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# BRIEF REPORT
# Outcome of Transplantation for Acute Lymphoblastic Leukemia in Children With Down Syndrome

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We report on 27 patients with Down syndrome (DS) and acute lymphoblastic leukemia (ALL) who received allogeneic hematopoietic cell transplantation (HCT) between 2000 and 2009. Seventy-eight percent of patients received myeloablative conditioning and 52% underwent transplantation in second remission. Disease-free survival (DFS) was 24% at a median of 3 years. Post-transplant leukemic relapse was more frequent than expected for children with DS-ALL (54%) than for non-DS ALL. These data suggest leukemic relapse rather than transplant toxicity is the most important cause of treatment failure. Advancements in leukemia control are especially needed for improvement in HCT outcomes for DS-ALL. Pediatr Blood Cancer 2014;61:1126–1128. 

**Key words:** acute lymhoblastic leukemia; Down syndrome; hematopoietic stem cell transplantation; pediatric; relapse; trisomy 21

HCT is used as treatment for high risk forms of relapsed ALL [1–3] and rare subgroups of children and young adults with primary ALL at very high risk of relapse [4], achieving a DFS of between 40% and 50% [5,6]. In contrast, the role of HCT as treatment for ALL in children with DS is unclear. Increased treatment-related mortality (TRM), mainly due to infection, has been reported for children with DS-ALL undergoing primary [7] and relapse therapy [8] as well as HCT [9]. In contrast, two recent reports suggest leukemic relapse rather than TRM is the main barrier to successful HCT in children with DS [10,11]. To clarify the optimal strategy to improve outcomes (reducing treatment intensity to lower TRM vs. intensification to lower relapse), we reviewed survival and causes of treatment failure after HCT in a contemporary, mainly pediatric cohort of patients with DS-ALL.

## PATIENTS AND METHODS

Data were obtained from the Center for International Blood and Marrow Transplant Research (CIBMTR), a working group of more than 400 transplant centers worldwide that provide detailed patient, disease, transplant characteristics and 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). Patients or guardians provide written informed consent for data submission and research participation. The Institutional Review Boards of the MCW and the NMDP approved this study. All patients with ALL and DS who received allogeneic HCT from an HLA-matched sibling, or a matched or mismatched unrelated donor between 2000 and 2009 were eligible. ALL with t(12;21), *ETV6-RUNX1* fusion transcript, or trisomy of chromosomes 4 and 10 were considered low risk; those with t(9;22), *BCR-ABL1* fusion transcript, *MLL* gene rearrangements (11q23) or hypodiploidy (<44 chromosomes) high risk and all others standard risk. Neutrophil recovery was defined as absolute neutrophil count (ANC) $\geq 0.5 \times 10^9$/L for three consecutive measurements; platelet recovery as a platelet count $>20 \times 10^9$/L for 7 days without transfusion. TRM was defined as any death during remission. Relapse was defined as morphological recurrence of leukemia at any site. DFS was defined as survival in continuous complete remission.


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**TABLE I. Patient, Disease, and Transplant Characteristics**

| | Number (%) |
|---|---|
| Number of patients | 27 |
| Number of centers | 21 |
| Age, median (range), years | 9 (4–31) |
| ≤5 years | 4 |
| 6–10 years | 11 |
| 11–18 years | 7 |
| 18–31years | 5 |
| Performance score prior to transplantation | |
| 100 | 11 |
| 90 | 5 |
| 80 | 6 |
| 50 | 1 |
| Not reported | 4 |
| Disease status prior to transplantation | |
| First complete remission | 4 |
| Second complete remission | 14 |
| Third complete remission | 4 |
| Relapse | 4 |
| Primary induction failure | 1 |
| Cytogenetics risk group | |
| Intermediate risk | 23 |
| Poor risk | 3 |
| Not reported | 1 |
| Time from diagnosis to HCT, median (range), months | 36 (3–128) |
| ≤12 months | 4 |
| 13–36 months | 10 |
| >36 months | 13 |
| Conditioning regimen | |
| Non-myeloablative/reduced intensity | |
| TBI + cyclophosphamdie + fludarabine (TBI dose: 200 cGy) | 2 |
| TBI + fludarabine+ alemtuzumab (TBI dose: 600 cGy, fractionated) | 1 |
| Busulfan + fludaarbine + anti-thymocyte globulin | 2 |
| Melphalan + fludarabine | 1 |
| Myeloablative | |
| TBI + cyclophosphamdie + anti-thymocyte globulin (TBI dose: 1,320 cGy) | 1 |
| TBI + cyclophosphamdie + cytarabine (TBI dose 1,200 cGy) | 2 |
| TBI + cyclophosphamdie + fludarabibe (TBI dose: 1,320 cGy) | 1 |
| TBI + cyclophosphamdie + etoposide (TBI dose: 1,200 cGy) | 1 |
| TBI + cyclophosphamdie + thiotepa (TBI dose: 1,200 cGy) | 1 |
| TBI + cyclophosphamdie (TBI dose: 550 single fraction N = 3 and >1,000 cGy N = 5) | 8 |
| TBI + busulfan + fludarabine + anti-thymocyte globulin (TBI 400 cGy, Bu > 9.0 mg/kg) | 3 |
| TBI + etoposide + anti-thymocyte globulin (TBI dose: 1,200 cGy) | 1 |
| TBI + etoposide (TBI dose: 1,200 cGy) | 1 |
| Busulphan + cyclophosphamdie | 1 |
| Busulphan + fludarabine + anti-thymocyte globulin | 1 |
| Donor type | |
| HLA-matched sibling | 13 |
| Other related | 1 |
| 8/8 HLA-matched unrelated | 6 |
| >1 HLA-loci mismatched unrelated | 7 |
| Graft type | |
| Bone marrow | 12 |
| Peripheral blood progenitor cells | 7 |
| Umbilical cord blood | 8 |
| Year of transplant | |
| 2000–2005 | 11 |
| 2006–2009 | 16 |
| Graft-versus-host disease prophylaxis | |
| Cyclosporine-containing | 18 |
| Tacrolimus-containing | 9 |
| Median (range) follow-up, months | 37 (12–120) |

TBI, total body irradiation; HLA, human leukocyte antigen; 8/8, matched at HLA-A, -B, -C and -DRB1 at the allele-level.

## Statistical Analysis

The probabilities of neutrophil and platelet recovery, acute and chronic GVHD, TRM and relapse were calculated using the cumulative incidence function estimator [12]. 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 [12]. Ninety-five percent of 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. All *P*-values are two-sided and ≤0.05 was considered significant. Analyses were performed using SAS version 9.1 (Cary, NC).

## RESULTS

Between 2000 and 2009, a total of 5,753 allogeneic HCT procedures were reported to CIBMTR for non-DS-ALL, compared to 27 for DS-ALL (<1% of all HCT). Patient, disease and transplant characteristics are shown in Table I. Fifty-five percent of patients were under 10 years of age at the time of transplantation and 19% were older than 18 years. Approximately half of all transplantations occurred in second remission, less than 20% in relapse or refractory disease. Approximately equal numbers of transplantations occurred within and after 3 years from the initial ALL diagnosis. For patients transplanted beyond first remission all patients, except one with an isolated central nervous system relapse, had a bone marrow relapse. Seventy-eight percent of recipients received myeloablative conditioning which included total body irradiation (TBI) in all but two cases. Bone marrow from an HLA-matched sibling was the predominant graft source. All patients received cyclosporine or tacrolimus containing GVHD prophylaxis and about a third received methotrexate (data not shown). The median follow-up was 3 years (Supplemental Tables I, II).

## Outcomes

In univariate analysis, probabilities of hematopoietic recovery, GVHD and TRM were in keeping with those reported for patients without DS [6] (Table II). Grade 2–4 acute GVHD [13] developed in 31% of patients by 180 days. Among 8 patients with acute GVHD, 3

**TABLE II. Results of Univariate Analysis**

| Outcomes | Number events/ evaluable | Probability (95% confidence interval) |
|---|---|---|
| Neutrophil recovery | 24/27 | |
| 28 days | | 81% (65–93) |
| Platelet recovery | 22/26 | |
| 100 days | | 85% (64–94) |
| Grade 2–4 acute graft vs. host disease | 8/26 | |
| 100 days | | 31% (15–49) |
| 180 days | | 31% (15–49) |
| Chronic graft vs. host disease | 7/26 | |
| 3 years | | 27% (12–45) |
| Transplant-related mortality | 6/27 | |
| 100 days | | 19% (6–35) |
| 3 years | | 22% (9–39) |
| Relapse | 12/27 | |
| 3 years | | 54% (33–74) |
| Disease-free survival | 18/27 | |
| 3 years | | 24% (8–45) |
| Overall survival | 17/27 | |
| 3 years | | 29% (12–50) |

had grade 2, 3 had grade 3, and 2 had grade 4. Seven patients developed chronic GVHD (6 limited and 1 extensive). The 3-year probability of chronic GVHD [14] was 27%. The 3-year cumulative incidence of TRM was 22%. Among the 6 patients with TRM, 3 patients died from infection, 1 from GVHD, 1 from organ failure, and the remaining patient from a secondary neoplasm. The probability of relapse was 54% at 3 years. Consequently, DFS and OS were low and only 9 of 27 patients with DS-ALL remained alive and disease-free after HCT. Leukemic relapse was the most frequent cause of death (11/17, 65%), followed by infection (4/17, 24%) and organ failure (1/17, 6%). Outcomes of patients limited to those aged 18 years or younger were consistent with the main analysis (data not shown).

## DISCUSSION

Available data on the impact of DS on HCT outcomes for ALL are derived from small case numbers [15–17], reflect prior treatment periods [18], and have resulted in conflicting conclusions [9,11]. In 1996, TRM of HCT in 27 children with DS, including 12 with ALL, was 39% [9] compared to 80% in an earlier report [18]. Although the feasibility of HCT for children with DS was stated [9], use of HCT in this group consistently remained lower than in the non-DS population [8,11,18]. Recently, a report including eight children with DS-ALL, questioned earlier conclusions by highlighting that leukemic relapse (5/11, 45%) rather than TRM (2/11, 18%) was the main barrier to successful HCT in children with DS [11]. Our analysis of HCT for DS-ALL extends and confirms the findings of the small case series [11] and is consistent with HCT outcomes for DS-AML [10]. Relapse is the predominant cause of treatment failure after HCT in children with DS limiting DFS and OS (Table II).

Although this report describes the largest cohort to date of children with DS-ALL undergoing HCT, it is retrospective, registry-based and thus subject to biases inherent in this form of patient ascertainment. Like all reports on this topic, ours did not escape the limits of sample size. Subgroup analyses to assess the contribution of conditioning regimens and GVHD prophylaxis to relapse and TRM were not feasible. Despite these limitations our observations lead us to three suggestions.

First, identification of relapse as main barrier to successful transplantation cautions against a primary focus on reducing TRM by choosing minimally intense conditioning. Second, better leukemia control prior to HCT needs to be achieved while avoiding the excessive toxicity of conventional ALL chemotherapy in this group by pursuing agents that target ALL blasts (e.g., via expression of CD19 and CD22) but lack toxicities of conventional chemotherapy. Finally, given sample size limitations an international collaborative study may be the best option to optimize HCT protocols for children with DS. In the interim, families and treating physicians of children with DS-ALL are advised to take into account realistic estimates of DFS and OS rates after HCT and to explore new ways of reducing leukemic cell burden prior to HCT to combat the excess risk of leukemia recurrence.

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