Title

Transplant Outcomes for Children with T Cell Acute Lymphoblastic Leukemia in Second Remission: A Report from the Center for International Blood and Marrow Transplant Research

Journal

Transplantation and Cellular Therapy, 21(12)

ISSN

2666-6375

Authors

Burke, Michael J
Verneris, Michael R
Le Rademacher, Jennifer
et al.

Publication Date

2015-12-01

DOI

10.1016/j.bbmt.2015.08.023

Peer reviewed

HHS Public Access

Author manuscript

Biol Blood Marrow Transplant. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Biol Blood Marrow Transplant. 2015 December ; 21(12): 2154–2159. doi:10.1016/j.bbmt.2015.08.023.

Transplant Outcomes for Children with T-Cell Acute Lymphoblastic Leukemia in Second Remission: A Report of the CIBMTR®

Michael J. Burke, MD[1], **Michael R. Verneris, MD**[2], **Jennifer Le Rademacher, PhD**[3,4], **Wensheng He, MS, PhD**[3], **Hisham Abdel-Azim, MD**[5], **Allistair A. Abraham, MD**[6], **Jeffery J. Auletta, MD**[7], **Mouhab Ayas, MD**[8], **Valerie I. Brown, MD, PhD**[9], **Mitchell S. Cairo, MD**[10], **Ka Wah Chan, MD**[11], **Miguel A. Diaz Perez, MD, PhD**[12], **Christopher C. Dvorak, MD**[13], **R. Maarten Egeler, MD, PhD**[14], **Lamis Eldjerou**[15], **Haydar Frangoul**[16], **Gregory M. T. Guilcher, MD**[17], **Robert J. Hayashi, MD**[18], **Ahmed Ibrahim**[19], **Kimberly A. Kasow, DO**[20], **Wing H. Leung, MD, PhD**[21], **Richard F. Olsson, MD, PhD**[22,23], **Michael A. Pulsipher, MD**[5], **Niketa Shah**[24], **Nirali N. Shah, MD, MHSc**[25], **Elizabeth Thiel, MD**[3], **Julie-An Talano**[1], and **Carrie L. Kitko, MD**[26]

[1]Division of Hematology/Oncology/Blood and Marrow Transplant, Department of Pediatrics, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, WI

[2]Department of Pediatrics, University of Minnesota, Minneapolis, MN

[3]CIBMTR® (Center for International Blood and Marrow Transplant Research), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

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

[5]Division of Hematology, Oncology and Blood & Marrow Transplantation, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, CA

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

[7]Divisions of Hematology/Oncology, Bone Marrow Transplantation and Infectious Diseases, Nationwide Children's Hospital, Columbus, OH

[8]Department of Pediatric Hematology Oncology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

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

Correspondence to: Michael J. Burke, MD, Associate Professor, Department of Pediatrics, Division of Hematology/Oncology/Blood and Marrow Transplant, Medical College of Wisconsin, Children's Hospital of Wisconsin, MACC Fund Research Center, 8701 Watertown Plank Rd, Milwaukee, WI 53226, Phone: 955-4170, Fax: 414-955-6543, mmburke@mcw.edu.

Conflict of Interest Statement: There are no relevant conflicts of interest to disclose.

[10]Department of Pediatrics, New York Medical College, Valhalla, NY

[11]Department of Pediatrics, Texas Transplant Institute, San Antonio, TX

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

[13]Department of Pediatrics, University of California San Francisco Medical Center, San Francisco, CA

[14]Department of Hematology/Oncology, Hospital for Sick Children, Toronto, ON, Canada

[15]Department of Pediatrics, University of Florida, Gainsville, FL

[16]Division of Hematology-Oncology, Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN

[17]Section of Paediatric Oncology and Blood and Marrow Transplant, Alberta Children's Hospital, Calgary, AB, Canada

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

[19]Department of Hematology/Oncology, Makassed General Hospital, Beiruit, Lebanon

[20]Division of Hematology-Oncology, Department of Pediatrics, University of North Carolina at Chapel Hill, Chapel Hill, NC

[21]Division of Bone Marrow Transplantation, St. Jude Children's Research Hospital, Memphis, TN

[22]Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

[23]Centre for Clinical Research Sörmland, Uppsala University, Uppsala, Sweden

[24]Division of Hematology/Oncology, Department of Pediatrics, Mayo Clinic Arizona and Phoenix Children's Hospital, Phoenix, AZ

[25]Pediatric Oncology Branch, Center for Cancer Research (CCR), National Cancer Institute (NIH), Bethesda, MD

[26]Stem Cell Transplant Program, Department of Pediatrics, Vanderbilt University, Nashville, TN

Abstract

Survival for children with relapsed T-ALL is poor when treated with chemotherapy alone and outcomes after allogeneic hematopoietic cell transplantation (HCT) is not well described. Two hundred and twenty-nine children with T-ALL in second complete remission (CR2) received a HCT following myeloablative conditioning between 2000–2011 and were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR). Median age was 10 (range, 2–18) years. Donor source was umbilical cord blood (26%), matched sibling bone marrow (38%) or unrelated bone marrow/peripheral blood (36%). Acute GVHD (grade 2–4) and chronic GVHD occurred in 35% (95% CI, 27–45) and 26% (95% CI, 20–33) of patients. Transplant related mortality at day 100 and 3-year relapse rates were 13% (95% CI, 9–18) and 30% (95% CI, 24–37) respectively. Three year overall survival and disease-free survival were 48% (95% CI, 41–55) and 46% (95% CI, 39–52%) respectively. In multivariate analysis, patients with bone marrow relapse,

with or without concurrent extramedullary relapse prior to HCT, were most likely to relapse (HR=3.94, p=0.005) as compared to isolated extramedullary disease. In conclusion, HCT for pediatric T-ALL in CR2 demonstrates reasonable and durable outcomes and consideration for HCT is warranted.

Keywords

Pediatric; T-Cell ALL; relapse; acute lymphoblastic leukemia; transplantation

Introduction

Each year approximately 3,000 children in the United States are diagnosed with acute lymphoblastic leukemia (ALL)[1] with 10–15% having T-cell ALL (T-ALL).[2–4] Historically, T-ALL portended a worse prognosis compared to B-ALL (75.2% versus 83.7% 5-year event-free survival (EFS)),[5, 6] but treatment with intensive, high-dose, multi-agent chemotherapy resulted in significantly improved outcomes (5-year EFS ~80%).[7] Recent pediatric ALL trials using a Berlin-Frankfurt-Munster (BFM) based backbone and/or intensified therapy with high-dose methotrexate have further improved outcomes for children with T-ALL, but have plateaued around 85% EFS.[8–12] In contrast, long term survival for patients who relapse and are re-treated with chemotherapy has been very disappointing, with >90% of patients dying of disease.[13–15] In a report of 207 children with T-ALL in first relapse treated with chemotherapy alone, the 10-year EFS was only 15%.[15] Therefore allogeneic hematopoietic cell transplantation (HCT) has typically been the standard approach for relapsed pediatric T-ALL.

There are limited data reporting HCT outcomes for children with relapsed T-ALL.[14, 15] Reported outcomes have generally been poor with predicted EFS <20% with either HCT or chemotherapy alone approaches.[14–16] Past analyses included older treatment eras (1980s and 1990s) with little data on current HCT outcomes for children with relapsed T-ALL receiving contemporary treatment strategies. Whether improvements in the current HCT era (post-2000) have resulted in improved survival, particularly with enhanced high-resolution HLA-typing[17] and better supportive care[18], is unclear. Likewise, whether patient-, disease-, or HCT-related variables impact outcomes in relapsed T-ALL in children is uncertain. To address these issues, we investigated the outcomes of 229 pediatric patients with relapsed T-ALL who received a myeloablative HCT in CR2 and were reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) between 2000 and 2011. These results comprise the largest HCT cohort reported to date of pediatric patients with relapsed T-ALL in CR2 and highlight the success of current transplant approaches which have contributed to the improved outcomes identified in this analysis.

Methods

Patients—Data were obtained from the CIBMTR, a working group of more than 500 transplant centers worldwide that provide patient, disease, transplant characteristics including outcomes for consecutive transplantations to a statistical center at the Medical

College of Wisconsin (MCW) or a data-coordinating center at the National Marrow Donor Program (NMDP). Information regarding pre-HCT chemotherapy (e.g. Nelarabine), detailed T-ALL immunophenotyping (e.g. Early T-Cell Progenitor (ETP) T-ALL) or pre-HCT minimal residual disease (MRD) results were not collected by the CIBMTR during the era of these patients. Patients or guardians provided written informed consent for data submission and research participation in accordance with the Declaration of Helsinki. The Institutional Review Boards of the MCW and the NMDP approved this study.

Eligibility Criteria—Eligible were patients with T-ALL who were 18 years or younger at the time of transplant, received a myeloablative conditioning regimen in CR2 and had an HLA-identical sibling or unrelated donor. Transplantations were performed between 2000 and 2011. Excluded were patients receiving transplant with ex-vivo T-cell depletion or having a predisposing condition prior to the diagnosis of T-ALL.

End points—Neutrophil recovery was defined as an absolute neutrophil count (ANC) $\geq 0.5\times10^9$/L for three consecutive days and platelet recovery as a platelet count $>20\times10^9$/L for 7 days without transfusion. Transplant related mortality (TRM) was defined as any death during remission and treatment failure is a composite endpoint that includes TRM and relapse. Disease-free survival (DFS) was defined as survival in continuous complete remission. Relapse was defined as morphological recurrence of leukemia at any site. Grade 2–4 acute graft-versus-host-disease (GVHD) and chronic GVHD were defined using standard criteria.[19, 2021]

Statistical Analysis

The probabilities of neutrophil and platelet recovery, acute and chronic GVHD,[19, 20] TRM and relapse were calculated using the cumulative incidence function estimator.[22, 23] For neutrophil and platelet recovery and GVHD, death without the event was the competing risk. For TRM, relapse was the competing event; and for relapse, TRM was the competing event. DFS and overall survival (OS) were calculated using the Kaplan Meier estimator.[22, 24] Ninety-five percent confidence intervals were calculated using log transformation. For OS, death from any cause was considered an event and patients surviving at last follow-up were censored. For DFS, relapse and death were considered events; and patients surviving in remission were censored at last follow-up.

Variables tested in the Cox proportional hazards regression model included age at HCT (≤10 versus 11–18 years), performance score prior to HCT (<80 versus ≥80), recipient CMV status (positive versus negative), interval between diagnosis and transplant (<18 (early) versus 18–36 (intermediate) versus >36 months (late)), graft type (bone marrow versus peripheral blood versus cord blood), and donor-recipient HLA match (HLA matched sibling, HLA matched unrelated, HLA mismatched unrelated and not reported). Graph source defined as HLA matched sibling, unrelated donor (including both BM/PBSC) and unrelated cord blood (UCB) were also compared. Donors and recipients were considered matched to each other if all 8/8 of the HLA-A, B, C, and DRB1 loci by high resolution typing were identical. Recipients of cord blood transplants were considered matched if 6/6 loci HLA-A and B loci (by low level typing), and HLA-DR (by high resolution typing) were all identical.

Statistically significant prognostic factors were selected using a stepwise selection procedure. A subset of patients had more detailed disease specific information including WBC at diagnosis and site of first relapse (n=112). An analysis was conducted to investigate the impact of WBC at initial diagnosis ($<100\times10^9$/L vs. $\geq100\times10^9$/L) and site of first relapse (isolated extramedullary site versus isolated bone marrow versus bone marrow with extramedullary site) on outcomes by adding these variables into the final models grouping patients with unreported WBC and site of first relapse into one group. The presence of GVHD was evaluated as a time-dependent covariate. All p-values were two-sided and ≤0.05 was considered significant. Analyses were performed using SAS version 9.1 (Cary, NC).

Results

Patient, disease and transplant characteristics are shown in Table 1. The median age at HCT was 10 years (range 2–18), with 174 (76%) patients being male. Duration of first complete remission is not routinely collected on CIBMTR forms; therefore time of initial diagnosis to transplant is used as a surrogate. Almost half of the patients (45%) relapsed early and came to HCT within 18 months of diagnosis (n=104, 45%), 77 (34%) were transplanted 18–36 months from diagnosis, and 47 (21%) were transplanted >36 months from diagnosis. One patient had an unknown time to transplant from initial diagnosis.

HCT conditioning included TBI and cyclophosphamide in 183 (80%) patients, 49 patients (31%) received TBI >1300 cGY compared to 108 patients (69%) whose TBI was <1300 cGY; 59 patients had missing TBI dosing data. Seventy-six patients (33%) received serotherapy with either alemtuzumab (Campath) or anti-thymocyte globulin (ATG). A cyclosporine-based regimen was the primary GVHD prophylaxis used (72%). Most patients received HLA-matched sibling bone marrow (BM) (n=86, 38%) followed by mismatched umbilical cord blood (UCB) (n=50, 22%), matched (n=27, 12%) or mismatched (n=20, 9%) unrelated BM/peripheral blood stem cells (PBSC) and HLA-matched UCB (n=10, 4%). The remaining 36 patients did not have HLA-matching reported (unrelated UCB, n=17; unrelated BM, n=15; and unrelated PBSC, n=4). There were 73 (32%) patients who received their HCT between 2000 and 2003, 78 (34%) between 2004 and 2007 and the remaining 78 (34%) during 2008 to 2011.

Patient, disease and transplant characteristics of the one hundred and twelve patients with more detailed research level data, including: presenting WBC, site of relapse, and duration of CR1 are shown in Table 2. Among these, forty-seven patients (42%) presented with an initial WBC $\geq100\times10^9$/L and 65 (58%) had their first relapse involving the bone marrow ± extramedullary disease.

Outcomes

Recovery and GVHD—In univariate analysis, the probability of neutrophil recovery by day 28 was 83% (95% CI, 78–88) and platelet recovery by day 100 was 76% (95% CI, 70–82). The incidence of acute GVHD (Grades 2–4) by day 100 was 35% (95% CI, 27–45) and 26% (95% CI, 20–33) of patients had chronic GVHD by 1-year (limited and extensive).

Transplant Related Mortality, Relapse and Disease-Free Survival—TRM at day 100 was 13% (95% CI, 9–18), increasing to 21% (95% CI, 16–26) at 1-year and 24% (95% CI, 18–30) at 3-years (Figure 1A). The rate of relapse at 3-years was 30% (95% CI, 24–37). The 3-year DFS (Figure 1B) and OS was 46% (95% CI, 39–52) and 48% (95% CI, 41–55), respectively. Relapse was the most frequent cause of death (59/116; 51%) in this analysis. Other causes of death were related to infection (n=13, 11%), TRM not specified (n=13, 11%), organ failure (n=10, 9%), idiopathic pneumonia syndrome/ARDS (n=8, 7%), GVHD (n=7, 5%), hemorrhage (n=4, 3%) and graft failure (n=2, 2%).

Univariate post-HCT outcomes analyzed included site of initial relapse (isolated bone marrow/combined BM versus isolated extramedullary (CNS/testes) and graft source (HLA identical sibling versus unrelated donor BM/PBSC versus unrelated cord blood). Patients who received a HCT for an isolated extramedullary relapse had a significantly lower rate of post-HCT relapse compared to isolated/combined BM patients (15%, 95% CI 5–28 vs. 45%, 95% CI 32–58; p<0.001) (Figure 2A) and greater DFS at 3-years (56%, 95% CI 39–72 vs. 35%, 95% CI 23–47; p=0.05) (Figure 2B). There was no difference in relapse or DFS based on graft source (Figure 3A/B). The remaining variables tested in univariate analysis including age at HCT, performance score, CMV status, donor-recipient HLA match, and presenting WBC and time period of HCT (2000–2003 versus 2004–2007 versus 2008–2011) were not significant for any outcome measure.

In multivariable analysis (Table 3), only the site of first relapse, either isolated bone marrow or combined BM and extramedullary disease, was strongly predictive of a subsequent relapse post-HCT (HR 3.94, 95% CI, 1.51–10.25; p=0.005) as compared to isolated extramedullary disease. The effect of GVHD on relapse was not statistically significant for either acute GVHD (p=0.51) or chronic GVHD (p=0.33). No other patient, disease or treatment variables were significant when tested in multivariable analysis, including time from diagnosis to HCT (< 18 months versus > 18 months).

Discussion

Children with relapsed T-ALL treated with chemotherapy alone have done poorly with an overall survival of <20% regardless of the duration of CR1.[14, 15, 25–28] As a result of poor outcomes with chemotherapy, HCT is often considered the standard of care for patients with relapsed T-ALL with either a bone marrow relapse or isolated extramedullary relapse[29], despite the lack of publications regarding HCT-specific outcomes for relapsed pediatric T-ALL. However a comparison of outcomes for children with relapsed T-ALL receiving chemotherapy alone versus HCT may be biased by the fact that many of these patients are not able to attain sufficient disease control to proceed to HCT.

Although HCT for relapsed T-ALL has produced durable remissions, there is limited data describing outcomes for these patients. The vast majority of literature supporting transplantation in childhood ALL combines T-ALL data with B-ALL, limiting the ability to distinguish the outcomes for T-ALL.[14] One recent publication focused on HCT outcomes for T-ALL in adolescents and adults who received a myeloablative HCT, the majority of whom were in CR1 (60%). The median patient age was 18 years with the majority of

patients (68%) being adolescents aged 14–20 years[16]. Patients who received HCT in ≥ CR2 (n=18) had a TRM of 32% and a relapse rate of 35%. The authors found that 5-year OS was best for those transplanted in CR1 (54%; n=32) compared to an OS of 32% for those in CR2 or greater at the time of HCT.[16] Though these results may be less applicable to our strictly pediatric population, the outcomes are comparable to our results which report 3-year rates for TRM, relapse and OS of 24%, 30% and 48%, respectively.

The improved outcomes with HCT versus chemotherapy alone in relapsed ALL patients are thought to be in part related to a graft-versus-leukemia (GVL) effect. The presence of GVHD is often used as a surrogate for GVL, since several publications have demonstrated that patients with GVHD have lower relapse rates.[30, 31] Our finding that neither acute nor chronic GVHD impacted relapse raises the question as to how significant the GVL effect is in pediatric patients with relapsed T-ALL in CR2. It is possible that the GVL effect is only seen in lower grades of acute GVHD such as in 1–2 or 1–3 versus 3–4 or 4 alone, where the latter groups are more likely to be associated with TRM and thus, losing any appreciable GVL effect. Given our relatively small cohort, we were unable to test this hypothesis. Additional studies are needed to further understand the role, if any, of GVL in T-ALL.

We found that patients with a bone marrow relapse ± extramedullary disease were almost four times as likely to relapse post-HCT compared to those patients with an isolated extramedullary relapse. This would suggest that isolated extramedullary T-ALL relapse may be a lower risk disease (as is the case for isolated extramedullary relapse in B-ALL) compared to relapses that include bone marrow involvement. Identifying a significantly higher risk group provides an opportunity to develop more novel approaches to improve transplant outcomes in this patient population.

Due to the limitations of a retrospective registry-based analysis, we were unable to include prior treatment history (e.g. Nelarabine), disease immunophenotyping (e.g. ETP T-ALL) or measurements of pre-HCT MRD. These are admittedly important aspects to determining the outcomes of HCT in this population, and we would advocate for their future inclusion in CIBMTR based data collection. As well, registry-based studies can have biases due to data collection and patient ascertainment.

We identified that patients with an initial relapse site of bone marrow ± extra medullary disease have significantly inferior survival. However, we did not find outcome associations with patient age at HCT, gender, presence of acute or chronic GVHD, CMV status, TBI ≥ or <1300 cGY, time from initial diagnosis to transplant, the year in which patients received their HCT or whether or not they received serotherapy. Importantly, there was no difference in relapse or disease free survival rates based on graft source, therefore, when considering HCT for relapsed T-cell ALL, transplant from the best available donor should be offered in suitable patients.

In summary, we report the largest series of pediatric transplant outcomes for patients with relapsed T-ALL in CR2 with a 3-year survival rate approaching 50%. These results are encouraging and appear durable, particularly when compared to chemotherapy alone for relapse T-ALL where survival is <20%, providing further evidence to support the role of

transplant in these patients. Based on this data, consideration for HCT for T-ALL in CR2 is warranted.

Acknowledgments

The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24-CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI) and the National Institute of Allergy and Infectious Diseases (NIAID); a Grant/Cooperative Agreement 5U10HL069294 from NHLBI and NCI; a contract HHSH250201200016C with Health Resources and Services Administration (HRSA/DHHS); two Grants N00014-13-1-0039 and N00014-14-1-0028 from the Office of Naval Research; and grants from *Actinium Pharmaceuticals; Allos Therapeutics, Inc.; *Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; *Blue Cross and Blue Shield Association; *Celgene Corporation; Chimerix, Inc.; Fred Hutchinson Cancer Research Center; Fresenius-Biotech North America, Inc.; *Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.;*Gentium SpA; Genzyme Corporation; GlaxoSmithKline; Health Research, Inc. Roswell Park Cancer Institute; HistoGenetics, Inc.; Incyte Corporation; Jeff Gordon Children's Foundation; Kiadis Pharma; The Leukemia & Lymphoma Society; Medac GmbH; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; *Milliman USA, Inc.; *Miltenyi Biotec, Inc.; National Marrow Donor Program; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Perkin Elmer, Inc.; *Remedy Informatics; *Sanofi US; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; St. Baldrick's Foundation; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; *Tarix Pharmaceuticals; *TerumoBCT; *Teva Neuroscience, Inc.; *THERAKOS, Inc.; University of Minnesota; University of Utah; and *Wellpoint, Inc. 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. Gurney JG, Severson RK, Davis S, Robison LL. Incidence of cancer in children in the United States. Sex-, race-, and 1-year age-specific rates by histologic type. Cancer. 1995; 75:2186–2195. [PubMed: 7697611]
2. Crist W, Boyett J, Pullen J, van Eys J, Vietti T. Clinical and biologic features predict poor prognosis in acute lymphoid leukemias in children and adolescents: a Pediatric Oncology Group review. Med Pediatr Oncol. 1986; 14:135–139. [PubMed: 3462459]
3. Pullen J, Shuster JJ, Link M, et al. Significance of commonly used prognostic factors differs for children with T cell acute lymphocytic leukemia (ALL), as compared to those with B-precursor ALL. A Pediatric Oncology Group (POG) study. Leukemia. 1999; 13:1696–1707. [PubMed: 10557041]
4. Ludwig WD, Teichmann JV, Sperling C, et al. Incidence, clinical markers and prognostic significance of immunologic subtypes of acute lymphoblastic leukemia (ALL) in children: experiences of the ALL-BFM 83 and 86 studies. Klin Padiatr. 1990; 202:243–252. [PubMed: 2203938]
5. Uckun FM, Sensel MG, Sun L, et al. Biology and treatment of childhood T-lineage acute lymphoblastic leukemia. Blood. 1998; 91:735–746. [PubMed: 9446631]
6. Hunger SP, Lu X, Devidas M, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. J Clin Oncol. 2012; 30:1663–1669. [PubMed: 22412151]
7. Pui CH, Sallan S, Relling MV, Masera G, Evans WE. International Childhood Acute Lymphoblastic Leukemia Workshop: Sausalito, CA, 30 November-1 December 2000. Leukemia. 2001; 15:707–715. [PubMed: 11368430]
8. Asselin BL, Devidas M, Wang C, et al. Effectiveness of high-dose methotrexate in T-cell lymphoblastic leukemia and advanced-stage lymphoblastic lymphoma: a randomized study by the Children's Oncology Group (POG 9404). Blood. 2011; 118:874–883. [PubMed: 21474675]
9. Rives S, Estella J, Camos M, et al. T-cell pediatric acute lymphoblastic leukemia: analysis of survival and prognostic factors in 4 consecutive protocols of the Spanish cooperative study group SHOP. Med Clin (Barc). 2012; 139:141–149. [PubMed: 22459573]

10. Reiter A, Schrappe M, Ludwig WD, et al. Chemotherapy in 998 unselected childhood acute lymphoblastic leukemia patients. Results and conclusions of the multicenter trial ALL-BFM 86. Blood. 1994; 84:3122–3133. [PubMed: 7949185]
11. Lauten M, Moricke A, Beier R, et al. Prediction of outcome by early bone marrow response in childhood acute lymphoblastic leukemia treated in the ALL-BFM 95 trial: differential effects in precursor B-cell and T-cell leukemia. Haematologica. 2012; 97:1048–1056. [PubMed: 22271901]
12. Schrappe M, Valsecchi MG, Bartram CR, et al. Late MRD response determines relapse risk overall and in subsets of childhood T-cell ALL: results of the AIEOP-BFM-ALL 2000 study. Blood. 2011; 118:2077–2084. [PubMed: 21719599]
13. Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008
14. Reismuller B, Peters C, Dworzak MN, et al. Outcome of children and adolescents with a second or third relapse of acute lymphoblastic leukemia (ALL): a population-based analysis of the Austrian ALL-BFM (Berlin-Frankfurt-Munster) study group. J Pediatr Hematol Oncol. 2013; 35:e200–204. [PubMed: 23652878]
15. Einsiedel HG, von Stackelberg A, Hartmann R, et al. Long-term outcome in children with relapsed ALL by risk-stratified salvage therapy: results of trial acute lymphoblastic leukemia-relapse study of the Berlin-Frankfurt-Munster Group 87. J Clin Oncol. 2005; 23:7942–7950. [PubMed: 16258094]
16. Bakr M, Rasheed W, Mohamed SY, et al. Allogeneic hematopoietic stem cell transplantation in adolescent and adult patients with high-risk T cell acute lymphoblastic leukemia. Biol Blood Marrow Transplant. 2012; 18:1897–1904. [PubMed: 22824185]
17. Harvey J, Green A, Cornish J, et al. Improved survival in matched unrelated donor transplant for childhood ALL since the introduction of high-resolution matching at HLA class I and II. Bone Marrow Transplant. 2012; 47:1294–1300. [PubMed: 22343674]
18. Mateos MK, O'Brien TA, Oswald C, et al. Transplant-related mortality following allogeneic hematopoeitic stem cell transplantation for pediatric acute lymphoblastic leukemia: 25-year retrospective review. Pediatr Blood Cancer. 2013; 60:1520–1527. [PubMed: 23733511]
19. Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. Hematol Oncol Clin North Am. 1999; 13:1091–1112. viii–ix. [PubMed: 10553263]
20. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant. 1995; 15:825–828. [PubMed: 7581076]
21. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. Biol Blood Marrow Transplant. 2005; 11:945–956. [PubMed: 16338616]
22. Klein, JMM. Survival Analysis: techniques of censored and truncated data. 2. Springer Verlag; New York, NY: 2003.
23. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med. 1999; 18:695–706. [PubMed: 10204198]
24. Kaplan ELMP. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958:457–481.
25. Nguyen K, Devidas M, Cheng SC, et al. Factors influencing survival after relapse from acute lymphoblastic leukemia: a Children's Oncology Group study. Leukemia. 2008; 22:2142–2150. [PubMed: 18818707]
26. Henze G, Fengler R, Hartmann R, et al. Six-year experience with a comprehensive approach to the treatment of recurrent childhood acute lymphoblastic leukemia (ALL-REZ BFM 85). A relapse study of the BFM group. Blood. 1991; 78:1166–1172. [PubMed: 1878583]
27. Tallen G, Ratei R, Mann G, et al. Long-term outcome in children with relapsed acute lymphoblastic leukemia after time-point and site-of-relapse stratification and intensified short-course multidrug chemotherapy: results of trial ALL-REZ BFM 90. J Clin Oncol. 2010; 28:2339–2347. [PubMed: 20385996]

28. Ko RH, Ji L, Barnette P, et al. Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol. 2010; 28:648–654. [PubMed: 19841326]

29. Oliansky DM, Camitta B, Gaynon P, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: update of the 2005 evidence-based review. ASBMT Position Statement. Biol Blood Marrow Transplant. 2012; 18:979–981. [PubMed: 22490784]

30. Pulsipher MA, Langholz B, Wall DA, et al. The addition of sirolimus to tacrolimus/methotrexate GVHD prophylaxis in children with ALL: a phase 3 Children's Oncology Group/Pediatric Blood and Marrow Transplant Consortium trial. Blood. 2014; 123:2017–2025. [PubMed: 24497539]

31. Horowitz MM, Gale RP, Sondel PM, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood. 1990; 75:555–562. [PubMed: 2297567]

HIGHLIGHTS

- Survival for children with relapsed T-ALL is poor when treated with chemotherapy alone and outcomes after allogeneic hematopoietic cell transplantation (HCT) is not well described.
- We report the largest pediatric HCT cohort to date of patients with relapsed T-ALL in CR2.
- Patients with relapsed T-ALL in CR2 and a bone marrow relapse, with or without concurrent extramedullary relapse, were most likely to relapse post-HCT as compared to patients with isolated extramedullary disease.
- Three-year overall survival and disease-free survival for patients with relapsed T-ALL who received a HCT in CR2 were 48% and 46%.
- These results are encouraging and appear durable, particularly when compared to chemotherapy alone for relapse T-ALL where survival is <20%, providing further evidence to support the role of transplant in these patients.

Figure 1A

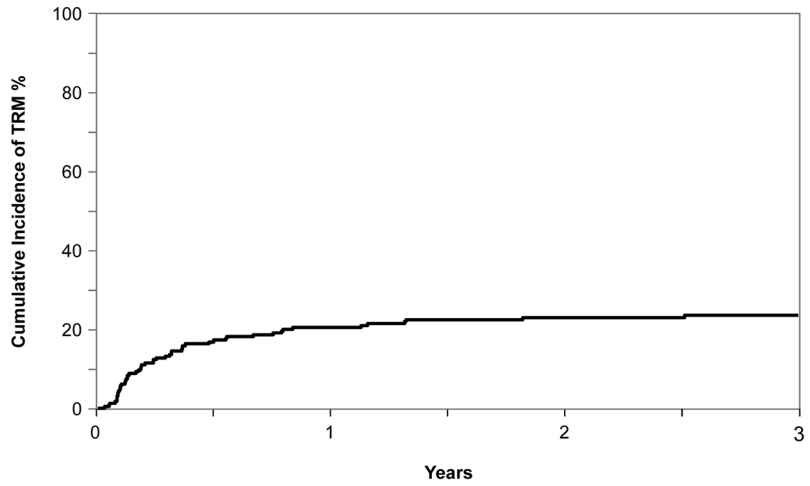

Figure 1B

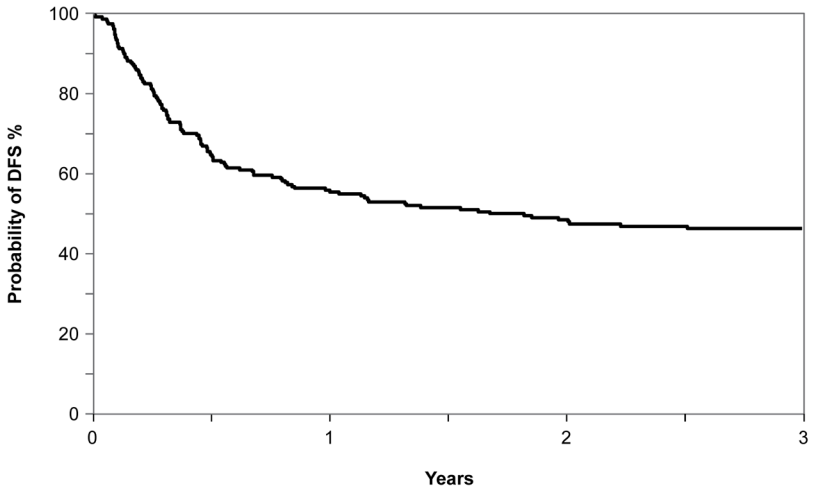

Figure 1.

Figure 1A: Cumulative incidence of transplant related mortality was 13% (95% CI, 9–18) at day 100, 21% (95% CI, 16–26) at 1-year and 24% (95% CI, 18–30) at 3-years.

Figure 1B: Probability of disease free survival at 3-years was 46% (95% CI, 39–52).

Figure 2A

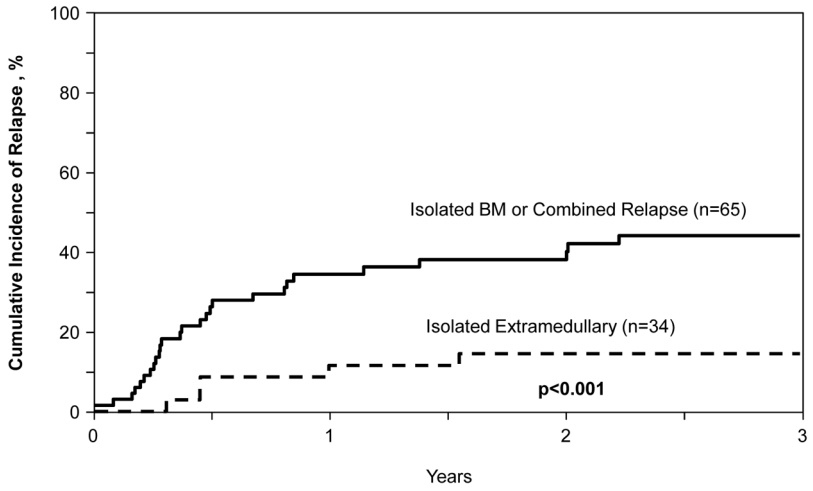

Figure 2B

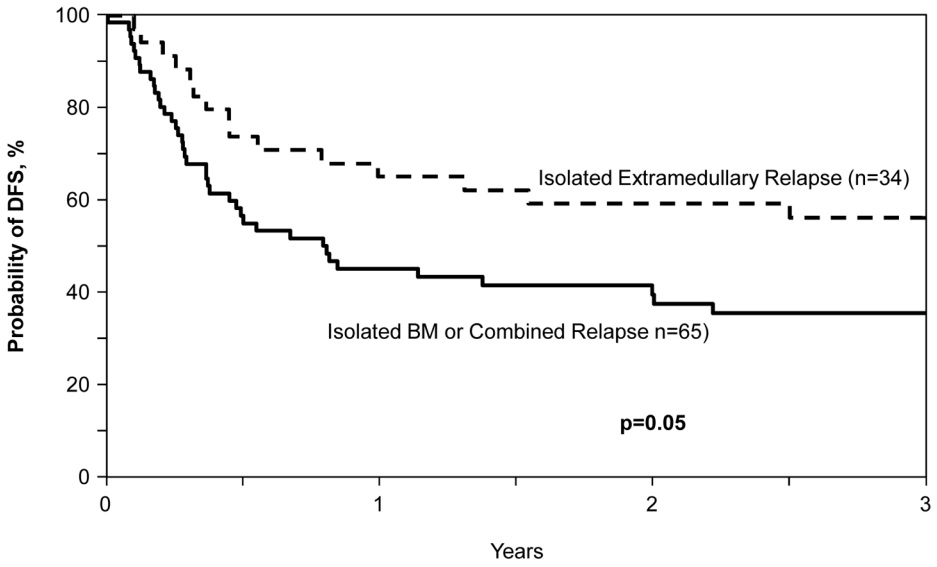

Figure 2.

Figure 2A: Cumulative incidence of relapse at 3-years for patients with an isolated extramedullary relapse (CNS/Testes) was 15% (95% CI, 5–28) compared to 45% (95% CI, 32–58) for patients with isolated or combined BM relapse ($p<0.001$).

Figure 2B: Probability of disease free survival at 3-years for patients with an isolated extramedullary relapse (CNS/Testes) was 56% (95% CI, 39–72) compared to 35% (95% CI, 23–47) for patients with isolated or combined BM relapse ($p=0.05$).

Figure 3A

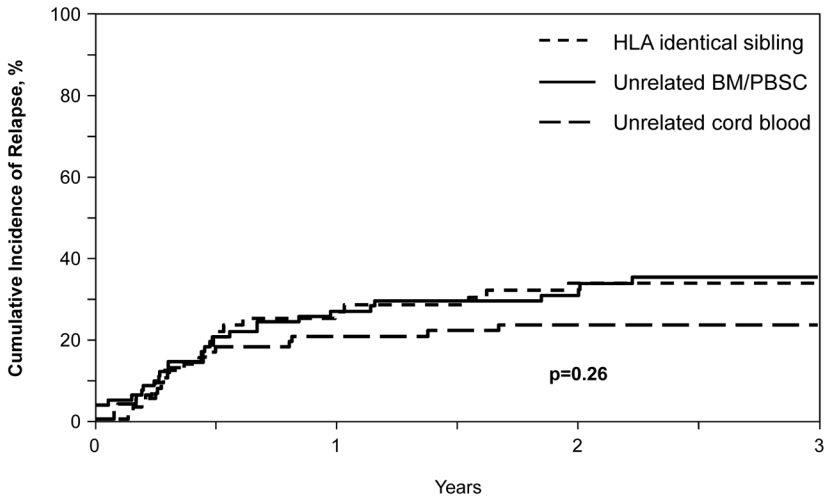

Figure 3B

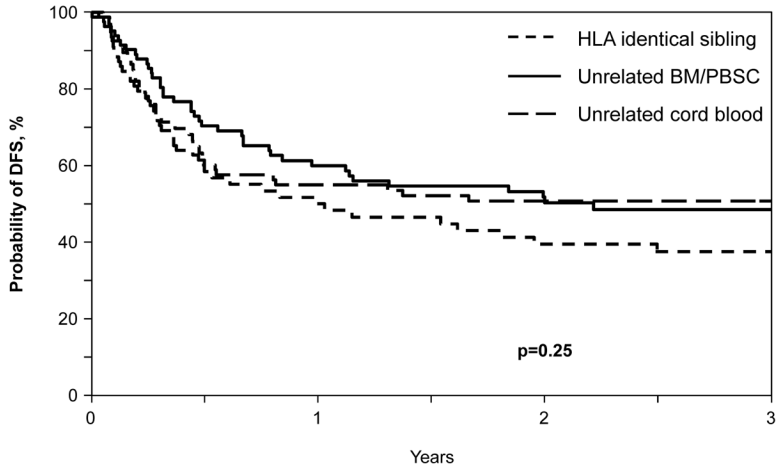

Figure 3.

Figure 3A: Cumulative incidence of relapse at 3-years for patients receiving HLA-matched sibling BM was 34% (95% CI, 24–45), unrelated BM/PBSC was 34% (95% CI, 23–46) and unrelated UCB was 24% (95% CI, 15–34) (p=0.26).

Figure 3B: Probability of disease free survival at 3-years for patients receiving HLA-matched sibling BM was 48% (95% CI, 37–59), unrelated BM/PBSC was 37% (95% CI, 25–49) and unrelated UCB was 50% (95% CI, 39–61) (p=0.25).

Table 1

Patient Characteristics

	Total
	N (%)
Number of patients	229
Number of centers	99
Age at transplant, median (range)	10 (2–18)
≤5	38 (17)
6–10	66 (29)
11–18	125 (55)
Recipient sex	
Male	174 (76)
Female	
Performance score prior to HCT	
<80	16 (7)
80–100	199 (87)
Unknown	14 (6)
Unknown	
Time from diagnosis to transplant, median (range), months	19 (<1–105)
<18	104 (45)
18 –36	77 (34)
>36	47 (21)
Unknown	1 (<1)
Conditioning regimen	
TBI + CY	183 (80)
TBI + Other	33 (14)
Bu + Cy	13 (6)
Donor recipient HLA match**	
HLA-identical Sibling (incl. 3 CB)	86 (38)
Matched unrelated BM/PBSC	27 (12)
Mismatched unrelated BM/PBSC	20 (9)
Matched unrelated CB	10 (4)
Mismatched unrelated CB	50 (22)
Unrelated BM/PBSC/CB	36 (16)
HLA Match not collected (n=15 URD BM, n=4 URD PBSC, n=17 URD CB)	
Recipient CMV status	
Negative	72 (31)
Positive	92 (40)
Unknown	65 (28)
Graft type	
BM	120 (52)
PBSC	29 (13)

	Total
	N (%)
CB	80 (35)
Received ATG or Campath	
No	139 (61)
Yes	76 (33)
Unknown	14 (6)
Year of Transplant	
2000–2003	73 (32)
2004–2007	78 (34)
2008–2011	78 (34)
GVHD prophylaxis	
CSA + MTX	94 (41)
CSA + MMF	31 (14)
CSA +-Corticosteroids	40 (17)
FK506 + MMF	7 (3)
FK506 + MTX	36 (16)
FK506 +-Other	3 (1)
Cyclophosphamide alone	1 (<1)
Unknown	17 (7)
Median (range) follow-up, months	56 (3 – 150)

Abbreviations: CMV = cytomegalovirus; CSA = Cyclosporine; MTX = Methotrexate

** Best available HLA matching information was used for unrelated. For unrelated donor transplantation, donor recipient HLA-match considered allele-level HLA typing at HLA-A, -B, -C and -DRB1. For umbilical cord blood transplantation, HLA-matching considered low resolution match at HLA-A and –B and allele-level at –DRB1

Table 2

Additional Patient Characteristics Available for Subset Analysis

	Total
	N (%)
Number of patients	112
WBC at diagnosis	
<100× 10^9/L	44 (39)
≥100×10^9/L	47 (42)
Unknown	21 (19)
Extramedullary disease prior to HCT	
No	46 (41)
Yes	65 (58)
Unknown	1 (1)
Duration of CR1 median (range)	13 mo (<1–76)
<18 months	74 (66)
18 – 36 months	17 (15)
>36 months	15 (13)

Abbreviations: WBC = White blood count, CR1 = First complete remission mo = months

Table 3

Multivariate Analysis of Risk of Post-HCT Relapse

	N	Hazard ratio (95% confidence interval)	p-value
Site of first relapse			Overall=0.008
Isolated CNS or Testes	34	1.00	
Isolated BM / Combined BM	65	3.94 (1.51 – 10.25)	0.005
Not reported	125	2.28 (0.89 – 5.83)	0.08

Other comparisons: site of first relapse not reported vs. BM +/− other: 0.58 (0.35 – 0.96), p-value= 0.03

The effect of GVHD on relapse was not statistically significant: Grade 2–4 acute GVHD (p-value=0.51) and chronic GVHD (p-value=0.33)