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


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Financial disclosure: See Acknowledgments on page 2159.

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http://dx.doi.org/10.1016/j.bbmt.2015.08.023
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INTRODUCTION

Each year approximately 3000 children in the United States are diagnosed with acute lymphoblastic leukemia (ALL) [1], 10% to 15% with T-cell ALL (T-ALL) [2-4]. Historically, T-ALL portended a worse prognosis compared with B-cell ALL (75.2% versus 83.7% 5-year event-free survival [EFS] rates) [5,6], but treatment with intensive, high-dose, multiagent chemotherapy resulted in significantly improved outcomes (5-year EFS rates of ~80%) [7]. Pediatric ALL trials using a Berlin-Frankfurt-Munster–based backbone and/or intensified therapy with high-dose methotrexate have further improved outcomes for children with T-ALL but have plateaued at rates of 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 rate 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 rates <20% with either HCT or chemotherapy alone [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 second complete remission (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 that 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, and transplant characteristics including outcomes for consecutive transplantations to a statistical center at the Medical College of Wisconsin or a data coordinating center at the National Marrow Donor Program. Information regarding pre-HCT chemotherapy (eg, nelarabine), detailed T-ALL immunophenotyping (eg, early T-cell progenitor T-ALL), or pre-HCT minimal residual disease 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 Medical College of Wisconsin and the National Marrow Donor Program 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 before the diagnosis of T-ALL.

Endpoints

Neutrophil recovery was defined as an absolute neutrophil count ≥5 × 10⁹/L for 3 consecutive days and platelet recovery as a platelet count ≥20 × 10⁹/L for 7 days without transfusion. Transplant-related mortality (TRM) was defined as any death during remission, and treatment failure was a composite endpoint that included TRM and relapse. Disease-free survival (DFS) was defined as survival in continuous CR. Relapse was defined as morphologic recurrence of leukemia at any site. Grades II to IV acute graft-versus-host-disease (GVHD) and chronic GVHD were defined using standard criteria [19-21].

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 (CIs) 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 to 18 years), performance score before HCT (<80 versus ≥80), recipient cytomegalovirus (CMV) status (positive versus negative), interval between diagnosis and transplant (<18 [early] versus 18 to 36 [intermediate] versus >36 months [late]), graft type (bone marrow [BM] 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

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Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tbody>
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<td>Number of patients</td>
<td>229</td>
</tr>
<tr>
<td>Number of centers</td>
<td>99</td>
</tr>
<tr>
<td>Median age at transplant, yr (range)</td>
<td>10 (2-18)</td>
</tr>
<tr>
<td>≤5 yr</td>
<td>38 (17)</td>
</tr>
<tr>
<td>6-10 yr</td>
<td>66 (29)</td>
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<tr>
<td>11-18 yr</td>
<td>125 (55)</td>
</tr>
<tr>
<td>Recipient sex</td>
<td>Male 174 (76); Female</td>
</tr>
<tr>
<td>Male</td>
<td>(6)</td>
</tr>
<tr>
<td>Female</td>
<td>Performance score before HCT</td>
</tr>
</tbody>
</table>

Cy indicates cyclophosphamide; Bu, Busulfan; CB, Cord Blood; PBSCs, Peripheral Blood Stem Cells; CSA, cyclosporine; MTX, methotrexate; MMF, Mycophenolate Mofetil; FK506, Tacrolimus. Values are number of cases with percent in parentheses, unless otherwise noted.

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

Table 2

<table>
<thead>
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<th>Characteristic</th>
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<tr>
<td>Number of patients</td>
<td>112</td>
</tr>
<tr>
<td>WBC at diagnosis</td>
<td>&lt;100 × 10^3/L 44 (39); ≥100 × 10^3/L 47 (42); Unknown 21 (19); Extramedullary disease before HCT</td>
</tr>
</tbody>
</table>

CR1 indicates 1st complete remission. Values are number of cases with percents in parentheses, unless otherwise noted.

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 count at diagnosis and site of first relapse (n = 112). An analysis was conducted to investigate the impact of WBC count at initial diagnosis (<100 × 10^3/L versus ≥100 × 10^3/L) and site of first relapse (isolated extramedullary site versus isolated BM versus BM with extramedullary site) on outcomes by adding these variables into the final models grouping patients with unreported WBC counts and site of first relapse into 1 group. The presence of GVHD was evaluated as a time-dependent covariate. All P values were 2-sided, and P < 0.05 was considered to be significant. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient, disease, and transplant characteristics are shown in Table 1. The median age at HCT was 10 years (range, 2 to 18), and 174 patients (76%) were male. Duration of CR1 is not routinely collected on CIBMTR forms; therefore, time of initial diagnosis to transplant was 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 to 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 total body irradiation (TBI) and cyclophosphamide in 183 patients (80%), 49 patients (31%) received TBI >1300 cGy compared with 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; Genzyme Corporation) or antithymocyte globulin. A cyclosporine-based regimen was the primary GVHD prophylaxis used (72%). Most patients received HLA-matched sibling BM (n = 86, 38%) followed by mismatched UCB (n = 50, 22%), matched (n = 27, 12%) or mismatched (n = 20, 9%) unrelated BM/PBSCs, 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 PBSCs, n = 4). Seventy-three patients (32%) 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 112 patients with more detailed research level data, including
presenting WBC count, site of relapse, and duration of CR1, are shown in Table 2. Among these, 47 patients (42%) presented with an initial WBC count \( \geq 10^9/L \) and 65 (58%) had their first relapse involving the BM/extramedullary disease.

**Outcomes**

**Recovery and GVHD**

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

**TRM, relapse, and DFS**

TRM at day 100 was 13% (95% CI, 9% to 18%), increasing to 21% (95% CI, 16% to 26%) at 1 year and to 24% (95% CI, 18% to 30%) at 3 years (Figure 1A). The rate of relapse at 3 years was 30% (95% CI, 24% to 37%). Rates of 3-year DFS (Figure 1B) and OS were 46% (95% CI, 39% to 52%) and 48% (95% CI, 41% to 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/acute respiratory distress syndrome (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 BM/combined BM versus isolated extramedullary [central nervous system/testes] and graft source (HLA identical sibling versus unrelated donor BM/PBSCs versus UCB). Patients who received an HCT for an isolated extramedullary relapse had a significantly lower rate of post-HCT relapse compared with isolated/combined BM patients (15% [95% CI, 5% to 28%] versus 45% [95% CI, 32% to 58%]; \( P < .001 \)) (Figure 2A) and greater rates of DFS at 3 years (56% [95% CI, 39% to 72%] versus 35% [95% CI, 23% to 47%]; \( P = .05 \)) (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 count and time period of HCT (2000 to 2003 versus 2004 to 2007 versus 2008 to 2011), were not significant for any outcome measure.

In multivariable analysis (Table 3), only the site of first relapse, either isolated BM or combined BM and extramedullary disease, was strongly predictive of a subsequent relapse post-HCT (hazard ratio, 3.94; 95% CI, 1.51 to 10.25; \( P = .005 \)) as compared with isolated extramedullary disease. The effect of GVHD on relapse was not statistically significant for either acute GVHD (\( P = .51 \)) or chronic GVHD (\( P = .33 \)). 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).
transplantation in childhood ALL combines T-ALL data with B cell ALL, limiting the ability to distinguish the outcomes for T-ALL [14]. One publication focused on HCT outcomes for T-ALL in adolescents and adults who received a myeloblastic HCT, most of whom were in CR1 (60%). The median patient age was 18 years, with most patients (68%) aged 14 to 20 years [16]. Patients who received HCT in at least 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 rate of 32% for those in CR2 or greater at the time of HCT [16]. Although these results may be less applicable to our strictly pediatric population, the outcomes are comparable with 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, because several publications have demonstrated that patients with GVHD have lower relapse rates [29,30]. 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 I to II or II to III versus III to IV or IV 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 BM relapse ± extramedullary disease were almost 4 times as likely to relapse post-HCT compared with 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 cell ALL) compared with relapses that include BM involvement.

Identifying a significantly higher risk group provides an opportunity to develop more novel approaches to improve transplant outcomes in this patient population.

Because of the limitations of a retrospective registry-based analysis, we were unable to include prior treatment history (eg, nelarabine), disease immunophenotyping (eg, early T cell progenitor T-ALL), or measurements of pre-HCT minimal residual disease. 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 BM ± extramedullary 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 DFS rates based on graft source; therefore, when considering HCT for relapsed T-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 to be durable, particularly when

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**Figure 3.** (A) Cumulative incidence of relapse at 3 years for patients receiving HLA-matched sibling BM was 34% (95% CI, 24% to 45%), unrelated BM/PBSCs was 34% (95% CI, 23% to 46%), and unrelated UCB was 24% (95% CI, 15% to 34%) (P = .26). (B) Probability of DFS at 3 years for patients receiving HLA-matched sibling BM was 48% (95% CI, 37% to 59%), unrelated BM/PBSCs was 37% (95% CI, 25% to 49%), and unrelated UCB was 50% (95% CI, 39% to 61%) (P = .25).

**Table 3**

<table>
<thead>
<tr>
<th>Site of first relapse</th>
<th>N</th>
<th>Hazard Ratio (95% CI)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated CNS or testes</td>
<td>34</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Isolated BM/combined BM</td>
<td>65</td>
<td>3.94 (1.51-10.25)</td>
<td>.005</td>
</tr>
<tr>
<td>Not reported</td>
<td>125</td>
<td>2.28 (1.89-5.83)</td>
<td>.08</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system.

Other comparisons: site of first relapse not reported vs BM or other was 58 (.35-.96); P = .03. The effect of GVHD on relapse was not statistically significant: grades II-IV acute GVHD (P = .51) and chronic GVHD (P = .33).

Overall P = .008.
compared with chemotherapy alone for relapse T-ALL where survival is <20%, providing further evidence to support the role of transplant in these patients. Based on these data, consideration for HCT for T-ALL in CR2 is warranted.

ACKNOWLEDGMENTS

Financial disclosure: 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; Grant/Cooperative Agreement 5U10HL69294 from the NHLBI and NCI; a contract (HHSN25201200016C) with Health Resources and Services Administration; 2 grants (N00014-13-1-0039 and N00014-13-1-0039) 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 Institutes of Health, the Department of the Navy, the Department of Defense, the Health Resources and Services Administration or any other agency of the U.S. Government.

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

REFERENCES