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Reduced-Intensity Conditioning Regimens for Allogeneic Transplantation in Children with Acute Lymphoblastic Leukemia

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Reduced-intensity conditioning regimens have been used extensively in adults with hematologic malignancies. To address whether this is a feasible approach for children with acute lymphoblastic leukemia, we evaluated transplant outcomes in 38 recipients transplanted from 1995-2005 for whom this was their first transplant. The median age at transplant was 12 years, and 47% had performance scores <90%. Disease status was first complete remission (CR) in 13%, ≥CR2 in 60% of patients, and 22% had active disease at transplantation. Matched related donors were available for a third of patients, about half of whom received bone marrow (BM) and the others, peripheral blood progenitor cells. Sixty percent of unrelated donor transplant recipients received peripheral blood progenitor cells. The day-100 probability of grade II-IV acute graft-versus-host disease was 37% and the 3-year probability of chronic graft-versus-host disease, 26%. At 3 years, the probability of treatment-related mortality was 40%, relapse 37%, and disease-free survival 30%. These data indicate long-term DFS can be achieved using reduced-intensity conditioning regimens in children with acute lymphoblastic leukemia. Given the relatively small cohort, these findings must be validated in a larger population.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is 1 of the most commonly diagnosed pediatric malignancies. Using conventional chemotherapy, up to 80% of patients are expected to achieve long-term hematologic remission [1]. However, the high prevalence of ALL in the pediatric population means that recurrent ALL remains a common indication for allogeneic hematopoietic cell transplantation (allo-HCT). Three-year disease-free survival (DFS) for children transplanted in second complete remission (CR) using myeloablative (MA) conditioning and allo-HCT has been reported to be ~30% to 40%, with some studies reporting DFS as high as 70% [2]. In common with most transplant studies, treatment failure is because of both treatment-related mortality (TRM) and disease recurrence.

Over the past 10 years considerable experience has been gained using reduced-intensity conditioning (RIC) regimens for allo-HCT. Although a number of different regimens have been tested, 1 unifying feature is that they have the potential for acceptable rates of donor engraftment and lower TRM relative to conventional or dose-intensive MA conditioning. Because most children tolerate conventional dose-intensive conditioning and TRM increases with age, RIC has mainly been reserved for older patients or those with poor performance status.

One fundamental difference between RIC and MA conditioning is the mechanism of disease control. With MA conditioning, relapse protection is provided by the dose-intensive chemotherapy and/or total body irradiation (TBI) and the allogeneic,

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graft-versus-leukemia (GVL) effect. In contrast, the lower dose of chemotherapy and/or irradiation associated with RIC may provide little up-front disease control, and thus, the efficacy of RIC has been ascribed to the posttransplant GVL effect. Although GVL reactions are difficult to document in real time, both the kinetics of disease regrowth and responsiveness to GVL have had bearing on patient selection for RIC. Thus, RIC has been more commonly used in patients with chronic leukemia and indolent lymphoma [3]. Enthusiasm for using RIC for ALL has been appropriately guarded, because of the poor responsiveness to post-HCT immune-based approaches in ALL, including rapid tapering of immune suppression and donor lymphocyte infusion (DLI) following relapse [4,5].

Under certain circumstances, RIC may be indicated for patients with ALL who require allo-HCT, but are ineligible for a dose-intensive conditioning. Such indications include: poor performance status, active infections, significant organ dysfunction, or advanced age. Transplant outcome data after various RIC regimens for ALL are few and, with 1 exception, are limited to reports in adults. To date, 6 reports have focused on the outcomes of HCT with RIC for ALL [6-11], whereas other reports have included patients with ALL and other leukemias [12-14]. The report by Pulsipher and colleagues [14] is the only 1 limited to children, and only 17 of 47 patients in that report had ALL. Thus, the effectiveness of RIC regimens for pediatric ALL has not been extensively reported. Here, we detail outcomes for children with ALL who received RIC allo-HCT as their first transplant and reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

METHODS

Data Collection

The CIBMTR is a voluntary working group of more than 450 transplant centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplants to a Statistical Center at the Medical College of Wisconsin. Participating centers are required to report all consecutive transplants. Data collected include disease type, age, sex, pretransplant disease stage and chemotherapy responsiveness, date of diagnosis, graft type, conditioning regimen, posttransplant disease progression and survival, development of a new malignancy, and cause of death. A subset of the reported transplants are selected for detailed reporting using a weighted randomization scheme and include detailed disease, and pre- and posttransplant clinical information. All subjects are followed longitudinally, with yearly follow-up. Computerized error checks, physicians' review of submitted data, and on-site audits of participating centers ensure data quality and compliance. As stated before, there has only been 1 other study to report outcomes of for RIC in pediatric ALL (PBMTC ONC313) [14]. Based on a number of factors (participating centers, conditioning regimen, date of transplant), only 1 patient (UPN #9) has potentially participated in that trial. This study was approved by the institutional review board of the Medical College of Wisconsin.

Endpoints

Neutrophil recovery was defined as achieving an absolute neutrophil count (ANC) of $\geq 0.5 \times 10^9$/L for 3 consecutive days and platelet recovery, $\geq 20 \times 10^9$/L for 7 days, unsupported. Diagnoses of grades II, III, and IV acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD) were based on published criteria [15,16]. TRM was defined as death in continuous CR and relapse, hematologic leukemia recurrence. Treatment failure (inverse of DFS) was defined as death from any cause or relapse.

Statistical Methods

The probability of neutrophil and platelet recovery, aGVHD and cGVHD, TRM, and relapse were calculated with the use of the cumulative-incidence-function method [17]. For neutrophil and platelet recovery and GVHD, death without the event (hematopoietic recovery or GVHD) was the competing event. Data on patients without an event were censored at last contact. For TRM, relapse was the competing event and for relapse, TRM, the competing event. Univariate probabilities of DFS and overall survival (OS) were calculated using the Kaplan-Meier estimator [17]. For DFS, death or relapse were events, and patients alive and in remission were censored at last contact. For OS, death from any cause was an event, and patients alive were censored at last contact. All *P*-values are 2-sided, and analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

RESULTS

Patient Demographics

Table 1 shows the pretransplant characteristics of the 38 patients aged ≤18 years with ALL who received RIC allo-HCT as their first transplant. Transplantations occurred between 1995 and 2005. Most patients (66%) were between the ages of 11 and 18 years. Approximately one-half (47%) had performance scores <90. Most patients were in second or subsequent CR at HCT. For patients transplanted in CR2 or beyond CR2, the median duration of CR1 was 32 (range: 6-89) months. Approximately 20% of patients had active disease at time of HCT (either primary induction failure [n = 1] or in relapse [n = 7]). The median follow-up for surviving patients was 48 (range: 3-131) months.

Table 1. Patient, Disease, and Transplant Characteristics

Variables	Number
Number of patients	38
Age, years	
1-10	13
11-18	25
Recipient cytomegalovirus seropositivity	20
Performance score	
90-100	18
<90	19
Unknown	1
Disease status prior to transplant	
1st complete remission	5
2nd complete remission	13
3rd complete remission	5
4th complete remission	5
Relapse/primary induction failure	8
Unknown	2
Conditioning regimen	
Total-body irradiation + other agents	13
Busulfan + other agents	12
Cyclophosphamide + other agents	6
Melphalan + other agents	7
Type of donor	
HLA-identical sibling	12
Matched related	1
Unrelated donor	25
GVHD prophylaxis	
T cell depletion	2
Calcineurin inhibitor ± other agents	17
Calcineurin inhibitor + methotrexate	16
Methotrexate + other agents	1
Unknown	2

GVHD indicates graft-versus-host disease.

Stem cell Sources and Conditioning Regimens

There was an increase in the use of RIC during the study period; approximately one-third of transplants in the current analysis were performed from 1995 to 2000 and two-thirds, from 2001 to 2005. Thirteen patients received allografts from matched related donors and the remaining patients received allografts from unrelated donors (Tables 2 and 3). Regimens were considered RIC if the cumulative dose of busulfan was <9 mg/kg, melphalan <150 mg/m^2 or TBI ≤450 cGy, single fraction or 600 to 800 cGy, multiple fractions [18]. Regimens that combined busulfan and melphalan were considered to be MA. The decision to use RIC for patients was at the discretion of the transplant center and 10 of 38 patients were treated on institutional protocols. None of the patients were reported to have organ dysfunction (renal, cardiac, or pulmonary) or a life-threatening infection immediately prior to transplantation. GVHD prophylaxis varied, although most patients received calcinuerin-inhibitor containing GVHD prophylaxis (Table 1).

Transplant-Associated Outcomes

All patients developed severe neutropenia (ANC ≥ 0.5×10^9/L) after transplant conditioning, and 35 of 38 patients achieved neutrophil recovery. The day-28 probability of neutrophil recovery was 82% (95% confidence interval [CI] 67-92); 31 of 38 patients. The remaining 4 patients remained neutropenic for a longer period. The day-100 probability of platelet recovery was 79% (95% CI 65-90). Twenty-four patients with an ANC ≥0.5×10^9/L had chimerism assay performed. Donor engraftment (>90% donor derived cells in the peripheral blood or marrow) was observed in 21 patients (88%) <3 months after transplant. Some patients (n = 9) had serial chimerism assays performed as late as 2 years. The frequency and timing of chimerism assay was at the discretion of the transplant center. One patient received DLI and another patient received a second transplant for treatment of mixed chimerism without evidence of relapse. For the patient who received DLI, this occurred 4 months after the first transplant and this patient died 7 months later of recurrent leukemia and the second transplant recipient underwent this procedure 4 months after the first transplant and died 1 month later from organ failure (Table 2).

In univariate analysis, the probability of TRM at 100 days and 3 years was 19% (95% CI 8%-33%) and 32% (95% CI 17%-49%), respectively (Figure 1A). Sixteen patients developed grade II and 9 patients, grade III-IV aGVHD (Tables 2 and 3). The day-100 probability of grade II-IV aGVHD was 37% (95% CI 22%-53%) and grade III-IV aGVHD, 24% (95% CI 12%-38%) (Figure 1B). The probability of grade II-IV or III-IV aGVHD did not change significantly at day-180. cGVHD occurred in 12 of 38 patients (Tables 2 and 3). The 3-year probability of cGVHD was 26% (95% CI 12%-42%), with the severity reported as limited in 2 patients and extensive in 10 patients.

Leukemia relapse occurred in 14 patients post-HCT; the 3-year probability of relapse was 38% (95% CI 23%-55%) (Figure 1C). One patient received a second HCT from a different unrelated donor and 5 patients, DLI. Twenty-three patients are dead: 14 from recurrent disease, and 9 from a treatment-related complication (Table 2). Fifteen patients are alive at last follow-up (Table 3). The 3-year probabilities of DFS and OS were 30% (95% CI 15%-47%) (Figure 1D) and 36% (95% CI 20%-53%), respectively.

Transplant outcomes according to performance score at transplantation were evaluated, as none of these patients were reported to have organ dysfunction or a life-threatening infection just prior to initiation of transplant conditioning. We did not observe statistically significant differences in TRM (39% versus 22%, $P = .27$) and DFS (28% versus 31%, $P = .84$) in patients with performance scores <90 and 90-100, respectively. The relatively small numbers of patients may explain our inability to detect a significant difference despite an absolute difference of 17% for TRM. We also examined for an effect of TBI-containing

Table 2. Characteristics of Patients Who Died of Leukemia Relapse or Transplant-Related Complication

Patient	Age	Performance Score	Disease Status	Donor/Graft	Conditioning Regimen	Acute GVHD	Chronic GVHD	Time to Death	Primary Cause of Death
1	17	80	CR2	MSD, BM	TBI (100 cGy) + Mel (136 mg/m^2)	grade 4		3 months	GVHD
2	10	20	relapse	MSD, BM	Bu (5mg/kg) + Cy			1 month	organ failure
3	2	90	relapse	Unrelated, CB	Cy + etoposide + ATG			1 month	infection
4*	16	70	relapse	MSD, PBPC	TBI (450 cGy) + FLU + ATG			1.5 month	relapse
5*	12	50	CR2	MSD, PBPC	Cy + FLU + ATG			11 months	relapse
6	3	40	unknown	Unrelated, BM	Cy + FLU			4 months	relapse
7	7	90	CR2	Unrelated, PBPC	FLU + Mel (140 mg/m^2) + ATG	grade 3		2 months	GVHD
8	12	90	CR2	Unrelated, PBPC	Bu (8 mg/kg)+ FLU + ATG		extensive	7 months	relapse
9	8	80	CR2	Unrelated, CB	Bu (8 mg/kg) + FLU + ATG			18 months	infection
10	6	80	relapse	Unrelated, PBPC	TBI (400 cGy) + Bu (6 mg/kg) + FLU	grade 4	extensive	7 months	GVHD
11	11	80	CR4	Unrelated, PBPC	FLU + Mel (111 mg/m^2) + ATG			2 months	hemorrhage
12	14	80	Induction failure	MSD, PBPC	Bu (6 mg/kg) + etoposide + FLU + ATG	grade 4	extensive	4 months	GVHD
13*	16	100	CR2	MSD, BM	TBI (600 cGy, frac) + Cy	grade 2	extensive	11 months	GVHD
14*	12	90	CR3	Unrelated, PBSC	TBI (450 cGy)+ FLU + alemtuzumab			7 months	relapse
15	13	100	CR3	Unrelated, PBPC	FLU + Mel (120 mg/m^2)+ thiotepa			7 months	relapse
16	13	90	CR4	Unrelated, PBPC	Bu (8 mg/kg) + FLU + ATG	grade 2	extensive	30 months	relapse
17	13	80	CR4	Unrelated, BM	Bu (6 mg/kg) + FLU + ATG	grade 2	extensive	25 months	GVHD
18	15	100	CR2	Unrelated, PBPC	Bu (6 mg/kg) + FLU + alemtuzumab	grade 3		2 months	GVHD
19*	15	80	CR1	Unrelated, CB	TBI (600 cGy frac) + Cy + Mel (137 mg/m^2) + ATG			4 months	organ failure
20	18	80	CR4	Unrelated, PBPC	FLU + Mel (100 mg/m^2) + ATG	grade 2	limited	43 months	relapse
21*	17	70	CR4	Unrelated, PBPC	FLU + Mel (130 mg/m^2) + alemtuzumab	grade 2		9 months	relapse
22	13	100	CR2	Unrelated, BM	TBI (600 cGy frac) + FLU + alemtuzumab			2 months	relapse
23	17	100	CR2	Unrelated, PBPC	Bu (7 mg/kg) + FLU	grade 3		3 months	GVHD

CR indicates complete remission; CB, cord blood; BM, bone marrow; DLI, donor lymphocyte infusion; RIC, reduced-intensity conditioning; HCT, hematopoietic cell transplantation; PBPC, peripheral blood progenitor cells; MSD, matched sibling donor; TBI, total body irradiation; Frac, fractionated TBI dose; Bu, busulfan; Cy, cyclophosphamide; FLU, fludarabine; ATG, antithymocyte globulin; Mel, melphalan.
Intervention post-RIC HCT and outcome.
*Patient # 4: donor lymphocyte infusion (DLI) for leukemia relapse 1 month after RIC HCT and died 15 days after DLI.
*Patient #5: DLI for mixed chimerism 5 months after RIC HCT and died 2 months after DLI.
*Patient #13: DLI for leukemia relapse 6 months after RIC HCT and died 5 months after DLI.
*Patient #14: DLI for leukemia relapse 5 months after RIC HCT and died 2 months after DLI.
*Patient #19: Second allo-HCT (different donor) for mixed chimerism 3 months after RIC HCT and 1 month after second HCT. Conditioning regimen for second HCT is not known.
*Patient #21: DLI for leukemia relapse 8 month after RIC HCT and died 1 month after DLI.

Table 3. Characteristics of Patients Who Are Alive

Patient	Age	Performance Score	Disease Status at Transplant	Donor/Graft	Conditioning Regimen	Acute GVHD	Chronic GVHD	Time to Last Contact
24	9	100	relapse	Matched relative, BM	TBI (800 cGy fractionated) + Bu + Cy		extensive	131 months
25	12	100	CR3	MSD, BM	Bu (8 mg/kg) + Cy + etoposide			100 months
26	16	80	CR1	MSD, BM	Cy + etoposide			67 months
27	6	100	relapse	MSD, BM	Cy + ARAC + Mel (140 mg/m^2)			57 months
28	7	100	CR3	MSD, PBPC	Cy + ARAC + Mel (142 mg/m^2)		extensive	48 months
29	12	100	CR3	Unrelated, PBPC	Bu (7 mg/kg) + FLU + ATG			16 months
30*	14	80	CR1	Unrelated, CB	TBI (200 cGy) + Cy + FLU + ATG	grade 3		25 months
31	6	Not reported	CR2	Unrelated, CB	TBI (200 cGy) + Cy + FLU + ATG	grade 2		8 months
32	9	100	CR2	Unrelated, CB	TBI (200 cGy) + Cy + FLU + ATG	grade 2	limited	4 months
33	15	90	CR1	MSD, PBPC	Bu (4 mg/kg) + FLU			3 months
34	16	100	CR2	MSD, PBPC	FLU + Mel (140 mg/m^2)			3 months
35	7	80	CR2	Unrelated, PBPC	Bu (5 mg/kg) + FLU + ATG			36 months
36*	3	80	relapse	Unrelated, BM	TBI (450 cGy) + Cy + alemtuzumab			37 months
37	13	70	CR1	Unrelated, PBPC	TBI (200 cGy) + FLU	grade 3	extensive	61 months
38	13	100	unknown	Unrelated, PBPC	FLU + Mel (137 mg/m^2)	grade 3	extensive	24 months

CR indciates complete remission; CB, cord blood; BM, bone marrow; GVHD, graft-versus-host disease; PBPC, peripheral blood progenitor cells; MSD, matched sibling donor; TBI, total body irradiation; Bu, busulfan; Cy, cyclophosphamide; Mel , melphalan; FLU, fludarabine; ATG, antithymocyte globulin.
Intervention post-RIC HCT and outcome.
*Patient #30: Second HCT (same donor, TBI 1200 cGY + Cy) for leukemia relapse 21 months after RIC HCT, leukemia relapse and third HCT 36 months after second HCT. Patient is alive, 4 months from the third HCT.
*Patient #36: DLI for cytogenetic relapse 4 months after RIC HCT, and alive, 33 months after DLI.

regimens on DFS and found none (30% with TBI containing versus 27% with non-TBI regimens, $P = .85$).

DISCUSSION

In this report we describe the transplant outcomes for children aged ≤18 years with ALL who received RIC before their first allo-HSCT. We found that RIC regimens were associated with myelosuppression in all patients along with high rates of TRM and aGVHD and cGVHD. Similarly, leukemia recurrence was also high, resulting in modest DFS rates at 3 years. Several patients reported herein had performance scores of 70 or 80 (Karnofsky or Lansky scale) and/or were in second or subsequent CR at HCT and were thus at significant risk for transplant-related complications and/or leukemia relapse.

An important limitation of this registry study is the lack of information regarding the rationale for the selection of RIC. We speculate patients who received RIC were either treated on an institutional protocol (26% of study population) or judged to be at high risk for TRM by the treating physician based on intensity of therapies received prior to HCT even though none of the patients were reported to have renal, cardiac, or pulmonary function dysfunction, poor performance score, and/or more advanced disease status (beyond second CR). There may also be several unmeasured factors that may have contributed to the selection of RIC for allo-HCT in these children. In this context, these data lend support to the notion that RIC regimens can expand HCT options for children and adolescents otherwise unsuitable for dose-intensive MA conditioning who would succumb to their disease with chemotherapeutic regimens alone.

One of the perceived benefits to RIC has been the lower TRM relative to traditional dose-intensive conditioning. We observed TRM rates (19% at day 100 and 32% at 3 years) consistent with other reports describing outcomes for RIC with adult ALL, where TRM ranged from 17% to 40% [6-11]. Moreover, in these reports, there appears to be a trend for higher TRM when patients with advanced disease or chemotherapy refractory leukemia are included. The high rate of TRM in our study sharply contrasts with the only other large multicenter pediatric RIC study were TRM was much lower (11%) [14]. This difference might be explained by the use of a uniform conditioning regimen in the report by Pulsipher and colleagues [14], together with the fact that transplants were carried out in a more contemporary era than this analysis, which spanned over a decade. Interestingly, Pulsipher and colleagues [14] report relapse rates of 43% at 2 years, which are higher than that observed in the current analysis. This may in part be attributed to the inclusion patients who had failed prior

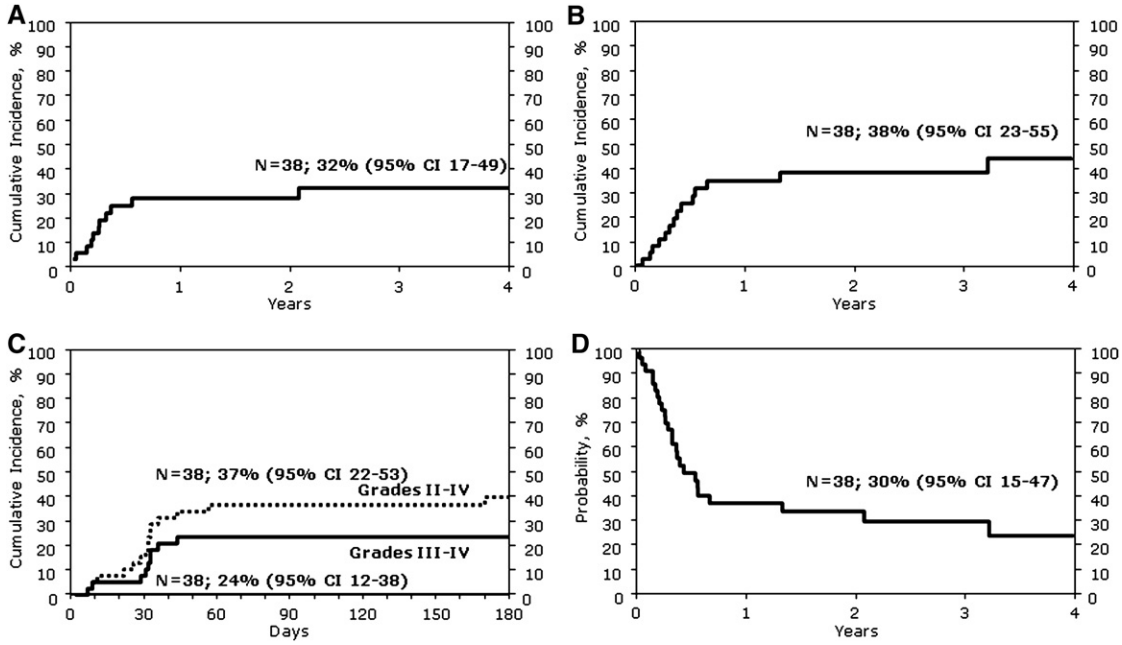

Figure 1. (A) Probability of TRM. (B) Probabilities of grade II-IV and III-IV aGVHD. (C) Probability of leukemia relapse. (D) Probability of DFS.

transplantation and at higher risk for recurrent leukemia compared to the population in this analysis. TRM is the competing event for relapse and TRM is expected to be low when recurrence rate is high.

Although RIC regimens are commonly used for adults with chronic leukemia and low to intermediate grade lymphoma [3], a major concern with using RIC regimens for pediatric ALL is the faster growth kinetic of ALL that might result in higher relapse rates. This concern is, perhaps, magnified by the fact that RIC relies mainly on immunologic mechanisms for eradication of disease (ie, GVL) and yet, post-HCT adoptive immunotherapies designed to exploit GVL, like DLIs or natural killer cells have been disappointing for treating relapsed ALL [4,19]. However, in the current study, the relapse rate at 3 years was 38%, which is comparable to that after dose-intensive MA conditioning regimens in children with ALL [2], and to that reported after RIC allo-HCT in adults with ALL [6-8,10,11]. Most patients in the current analysis were in second or subsequent CR or had active disease at HCT, and despite the relatively high relapse rate, one-third of the patients are alive and disease free, which supports the notion that sustained remission in ALL can also be achieved in children after RIC and allo-HCT. Given the relatively small numbers of patients in the current analysis, these findings must be validated in a larger series. Further, the relatively small numbers of patients prevented us from examining for an effect of aGVHD or cGVHD on relapse in the current analysis. Nevertheless, a potent effect of aGVHD in reducing relapse in children with ALL receiving unrelated donor transplants after dose-intensive MA conditioning has been reported, suggesting a role for immune-based mediation of relapse risk [20]. Similarly, lower doses of immune suppression (CsA) after transplantation have been associated with relapse protection in ALL [21,22]. In some studies adoptive transfer of donor lymphocytes can reverse rising host chimerism associated with minimal residual disease [23]. As well, an association between cGVHD and sustained remission following RIC and allo-HCT has been reported for ALL [11]. Taken together, these reports support the assertion that ALL is sensitive to a GVL effect [24-26].

Despite the small numbers of patients and their heterogeneity with respect to performance score, disease status at HCT, and donor source, this is the first report on the use of RIC regimens for pediatric ALL. All children received RIC and allo-HCT as their first transplant. The observed 3-year DFS rates are comparable to those after dose-intensive MA conditioning regimens and allo-HCT. Although our observations must be interpreted with caution, the modest success reported herein offers a potentially life-saving treatment option to children who may otherwise not be eligible for allo-HCT. Only a clinical trial that uses a uniform RIC regimen, GVHD prophylaxis, and donor-graft source can further establish the role of RIC allo-HCT for pediatric ALL.

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