Title

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Journal

Transplantation and Cellular Therapy, 25(2)

ISSN

2666-6375

Authors

Lund, Troy C
Ahn, Kwang Woo
Tecca, Heather R
et al.

Publication Date

2019-02-01

DOI

10.1016/j.bbmt.2018.09.016

Peer reviewed

HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2019 February ; 25(2): 301–306. doi:10.1016/j.bbmt.2018.09.016.

Outcomes After Second Hematopoietic Cell Transplant for Children and Young Adults with Relapsed Acute Leukemia

Troy C. Lund[1], **Kwang Woo Ahn**[2,3], **Heather R. Tecca**[2], **Megan V. Hilgers**[1], **Hisham Abdel-Azim**[4], **Allistair Abraham**[5], **Miguel Angel Diaz**[6], **Sherif M. Badawy**[7], **Larisa Broglie**[8], **Valerie Brown**[9], **Christopher C. Dvorak**[10], **Marta Gonzalez-Vicent**[6], **Hasan Hashem**[11], **Robert J. Hayashi**[12], **David A. Jacobsohn**[13], **Michael W. Kent**[14], **Chi-kong Li**[15], **Steven P. Margossian**[16], **Paul L. Martin**[17], **Parinda Mehta**[18], **Kasiani Myers**[18], **Richard Olsson**[19], **Kristin Page**[20], **Michael A. Pulsipher**[4], **Peter J. Shaw**[21], **Angela R. Smith**[1], **Brandon M. Triplett**[22], **Michael R. Verneris**[23], and **Mary Eapen**[2]

[1]Division of Pediatric Blood and Marrow Transplant, University of Minnesota, Minneapolis, MN

[2]Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

[3]Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, WI

[4]Division of Hematology, Oncology, and Blood and Marrow Transplantation, Children's Hospital Los Angeles, USC Keck School of Medicine, Los Angeles, CA

[5]Division of Blood and Marrow Transplantation, Center for Cancer and Blood Disorders, Children's National Medical Center, Washington, DC

[6]Department of Hematology/Oncology, Hospital Infantil Universitario Nino Jesus, Madrid, Spain

[7]Division of Hematology, Oncology and Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL

[8]Division of Pediatric Bone Marrow Transplantation, Columbia University Medical Center, New York, NY

[9]Division of Pediatric Oncology/Hematology, Department of Pediatrics, Penn State Hershey Children's Hospital and College of Medicine, Hershey, PA

[10]Pediatric Allergy Immunology and Blood and Marrow Transplant Division, UCSF Benioff Children's Hospital, San Francisco, CA

[11]Division of Pediatric Hematology/Oncology/BMT, Department of Pediatrics, Nationwide Children's Hospital, Columbus, OH

Corresponding author: Mary Eapen, MBBS, MS, Medical College of Wisconsin, 9200 West Wisconsin, Suite C5500, Milwaukee, WI 53226, Phone: 414-805-0700, Fax: 414-805-0714, meapen@mcw.edu.

[12]Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St. Louis, St. Louis, MO

[13]Children's National Health System, George Washington University School of Medicine and Health Sciences, Washington, DC

[14]Atrium Health/Levine Children's Hospital, Charlotte, NC

[15]Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

[16]Department of Pediatric Oncology, Boston Children's Hospital and Dana-Farber Cancer Institute, Boston, MA

[17]Department of Pediatrics, Duke University, Durham, NC

[18]Division of Bone Marrow Transplant and Immune Deficiency, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

[19]Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institute, Stockholm, Sweden

[20]Division of Pediatric Blood and Marrow Transplantation, Duke University Medical Center, Durham, NC

[21]The Children's Hospital at Westmead, Westmead, New South Wales, Australia

[22]Department of Bone Marrow Transplantation and Cellular Therapy, St. Jude Children's Research Hospital, Memphis, Tennessee

[23]Pediatric Hematology/Oncology/Bone Marrow Transplant, University of Colorado Anschutz Medical Campus, Aurora, CO

Abstract

Children with acute leukemia who relapse after hematopoietic cell transplant (HCT) have few therapeutic options. We studied 251 children and young adults with acute myeloid or lymphoblastic leukemia who underwent a second HCT for relapse after their first HCT. The median age at second HCT was 11 years and the median interval between first and second HCT, 17 months. Most (n=187; 75%) were in remission, received myeloablative conditioning regimen (n=157; 63%) and unrelated donor HCT (n=230; 92%). The 2-year probability of leukemia-free survival (LFS) after transplantation in remission was 33% compared to 19% for transplantations that were not in remission (p=0.02). The corresponding 8-year probabilities were 24% and 10% (p=0.003). Higher relapse contributed to the difference in leukemia-free survival. The 2-year probability of relapse for transplantations in remission was 42% compared to 56% for transplantations in relapse (p=0.05). The corresponding 8-year probabilities were 49% and 64% (p=0.04). These data extend the findings of others in that those with low disease burden are more likely to benefit from second transplantation. Late relapse led to a 10% decrement in LFS beyond the second year after second HCT. This differs from first HCT were most relapses occur within 2 years after HCT.

INTRODUCTION

For children with acute myeloid (AML) or lymphoblastic (ALL) leukemia who relapse after their first allogeneic hematopoietic cell transplant (HCT), treatment options are limited. Although a second HCT is an option, its outcome is dependent on morbidities experienced from initial and salvage chemotherapies, as well as the first HCT, performance status, interval between first HCT and relapse and disease status at second HCT.(1–8) These reports have largely focused on adults with acute and chronic leukemia, with only modest inclusion of children.(2, 7, 9) The largest study of 2632 second HCT recipients included 569 (21%) children and adolescents.(2) That study concluded survival after second HCT was better when the diagnosis was chronic myeloid leukemia, longer remission duration after first HCT, longer interval between first and second HCT, low disease burden at second HCT, younger age, no prior acute or chronic graft-versus-host disease (GVHD) and most recent transplant period. The study also concluded there was no usefulness in changing the donor for the second HCT.(2) The three earlier studies that included children also concluded age at second HCT was an important determinant of survival in addition to low disease burden, duration of remission after first HCT and the interval between first and second HCT.(7–9)

It is important to recognize that in the reports that included children and adolescents the predominant donor type was an HLA-matched sibling.(2, 7–9) Donor choice has evolved over time and 60% of allogeneic HCTs for pediatric AML and ALL now use grafts from unrelated donors.(10) Therefore to better understand prognostic factors associated with relapse and leukemia-free survival after second HCT in children, adolescents and young adults who had received both HLA-matched sibling and unrelated donor first HCT we studied 251 patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). Our primary objective was to identify subset(s) within a cohort of relatively young patients (aged <25 years) who are most likely to benefit from second HCT and provide objective data that my be used to counsel patients and families in regards to treatment for relapse after a first allogeneic HCT.

METHOD

Patients

The CIBMTR is a voluntary group of over 400 transplant centers that report data prospectively on consecutive transplants. Patients are followed longitudinally until death or lost to follow-up. Included in the current analyses are patients, aged less than 25 years with AML (n=141) or ALL (n=110) who received a second HCT for relapse (morphologic, cytogenetic or molecular) after their first allogeneic HCT. Recipients of myeloablative (TBI dose ≥1000 cGy, busulfan ≥10 mg/kg), melphalan >140 mg/m^2) and reduced intensity conditioning regimens were included. All second transplants occurred between 2001 and 2014. Parents or patients aged 18 years or older provided written informed consent for research. The Institutional Review Board of the National Marrow Donor Program approved this study.

Endpoints

The primary endpoint was leukemia-free survival defined as the likelihood of being in remission and alive. Relapse or as death from any cause were considered as events (treatment failure). Overall survival was defined as the likelihood of being alive. Death from any cause was considered an event and surviving patients were censored at last follow-up. Neutrophil recovery was defined as achieving absolute neutrophil count $\geq 0.5 \times 10^9$/L for 3 consecutive days and platelets $\geq 20 \times 10^9$/L, for 7 days unsupported by transfusion. Grade II-IV acute GVHD and chronic GVHD were based on reports from each transplant center using standard criteria.(11, 12) Relapse was defined as morphologic, cytogenetic, or molecular recurrence of leukemia. Non-relapse mortality was defined as death in remission.

Statistical Methods

The probabilities of overall and leukemia-free survival were calculated using the Kaplan-Meier estimator(13) The cumulative incidences of neutrophil and platelet recovery, acute and chronic GVHD, non-relapse mortality and relapse were calculated using the cumulative incidence estimator to accommodate competing risks.(14) Cox regression models were built to identify patient, disease and transplant characteristics on leukemia-free and overall survival, non-relapse mortality and relapse.(15) The variables tested are shown in Table 1. Only variables that attained p-value ≤ 0.05 were held in the final multivariate model. The potential effect of transplant center was tested using the frailty model.(16) All p-values are two-sided and analyses were done using SAS version 9.4 (Cary, NC).

RESULTS

Patient, disease and transplant characteristics

The characteristics of the study population are shown in Table 1. The median age at second HCT was 11 years and 21% of the study population was young adults (18–24 years). Seventy-two percent of patients had performance scores of 90 or 100 and 75% were in hematologic remission at transplantation. The median time between first and second HCT was 17 months with a third of patients receiving their second HCT less than a year after their first HCT. Most (92%) of patients received their graft from an unrelated donor and the same donor was used for both transplants in only 14% of patients. Of the 36 patients who received grafts from the same donor for both transplants, 12 donors were HLA-matched siblings, 13 were HLA-matched and 11 were HLA-mismatched unrelated donors. Myeloablative regimens were more commonly used than reduced intensity regimens (66% versus 34%). In contrast, 93% of regimens for the first HCT was myeloablative. About 25% of patients developed grade 2–4 acute GVHD and 25% chronic GVHD after their first HCT. The proportion of patients who developed grade 2–4 acute GVHD and chronic GVHD did not differ between those who received grafts from the same or different donor for their first and second transplants. The median follow up of surviving patients was 72 months (range 11 – 170).

Hematopoietic recovery

The median time to neutrophil recovery was 16 days and that for platelet recovery, 27 days. The day-28 incidence of neutrophil recovery was 82% (95% confidence interval [CI] 77 – 87) and the day-100 incidence of platelet recovery was 72% (95% CI 66 – 78).

Graft versus Host Disease

The day-100 incidence of grade 2–4 acute GVHD was 36% (95% CI 32 – 44). Of the 96 patients with acute GVHD, almost half (n=45; 47%) were grade 2. The 2- and 8-year incidences of chronic GVHD were 31% (95% CI 25 – 37) and 32% (95% CI 26 – 38), respectively. The severity of chronic GVHD was reported a mild in 34 patients (41%), moderate in 25 (31%) patients and severe in 23 (28%) patients.

Leukemia-free and Overall Survival

Leukemia-free survival was higher for patients transplanted in remission, when the interval between relapse and second HCT was 5 months or less, history of chronic GVHD after first HCT and the same donor was used for both first and second HCT (Table 2). The 1, 2, 5 and 8-year probabilities of leukemia-free survival are shown in Table 3, Figure 1. Overall survival was also higher for patients transplanted in remission but was not associated with timing of second HCT, history of chronic GVHD or whether the same donor was used for both transplants (Table 2). Overall survival was lower after transplantation of unrelated cord blood graft compared to transplantation of grafts from HLA-matched and HLA-mismatched unrelated donors. Survival was also lower compared to transplantation of grafts from HLA-matched siblings but this did not reach the level of significance set for this study. The 1, 2, 5 and 8-year probabilities of overall survival are shown in Table 3. There were 180 deaths and recurrent leukemia was the most common cause of death (n=95; 53%). Other causes of death were infection (n=23; 13%), multi-organ failure (n=27; 15%), GVHD (n=12; 7%), interstitial pneumonitis/acute respiratory distress syndrome (n=13; 7%) and not reported (n=10; 5%).

Relapse and Transplant-related mortality

Relapse risks were higher for transplantations in relapse and with different donors for first and second HCT (Table 3). The 1, 2, 5 and 8-year probabilities of relapse are shown in Table 3, Figure 2. Transplant-related mortality was higher in older patients (10 years and older), performance scores 80 or lower and after transplantation of unrelated cord blood graft (Table 3). Transplant related mortality was lower after non-irradiation myeloablative and reduced intensity conditioning regimens compared to radiation-containing myeloablative regimens. The 1, 2, 5 and 8-year probabilities of non-relapse mortality are shown in Table 3.

DISCUSSION

There are several reports on outcomes after second HCT with a primary focus on adults. Factors that have been consistently identified as prognostic for survival have included age, interval between first HCT and relapse and disease status prior to transplantation.(1–8,17) Therefore, our study population with its median age of 11 years reports outcomes after second HCT in a relatively young cohort of patients with AML or ALL who relapsed after

their first HCT. Consistent with all other reports, including a recent European paper(18), disease status at second HCT was associated with relapse, leukemia-free and overall survival implying careful selection of patients for second HCT can extend leukemia-free and overall survival. Non-relapse mortality was high in the first year after HCT ranging from 20–25%. Thereafter relatively few events occurred with a 5% absolute increment from between year 1 and year 8 after HCT. Recurrent leukemia was the predominant cause of failure of second HCT. However, the pattern of recurrence differed by disease burden. For patients transplanted in relapse, most events occurred within the first year after HCT. Relapse occurred over a longer period for patients transplanted in remission resulting in a 10% decrement in leukemia-free survival beyond the second year after HCT. These data are informative and challenging. First, careful selection of patients for second HCT is key as disease burden is critical for a successful outcome. The transplantations in this analyses spanned over 15 years and the indications for proceeding to transplantation has evolved during that period. With the body of literature supporting the adverse effect of “minimal residual disease” on relapse and survival for ALL it is compelling to suggest that second HCT should be offered for those in whom minimal residual disease (MRD) cannot be detected.(19–21) There is also growing evidence that detection of subclinical levels of leukemia using molecular-based or multiparameter flow cytometry in AML is also independently prognostic prior to transplantation.(22, 23) Second, with increasing availability of novel agents for the treatment of ALL and AML our observations make for a compelling argument for planned therapy to achieve MRD negativity to lower relapse risks after second HCT underscoring the need for careful selection of patients who can tolerate continued treatment post-HCT.(24–27)

Others have reported on the importance of duration of remission after first HCT as a prognostic factor for survival.(2, 7, 8) Instead we observed that the interval between relapse and second HCT was associated with improved leukemia-free survival. The observed advantage in regards to leukemia-free survival in the timing of second HCT (i.e., <5 months after relapse) in our study is a surrogate for the duration of remission after first HCT. The duration of remission between first HCT and relapse post-HCT was longer than 12 months for half of patients transplanted less than 6 months after their relapse. In contrast, the duration of remission between first HCT and subsequent relapse was less than 12 months for 56% of patients transplanted 6 months or later after a relapse.

Although others have reported there is no advantage to using a different donor for the second HCT we observed significantly lower relapse and higher leukemia-free survival with the same donor for both transplants.(2, 5, 8, 28) Consequently, we conclude that our findings do not support the need to change the donor for the second HCT or to use an unrelated instead of a sibling donor. We observed similar mortality risks after HLA-matched and mismatched unrelated donor compared to HLA-matched sibling transplants but acknowledge a modest sample of 251 donor-recipient pairs is not adequately powered to detect differences in HLA disparity.

There are likely several reasons as to why non-relapse and overall mortality risks are higher with cord blood transplants in this population. The majority of cord blood units were mismatched at 1 or 2 HLA-loci considering lower resolution HLA matching at HLA A and

B and did not consider matching at HLA-C locus. Consequently, the majority of cord blood units would have been mismatched to their recipients at 2, 3 or more HLA-loci when considering allele-level HLA matching at HLA-A, B, C and DRB1.(29) HLA-mismatching leads to slower hematopoietic recovery and increases the risk for acute GVHD and severe infections in heavily pre-treated patients, which in turn increases mortality risks. Therefore, our findings lend support to selecting HLA-matched sibling or HLA-matched unrelated donors when available and if umbilical cord blood is the only option to prioritize HLA-match (allele-level) after ensuring potential units have the minimum pre-freeze total nucleated cell dose of 3×10^7/kg.(29) Selecting units that contain total nucleated cell dose in excess of the required minimum does not overcome mortality risks associated with HLA disparity.(29) The use of bone marrow or peripheral blood had no significant predictive value for non-relapse mortality, relapse or survival and is consistent with an earlier report.(30)

Consistent with other reports, we also observed a significant association of age and performance score with transplant outcomes. Those reports concluded patients aged less than 20 years fare better. In our population that was predominantly children, we showed patients aged less than 10 years fared better. Similarly, performance score of 80 or lower at HCT was associated with higher non-relapse mortality. Arguably, the HCT-comorbidity index is a better predictor for mortality but this was not available for all patients as about half of the transplants were performed prior to the introduction and validation of the HCT-comorbidity index.(31) The intensity of the conditioning regimen was not associated with relapse or overall survival and this is consistent with the recent European paper.(18) An earlier European report, which included children and adults, showed a difference in outcomes by conditioning intensity, that is most likely explained by the inclusion of adults.(2) However, non-relapse mortality was lower with non-irradiation containing myeloablative and reduced intensity conditioning regimens compared to irradiation containing myeloablative regimens.(28) The spectrum of conditioning regimens used in the current analysis is wide and in the absence of an association with relapse or survival we conclude the transplant-conditioning regimen for second HCT be tailored for the individual patient considering his or her HCT-comorbidity index, overall fitness to undergo second HCT and perhaps their response to re-induction chemotherapy (i.e., remission and MRD status) prior to transplant. We observed higher leukemia-free survival in patients with history of chronic GVHD after first transplant, consistent with other reports.(18) However, in another study from our group that focused on predictors for late mortality chronic GVHD was a significant predictor of death.(32)

Our study has limitations in its retrospective nature, the factors that led to the decision to offer second HCT, inability to evaluate ALL and AML separately and to control for unknown or unmeasured factors. Nevertheless, the report is limited to children and young adults and we were able to identify disease and transplant-related prognostic factors as well as patterns in treatment failure that may prove insightful in the planning of prospective trials to lower relapse risks after second HCT. Our findings confirm using a different donor for the second HCT does not improve outcomes and that umbilical cord blood transplants be avoided whenever possible.

ACKNOWLEDGEMENT

The Center for International Blood and Marrow Transplant Research is supported primarily by Public Health Service Grant U24CA076518 from the National Cancer Institute, the National Heart, Lung and Blood Institute and the National Institute of Allergy and Infectious Diseases; U10HL069294 from National Heart, Lung and Blood Institute and National Cancer Institute, and Contract HHSH250201200016C from Health Resources and Services Administration, Department of Health and Human Services. The views expressed in this article do not reflect the official policy or position of the National Institute of Health, the Department of the Navy, the Department of Defense, Health Resources and Services Administration (HRSA) or any other agency of the U.S. Government.

References

1. Orti G, Sanz J, Bermudez A, Caballero D, Martinez C, Sierra J, et al. Outcome of second allogeneic hematopoietic cell transplantation after relapse of myeloid malignancies following allogeneic hematopoietic cell transplantation: a retrospective cohort on behalf of the Grupo Español de Trasplante Hematopoyetico. Biology of Blood and Marrow Transplantation 2016;22(3):584–8. [PubMed: 26631751]
2. Ruutu T, De Wreede L, Van Biezen A, Brand R, Mohty M, Dreger P, et al. Second allogeneic transplantation for relapse of malignant disease: retrospective analysis of outcome and predictive factors by the EBMT. Bone marrow transplantation 2015;50(12):1542. [PubMed: 26367221]
3. Bejanyan N, Weisdorf DJ, Logan BR, Wang H-L, Devine SM, de Lima M, et al. Survival of patients with acute myeloid leukemia relapsing after allogeneic hematopoietic cell transplantation: a center for international blood and marrow transplant research study. Biology of Blood and Marrow Transplantation 2015;21(3):454–9. [PubMed: 25460355]
4. Andreola G, Labopin M, Beelen D, Chevallier P, Tabrizi R, Bosi A, et al. Long-term outcome and prognostic factors of second allogeneic hematopoietic stem cell transplant for acute leukemia in patients with a median follow-up of⩾ 10 years. Bone marrow transplantation 2015;50(12):1508. [PubMed: 26389832]
5. Christopeit M, Kuss O, Finke J, Bacher U, Beelen DW, Bornhäuser M, et al. Second allograft for hematologic relapse of acute leukemia after first allogeneic stem-cell transplantation from related and unrelated donors: the role of donor change. Journal of clinical oncology 2013;31(26):3259–71. [PubMed: 23918951]
6. Spyridonidis A, Labopin M, Schmid C, Volin L, Yakoub-Agha I, Stadler M, et al. Outcomes and prognostic factors of adults with acute lymphoblastic leukemia who relapse after allogeneic hematopoietic cell transplantation. An analysis on behalf of the Acute Leukemia Working Party of EBMT. Leukemia 2012;26(6):1211. [PubMed: 22290066]
7. Bosi A, Laszlo D, Labopin M, Reffeirs J, Michallet M, Gluckman E, et al. Second allogeneic bone marrow transplantation in acute leukemia: results of a survey by the European Cooperative Group for Blood and Marrow Transplantation. Journal of clinical oncology 2001;19(16):3675–84. [PubMed: 11504749]
8. Eapen M, Giralt S, Horowitz M, Klein J, Wagner J, Zhang M, et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. Bone marrow transplantation 2004;34(8):721. [PubMed: 15322568]
9. Michallet M, Tanguy M, Socie G, Thiebaut A, Belhabri A, Milpied N, et al. Second allogeneic haematopoietic stem cell transplantation in relapsed acute and chronic leukaemias for patients who underwent a first allogeneic bone marrow transplantation: a survey of the Societe Francaise de Greffe de moelle (SFGM). British journal of haematology 2000;108(2):400–7. [PubMed: 10691873]
10. D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides Available at: http://cibmtrorg 2017.
11. Przepiorka D, Weisdorf D, Martin P, Klingemann HG, Beatty P, Hows J, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 1995 6;15(6):825–8. [PubMed: 7581076]
12. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 1980 8;69(2):204–17. [PubMed: 6996481]

13. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. J Am Stat Assoc 1958;53(282):457–81.
14. Lin DY. Non-parametric inference for cumulative incidence functions in competing risks studies. Stat Med 1997 4 30;16(8):901–10. [PubMed: 9160487]
15. Cox DR. Regression Models and Life-Tables. J R Stat Soc Series B Stat Methodol 1972;34(2): 187–220.
16. Andersen PK, Klein JP, Zhang MJ. Testing for centre effects in multi-centre survival studies: a Monte Carlo comparison of fixed and random effects tests. Stat Med 1999 6 30;18(12):1489–500. [PubMed: 10398287]
17. Naik S, Martinez C, Leung K, Sasa G, Nguyen N-Y, Wu M-F, et al. Outcomes after second hematopoietic stem cell transplantations in pediatric patients with relapsed hematological malignancies. Biology of Blood and Marrow Transplantation 2015;21(7):1266–72. [PubMed: 25765555]
18. Yaniv I, Krauss AC, Beohou E, Dalissier A, Corbacioglu S, Zecca M, et al. Second Hematopoietic Stem Cell Transplantation for Post-Transplantation Relapsed Acute Leukemia in Children: A Retrospective EBMT-PDWP Study. Biology of Blood and Marrow Transplantation 2018.
19. Bader P, Hancock J, Kreyenberg H, Goulden N, Niethammer D, Oakhill A, et al. Minimal residual disease (MRD) status prior to allogeneic stem cell transplantation is a powerful predictor for post-transplant outcome in children with ALL. Leukemia 2002;16(9):1668. [PubMed: 12200679]
20. Bader P, Kreyenberg H, Henze GnH, Eckert C, Reising M, Willasch A, et al. Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group. Journal of Clinical Oncology 2009;27(3):377–84. [PubMed: 19064980]
21. Bader P, Kreyenberg H, von Stackelberg A, Eckert C, Salzmann-Manrique E, Meisel R, et al. Monitoring of minimal residual disease after allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia allows for the identification of impending relapse: results of the ALL-BFM-SCT 2003 trial. J Clin Oncol 2015;33(11):1275–84. [PubMed: 25605857]
22. Grimwade D, Freeman SD. Defining minimal residual disease in acute myeloid leukemia: which platforms are ready for" prime time"? Blood 2014:blood-2014–05-577593.
23. Jongen-Lavrencic M, Grob T, Hanekamp D, Kavelaars FG, al Hinai A, Zeilemaker A, et al. Molecular minimal residual disease in acute myeloid leukemia. New England Journal of Medicine 2018;378(13):1189–99. [PubMed: 29601269]
24. Von Stackelberg A, Locatelli F, Gerhard G, Rupert R, Tanya M, Rizzari C, et al. Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia. Journal of Clinical Oncology 2016;34(36):4381–9. [PubMed: 27998223]
25. Rettinger E, Merker M, Salzmann-Manrique E, Kreyenberg H, Krenn T, Dürken M, et al. Pre-emptive immunotherapy for clearance of molecular disease in childhood acute lymphoblastic leukemia after transplantation. Biology of Blood and Marrow Transplantation 2017;23(1):87–95. [PubMed: 27742575]
26. Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. New England Journal of Medicine 2018;378(5):439–48. [PubMed: 29385370]
27. O'hear C, Inaba H, Pounds S, Shi L, Dahl G, Bowman WP, et al. Gemtuzumab ozogamicin can reduce minimal residual disease in patients with childhood acute myeloid leukemia. Cancer 2013;119(22):4036–43. [PubMed: 24006085]
28. Savani B, Mielke S, Reddy N, Goodman S, Jagasia M, Rezvani K. Management of relapse after allo-SCT for AML and the role of second transplantation. Bone marrow transplantation 2009;44(12):769. [PubMed: 19855439]
29. Eapen M, Klein JP, Ruggeri A, Spellman S, Lee SJ, Anasetti C, et al. Impact of allele-level HLA matching on outcomes after myeloablative single unit umbilical cord blood transplantation for hematologic malignancy. Blood 2013:blood-2013–05-506253.
30. Guardiola P, Kuentz M, Garban F, Blaise D, Reiffers J, Attal M, et al. Second early allogeneic stem cell transplantations for graft failure in acute leukaemia, chronic myeloid leukaemia and aplastic anaemia. British journal of haematology 2000;111(1):292–302. [PubMed: 11091216]

31. Sorror ML, Maris MB, Storb R, Baron F, Sandmaier BM, Maloney DG, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 2005 10 15;106(8):2912–9. [PubMed: 15994282]

32. Bitan M, Ahn KW, Millard HR, Pulsipher MA, Abdel-Azim H, Auletta JJ, et al. Personalized prognostic risk score for long-term survival for children with acute leukemia after allogeneic transplantation. Biology of Blood and Marrow Transplantation 2017;23(9):1523–30. [PubMed: 28527984]

Highlights:

1. Remission at second transplant extends survival
2. Same donor preferred for both transplants
3. Avoid mismatched cord blood for second transplant

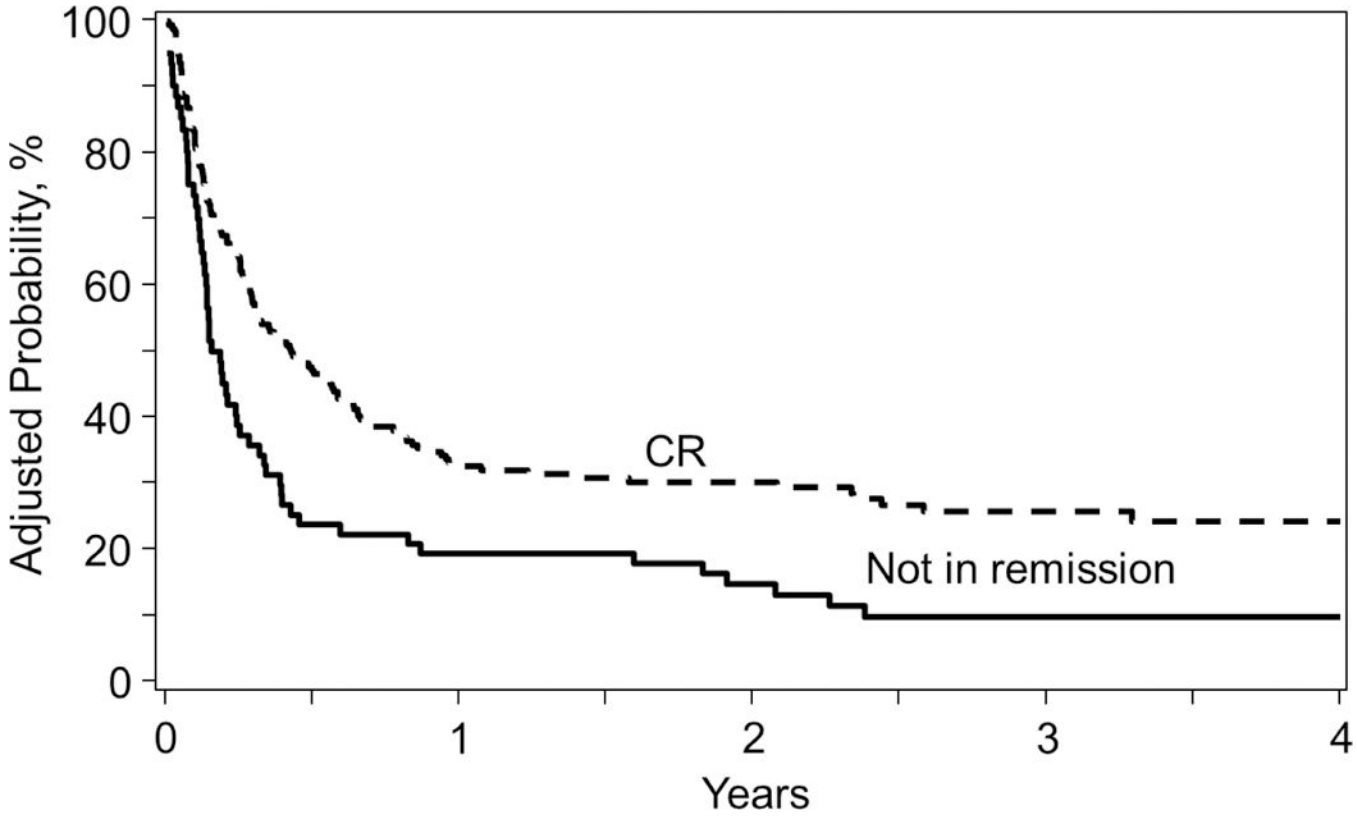

Figure 1.
Leukemia-free survival by disease status at second transplant

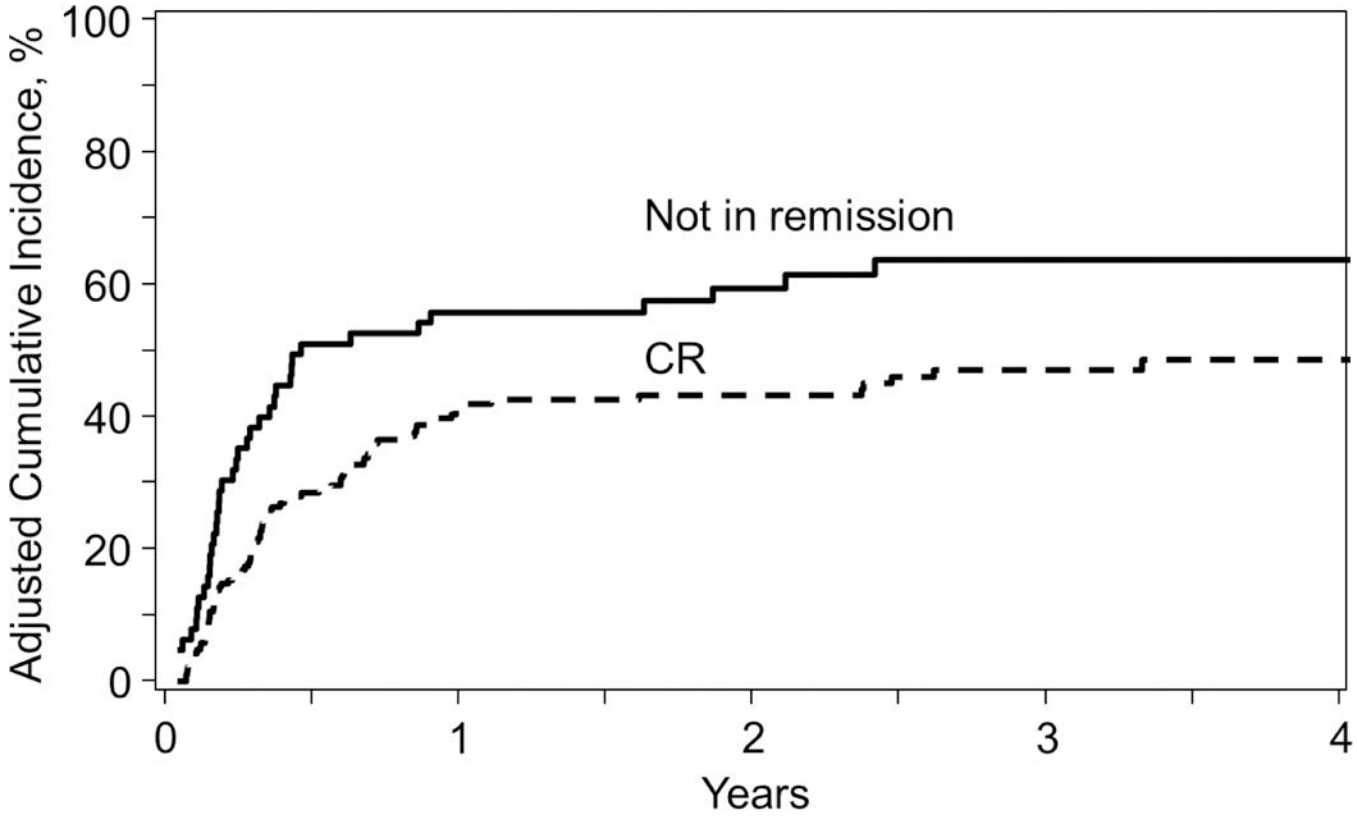

Figure 2.
Relapse by disease status at second transplant

Table 1.

Patient, disease and transplant characteristics

Number	**251**
Disease	
Acute myeloid leukemia	141 (56%)
Acute lymphoblastic leukemia	110 (44%)
Age, years	
1 – 9	111 (44%)
10–24	140 (56%)
Sex	
Male	160 (64%)
Female	91 (36%)
Performance score	
90 – 100	181 (72%)
<90	53 (21%)
Not reported	17 (7%)
Disease status	
Complete remission	187 (75%)
Relapse	64 (25%)
Conditioning regimen intensity	
Myeloablative	
Total body irradiation + cyclophosphamide ± other	55 (22%)
Total body irradiation + other	17 (7%)
Busulfan + cyclophosphamide	37 (15%)
Busulfan + melphalan ± other	27 (11%)
Busulfan + fludarabine	19 (8%)
Melphalan + fludarabine	8 (3%)
Reduced intensity	
Total body irradiation + cyclophosphamide + fludarabine	9 (3%)
Total body irradiation + other	24 (10%)
Busulfan + fludarabine	15 (6%)
Melphalan + fludarabine	36 (14%)
Cyclophosphamide + fludarabine	4 (1%)
Donor	
HLA-matched sibling	21 (8%)
Unrelated donor	230 (92%)
Same donor for both transplants	
Yes	36 (14%)
No	215 (86%)
Graft	

Number	**251**
Bone marrow	72 (29%)
Peripheral blood	96 (38%)
Cord blood	83 (33%)
Duration of remission after first transplant	
< 6 months	53 (21%)
6–12 months	53 (21%)
12–24 months	56 (22%)
> 24 months	39 (16%)
Unknown	50 (20%)
Interval between relapse and second transplant	
≤ 5 months	64 (25%)
> 5 months	137 (55%)
Unknown	50 (20%)
Interval between first and second transplant	
<12 months	74 (29%)
12–23 months	105 (42%)
≥24 months	72 (28%)
Graft-versus-host disease prophylaxis	
Cyclosporine-containing	119 (47%)
Tacrolimus-containing	110 (44%)
Other agents	22 (9%)
Prior grade II-IV acute graft-versus-host disease	
None	185 (74%)
Yes	66 (26%)
Prior chronic graft-versus-host disease	
None	185 (74%)
Yes	66 (26%)
Transplant period	
2001–2005	59 (24%)
2006–2010	126 (50%)
2011–2014	66 (26%)
Median follow-up of survivors (range), months	72 (11–170)

Table 2.

Risk factors for treatment failure, overall mortality, relapse and non-relapse mortality

	Hazard Ratio (95% confidence interval)	P-value
Treatment failure (inverse of leukemia-free survival)		
Disease status at transplant		
Complete remission	1.00	
Not in remission	1.79 (1.30 – 2.47)	0.0003
Interval from relapse to 2nd transplant		
> 5 months	1.00	
≤ 5 months	0.63 (0.45 – 0.88)	0.017
Same donor for both transplants		
No	1.00	
Yes	0.56 (0.36 – 0.87)	0.009
History of chronic graft-versus-host disease		
No	1.00	
Yes	0.65 (0.47 – 0.91)	0.012
Overall mortality		
Disease status at transplant		
Complete remission	1.00	
Not in remission	1.63 (1.17 – 2.27)	0.004
Donor type		
Unrelated cord blood	1.00	
HLA-matched sibling	0.59 (0.32 – 1.07)	0.082
HLA-matched unrelated	0.63 (0.44 – 0.89)	0.011
HLA-mismatched unrelated	0.67 (0.45 – 1.00)	0.053
Relapse		
Disease status at transplant		
Complete remission	1.00	
Not in remission	2.02 (1.37 – 2.98)	0.0004
Same donor for both transplants		
Yes	1.00	
No	2.09 (1.18 – 3.69)	0.011
Non-relapse mortality		
Age		
1 – 9 years	1.00	
≥ 10 years	2.13 (1.24 – 3.66)	0.006
Performance score		
90 – 100	1.00	
< 90	1.89 (1.10 – 3.27)	0.039

	Hazard Ratio (95% confidence interval)	**P-value**
Conditioning regimen intensity		
Myeloablative, irradiation-containing	1.00	
Myeloablative, non irradiation-containing	0.54 (0.31 – 0.93)	0.027
Reduced intensity irradiation-containing	0.16 (0.06 – 0.48)	0.001
Reduced intensity non irradiation-containing	0.34 (0.16 – 0.72)	0.005
Donor type		
Unrelated cord blood	1.00	
HLA-matched sibling	0.29 (0.10 – 0.85)	0.023
HLA-matched unrelated	0.54 (0.30 – 0.97)	0.038
HLA-mismatched unrelated	0.52 (0.26 – 1.03)	0.062

Table 3.

Probabilities of leukemia-free survival, overall survival, relapse and non-relapse mortality by disease status at transplantation

	1 year	2 years	5 years	8 years
Leukemia-free survival				
Complete remission	47% (95% CI 40–54)	32% (95% CI 26–39)	27% (95% CI 20–33)	24% (95% CI 18–31)
Not in remission	24% (95% CI 14–34)	19% (95% CI 10–28)	10% (95% CI 3–17)	10% (95% CI 3–17)
Overall survival				
Complete remission	56% (95% CI 49–63)	43% (95% CI 36–50)	31% (95% CI 24–38)	28% (95% CI 21–36)
Not in remission	38% (95% CI 26–49)	26% (95% CI 16–37)	15% (95% CI 6–23)	15% (95% CI 6–23)
Relapse				
Complete remission	29% (95% CI 23–35)	42% (95% CI 35–49)	46% (95% CI 39–53)	49% (95% 41–56)
Not in remission	51% (95% CI 39–63)	56% (95% CI 43–68)	64% (95% CI 52–76)	64% (95% CI 52–76)
Non-relapse mortality				
Complete remission	25% (95% CI 19–31)	27% (95% CI 21–33)	29% (95% CI 23–35)	29% (95% CI 23–35)
Not in remission	20% (95% CI 11–30)	20% (95% CI 11–30)	22% (95% CI 12–31)	24% (95% CI 14–34)