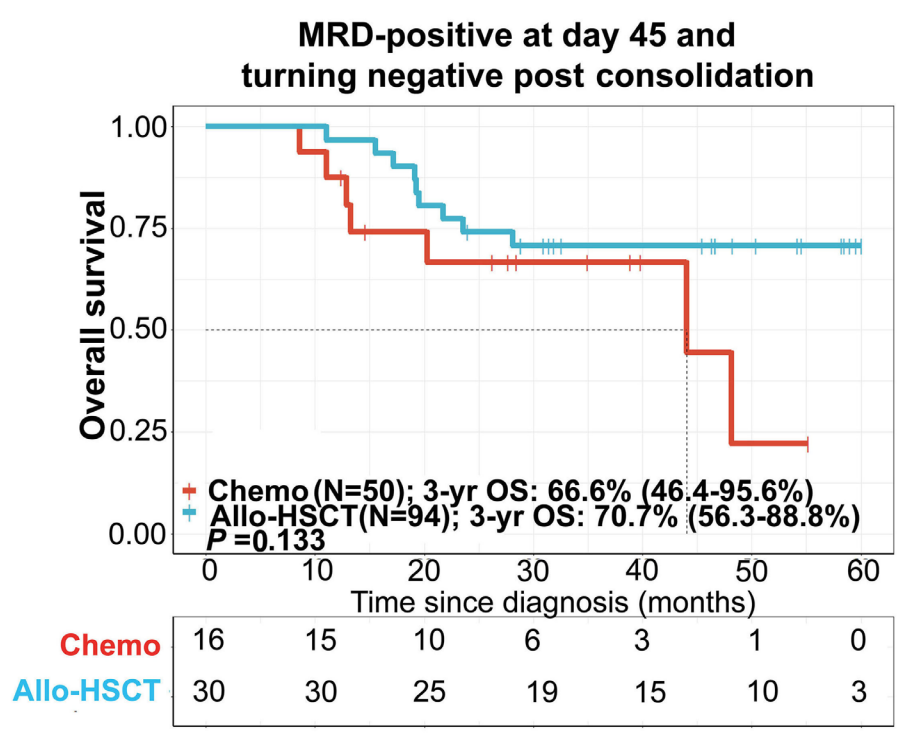

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Figure 2. Survival outcomes. (A) Event-free survival (EFS) and overall survival (OS) for patients who had positive minimal residual disease (MRD) at day 45 (post induction) according to allogeneic hematopoietic stem cell transplantation (allo-HSCT) *versus* chemotherapy (chemo) by left-truncated Kaplan-Meier method. (B) EFS and OS for patients who had negative MRD at post-induction according to allo-HSCT *versus* chemotherapy by left-truncated Kaplan-Meier method. (C) EFS and OS for patients who had positive post-induction MRD and turning negative post consolidation, according to allo-HSCT *versus* chemotherapy by left-truncated Kaplan-Meier method.

For HR-ALL, chemotherapy alone may not be sufficient to maintain the remission status, even for patients who achieved MRD negativity; for these patients, more sensitive techniques, such as next-generation sequencing-based MRD, may detect residual leukemic cells.[13] These surviving leukemic cells, which were resistant to the prior chemotherapy, increase the risk of relapse, necessitating more intensive interventions such as allo-HSCT. A limitation associated with allo-HSCT is the high NRM. The ability of allo-HSCT to reduce the relapse rate may be offset by the excessively high NRM of transplantation. In the present study, the 3-year NRM was 11.8% (9.5-20.5%), a relatively low rate compared with other reports,[3,14,15] which might have benefited from the great experience in the management of allo-HSCT in our center.

Limitations of our study include the fact that this is a single-center analysis. In conclusion, we demonstrated that allo-HSCT still has an irreplaceable role in adult HR-ALL post-remission therapy in the era of pediatric-inspired regimens. We have highlighted the importance of total therapy for adult HR-ALL, and that post-consolidation allo-HSCT should be considered for patients who achieve MRD negativity.

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Disclosures

No conflicts of interest to disclose.

Contributions

HZ and JC contributed to the conception of the study. JieL, ZW, JO, XX, BT, CD, JiaL, RL, TZ and LX contributed to the provision of study materials and acquisition of the clinical data. JC, ZC, ZH, JieL and ZW performed the statistical analyses. JC, ZC and ZH drafted the manuscript. HZ and QL revised the final manuscript. All authors reviewed the final manuscript and approved its publication.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008;111(4):1827-1833.
2. DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged

18-50 years with newly diagnosed acute lymphoblastic leukemia. Leukemia. 2015;29(3):526-534.
3. Seftel MD, Neuberg D, Zhang MJ, et al. Pediatric-inspired therapy compared to allografting for Philadelphia chromosome-negative adult ALL in first complete remission. Am J Hematol. 2016;91(3):322-329.
4. Wieduwilt MJ, Stock W, Advani A, et al. Superior survival with pediatric-style chemotherapy compared to myeloablative allogeneic hematopoietic cell transplantation in older adolescents and young adults with Ph-negative acute lymphoblastic leukemia in first complete remission: analysis from CALGB 10403 and the CIBMTR. Leukemia. 2021;35(7):2076-2085.
5. Ribera J-M, Morgades M, Ciudad J, et al. Chemotherapy or allogeneic transplantation in high-risk Philadelphia chromosome-negative adult lymphoblastic leukemia. Blood. 2021;137(14):1879-1894.
6. Dhédin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. Blood. 2015;125(16):2486-2496.
7. Xu X, Huang Z, Ding C, et al. STAT5 phosphorylation plus minimal residual disease defines a novel risk classification in adult B-cell acute lymphoblastic leukaemia. Br J Haematol. 2024;205(2):517-528.
8. Wang Z, Fan Z, Wu Z, et al. PASS-ALL study of paediatric-inspired versus adult chemotherapy regimens on survival of high-risk Philadelphia-negative B-cell acute lymphoblastic leukaemia with allogeneic haematopoietic stem cell transplantation. Br J Haematol. 2024;204(2):628-637.
9. Wieduwilt MJ, Metheny L, Zhang MJ, et al. Haploidentical vs sibling, unrelated, or cord blood hematopoietic cell transplantation for acute lymphoblastic leukemia. Blood Adv. 2022;6(1):339-357.
10. Huang XJ, Zhu HH, Chang YJ, et al. The superiority of haploidentical related stem cell transplantation over chemotherapy alone as postremission treatment for patients with intermediate- or high-risk acute myeloid leukemia in first complete remission. Blood. 2012;119(23):5584-5590.
11. Xue YJ, Suo P, Huang XJ, et al. Superior survival of unmanipulated haploidentical haematopoietic stem cell transplantation compared with intensive chemotherapy as post-remission treatment for children with very high-risk philadelphia chromosome negative B-cell acute lymphoblastic leukaemia in first complete remission. Br J Haematol. 2020;188(5):757-767.
12. Liu J, Yan W, Fan H, et al. Clinical benefit of autologous stem cell transplantation for patients with multiple myeloma achieving undetectable minimal residual disease after induction treatment. Cancer Res Commun. 2023;3(9):1770-1780.
13. Svaton M, Skotnicova A, Reznickova L, et al. NGS better discriminates true MRD positivity for the risk stratification of childhood ALL treated on an MRD-based protocol. Blood. 2023;141(5):529-533.
14. Giebel S, Labopin M, Socié G, et al. Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica. 2017;102(1):139-149.
15. Shem-Tov N, Peczynski C, Labopin M, et al. Haploidentical vs. unrelated allogeneic stem cell transplantation for acute lymphoblastic leukemia in first complete remission: on behalf of the ALWP of the EBMT. Leukemia. 2020;34(1):283-292.