Myeloablative Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia: Analysis of Graft Sources and Long-Term Outcome

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ABSTRACT

Purpose

Analysis of hematopoietic cell transplantation (HCT) for high-risk or recurrent acute lymphoblastic leukemia (ALL) using different donor sources is confounded by variable conditioning and supportive care.

Patients and Methods

We studied 623 consecutive ALL myeloablative HCT (1980 to 2005). Donors were autologous (n = 209), related (RD; n = 245), unrelated (URD; n = 100), and umbilical cord blood (UCB; n = 69).

Results

After median of 8.3 years of follow-up, 5-year overall survival (OS), leukemia-free survival (LFS), and relapse were 29% (95% CI, 26% to 32%), 26% (95% CI, 23% to 29%), and 43% (95% CI, 39% to 47%), respectively. Treatment-related mortality (TRM) at 2 years was 28% (95% CI, 25% to 31%). Mismatched URD sources yielded higher TRM (relative risk [RR], 2.2; $P < .01$) and lower OS (RR, 1.5; $P = .05$) than RD or UCB HCT. Autografting yielded significantly more relapse (68%; 95% CI, 59% to 77%; $P < .01$) and poorer LFS (14%; 95% CI, 10% to 18%; $P = .01$). HCT in first complete remission (CR1) yielded significantly better outcomes than later HCT. In a 1990 to 2005 allogeneic CR1/second complete response cohort, 5-year OS, LFS, and relapse rates were 41% (95% CI, 35% to 47%), 38% (95% CI, 32% to 44%), and 25% (95% CI, 19% to 31%), respectively; 2-year TRM was 34% (95% CI, 28% to 40%). With RD, well-matched URD and UCB sources, 5-year LFS was 40% (95% CI, 31% to 49%), 42% (95% CI, 14% to 70%), and 49% (95% CI, 34% to 64%), respectively, while relapse was 31% (95% CI, 22% to 40%), 17% (95% CI, 0% to 37%), and 27% (95% CI, 13% to 41%). Acute graft-versus-host disease was associated with fewer relapses. Since 1995, we noted progressive improvements in OS, LFS, and TRM.

Conclusion

Allogeneic, but not autologous, HCT for ALL results in durable LFS. Importantly, HCT using UCB led to similar outcomes as either RD or well-matched URD. HCT in early remission can best exploit the potent antileukemic efficacy of allografting from UCB, RD, or URD sources.

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common leukemia of childhood, yet adults make up approximately one third of patients diagnosed each year.¹ The treatment of this disease has improved significantly over the past several decades, with children now enjoying up to 80% long-term survival.² Adults generally exhibit higher risk phenotypic and cytogenetic subsets of ALL, with survival rates below 40% in patients younger than 60 years of age and even worse for older patients.³ Nonrandomized studies have demonstrated favorable outcomes in

high-risk or recurrent ALL using hematopoietic cell transplantation (HCT) in both pediatric and adult populations.⁴⁻¹⁰

Autologous HCT had been considered an attractive option, given the low associated treatment-related mortality (TRM).¹¹ However, the risk of relapse remains high.^{12,13} The recently reported Medical Research Council (MRC)/Eastern Cooperative Oncology Group (ECOG) ALL trial showed that autologous HCT is no better than standard consolidation and maintenance chemotherapy in adults from any risk group.¹⁴ Allogeneic HCT from a related, usually sibling donor (RD) is now

the preferred transplant option, with a documented graft-versus-leukemia (GVL) effect substantially reducing the risk of post-transplant relapse.^{5,15-21} The MRC/ Eastern Cooperative Oncology Group study also showed superior survival in patients with an available matched sibling donor in first complete remission (CR1) for both standard risk and high-risk adult patients. However, allogeneic HCT is also associated with higher TRM, particularly in older patients due to regimen-related toxicities, complications associated with acute and chronic graft-versus-host disease (GVHD), and post-transplant immunodeficiency.²²

Previous reports from the Center for International Blood and Marrow Transplant Research have also demonstrated the superiority of allogeneic over autologous HCT.^{7,9} Because only a small proportion of ALL patients eligible for HCT have an HLA-matched sibling to serve as an RD,⁷ alternative allogeneic stem cell sources include matched unrelated donors (URD),²³ partially matched URD and umbilical cord blood (UCB).²⁴

We report 25 years experience in myeloablative HCT using total-body irradiation (TBI) for patients with ALL treated at the University of Minnesota, including HCT from RD, URD, UCB, and autologous graft sources. This allows a unique opportunity to examine transplant outcomes from a single center utilizing similar preparative and supportive care techniques. In this analysis, we examine clinical outcomes for 623 consecutive ALL patients undergoing myeloablative HCT and examine donor-specific differences in outcome with long-term follow-up.

PATIENTS AND METHODS

This analysis includes all consecutive adult and pediatric ALL patients undergoing myeloablative HCT with a TBI-based regimen at the University of Minnesota between 1980 and 2005. All patients were enrolled on institutional review board–approved protocols. Data were analyzed as of June 2007.

Treatment

All patients received a myeloablative preparative regimen including TBI (Table 1). Approximately 90% of the patients received a cyclophosphamide (Cy)/TBI-based regimen.^{25,26} While supportive care and management practices evolved over time, all patients were treated in single, HEPA-filtered isolation rooms with antimicrobial prophylaxis directed toward bacterial, fungal, and viral pathogens plus irradiated red cell and platelet transfusion support as previously reported.²⁷⁻²⁹

Definitions

Overall survival (OS) was measured from the time of transplant until death or last follow-up. TRM was defined as death without evidence of relapse. Leukemia-free survival (LFS) includes patients alive without relapse. Relapse was defined as hematologic recurrence of leukemia. URD donor sources were identified as well-matched (WM), partially matched (PM), or mismatched (MM) based on published guidelines.³⁰

UCB grafts were selected and administered as previously reported.²⁷⁻²⁹

Statistics

Statistical analyses comparing demographic and disease-specific variables across donor sources and disease status utilized the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. Kaplan-Meier estimation was performed for univariate probabilities of OS and LFS end points. Cumulative incidence curves were used to estimate relapse, TRM, and acute and chronic GVHD using a competing risks model. Multivariate analyses (Cox regression for OS and LFS; Fine and Gray models for other end points) were performed to determine the independent effect of variables. All reported *P* values were two sided. Variables included in the multivariate analyses were: donor type (with HLA disparity), disease status at the time of transplant (and remission duration as appropriate), conditioning regimen,

Table 1. Characteristics of Patients Undergoing Myeloablative HCT for Acute Lymphoblastic Leukemia

Characteristic	All Patients		Allogeneic CR1/CR2 (1990-2005)	
	No.	%	No.	%
Total No. of patients	623		242	
Age at HCT, years				
< 18	422	67	151	62
18-40	159	25	66	27
> 40	46	7	25	10
Male sex	392	63	145	60
Year of transplant				
1980-1984	100	16	NA	
1985-1989	178	29	NA	
1990-1994	142	23	72	30
1995-1999	109	18	94	39
2000-2005	94	15	76	31
Donor type				
Autologous	209	34	NA	
Allogeneic	414	66	242	100
Related	245	39	113	47
Well-matched URD	19	3	12	5
Partially matched URD	23	4	21	9
Mismatched URD	58	9	45	19
Cord blood	69	11	51	21
Immunophenotype				
B lineage	419	67	170	70
T lineage	86	14	25	10
Unspecified	118	19	47	19
Philadelphia chromosome+	71	11	44	18
WBC at diagnosis, $\times 10^9/L$				
Median	18.9		21.4	
Range	0.3-1,533		0.6-1,533	
< $30 \times 10^9/L$	340	60	122	56
$\geq 30 \times 10^9/L$	228	40	95	44
Missing	55		25	
Disease status at HCT				
CR1	152	24	101	42
CR2	310	50	141	58
CR3+	111	18	NA	
Relapse	50	8	NA	
CMV serostatus (recipient/donor)				
Autologous				
Negative	101	48	NA	
Positive	108	52	NA	
Allogeneic				
Negative/negative	173	42	102	42
Negative/positive	57	14	34	14
Positive/negative	109	26	62	26
Positive/positive	75	18	44	18
Conditioning regimen				
Cy/TBI	406	65	145	60
Cy/TBI + VP-16	100	16	72	30
Cy/TBI + Flu or Ara-C	45	7	22	9
TBI + Ara-C or VP-16	72	12	3	1
GVHD prophylaxis (allogeneic)				
CSA or Tac $\pm$ MTX or MMF	236	57	190	79
Methotrexate	123	30	15	6
T depletion	55	13	37	15

Abbreviations: HCT, hematopoietic cell transplantation; CR1, first complete response; CR2, second complete response; Ara-C, cytarabine; CMV, cytomegalovirus; CSA, cyclosporine; Cy, cyclophosphamide; Flu, fludarabine; GVHD, graft-versus-host disease; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; Tac, tacrolimus; TBI, total body irradiation; URD, unrelated; VP-16, etoposide.

age, sex, cytomegalovirus (CMV) serostatus, GVHD prophylaxis, year of transplant, WBC at diagnosis, type of ALL (immunophenotype and cytogenetic risk), and acute GVHD as a time-dependent covariate.

RESULTS

Patients

This study includes 623 consecutive patients undergoing myeloablative transplantation using TBI at the University of Minnesota between 1980 and 2005. Patient demographics and transplant characteristics for all patients and a secondary cohort of only allogeneic HCT recipients with ALL in CR1 or second complete response (CR2) treated from 1990 to 2005 are presented in Table 1. The majority of patients were male (63%). The median age of patients was 13 years, ranging from 6 months to 55 years at transplant. One third were older than the age of 18 and 15% were older than 35 years. Approximately one third of patients ($n = 209$) received an autologous transplant. Of the whole group, 39% had a matched RD ($n = 245$), 16% received URD grafts ($n = 100$; 58 of 100 were HLA mismatched), and 11% received an UCB graft ($n = 69$; 48 single, 21 double units). Approximately one fourth of patients received transplant in CR1, half in CR2, and the remainder in third or later CR (CR3+) or in relapse. Median follow-up of survivors was 8.3 years (range, 1 to 23 years).

Survival

OS at 5 years was poorest for patients receiving either autologous (17%; 95% CI, 12% to 22%) or MM-URD sources (28%; 95% CI, 17% to 39%), while OS was similar for recipients of RD (95% CI, 34% to 49%), WM-URD, PM-URD, and UCB grafts (Fig 1A). In multivariate analysis, compared to transplantation in first CR, HCT during CR2 or later led to significantly lower OS (Table 2). Of note, the survival curves (Fig 1A) show only few events (53 of 445 deaths; 12%) beyond 2 years after transplantation, even with follow-up to nearly 23 years. Older age, female sex, WBC $\geq 30,000/\mu\text{L}$ at diagnosis, and CMV seropositivity in either donor or recipient were all associated with significantly poorer OS (Table 2).

RD, WM-URD, PM-URD, and UCB HCT led to similar 5-year LFS (95% CI, 31% to 44%; Fig 1B). As with OS, LFS was lower using autologous or MM-URD, although these differences were at the margin of statistical significance ($P = .07$; Table 2). In multivariate regression, LFS was superior for younger patients, patients who received transplants in CR1, WBC lower than $30,000/\mu\text{L}$ at diagnosis, and CMV seronegativity for both donor and recipient (Table 2).

Similar results were seen in an analysis of the 203 adult patients undergoing HCT for ALL. At 5 years, OS ranged from 0% (MM-URD and PM-URD) to 51% for UCB. In multivariate analysis of the adult recipients, OS at 5 years was poorest for MM-URD (relative risk [RR], 2.7; 95% CI, 1.5 to 4.6; $P < .01$) and best for UCB (RR, 0.3; 95% CI, 0.2 to 0.7; $P < .01$) compared to sibling donor sources. LFS for the 203 adults showed a similar trend as in the entire cohort, ranging from 0% (MM-URD and PM-URD) to 63% for UCB. In multivariate analysis, LFS was inferior for MM-URD (RR, 2.3; 95% CI, 1.3 to 3.9; $P < .01$) and improved with UCB (RR, 0.5; 95% CI, 0.2 to 0.9; $P = .02$) compared to related donors.

TRM

The cumulative incidence of TRM at 2 years was 66% for MM-URD versus 17% for autologous, 29% for RD, 32% for WM-URD,

Fig 1. Transplant outcomes by donor group for 623 acute lymphoblastic leukemia patients who underwent myeloablative hematopoietic cell transplantation. (A) Overall survival; (B) Leukemia-free survival; (C) treatment-related mortality. MM, mismatched; URD, unrelated donor; PM, partially matched; WM, well matched; RD, related donor; UCB, umbilical cord blood.

35% for PM-URD, and 27% for UCB ($P < .01$; Fig 1C). Factors significantly associated with higher TRM include older age, transplant in CR3, CMV seropositivity of either donor or recipient, and grade 3-4 acute GVHD (Table 2).

Relapse

At 5 years, 68% of autologous and 9% to 37% of the allogeneic donor subgroups had relapsed ($P < .01$). As presented in Table 2, the RR of relapse was more than two-fold higher for autologous

Table 2. Outcomes for Patients Undergoing Myeloablative HCT for Acute Lymphoblastic Leukemia: Multivariate Analyses (n = 623)

Variable	Relative Risk	95% CI	P
Overall survival			
Age			
< 18	1.0		
18-40	1.7	1.3 to 2.1	< .01
> 40	2.0	1.4 to 2.9	< .01
Sex			
Male	1.0		
Female	1.2	1.0 to 1.5	.04
Donor type			
Related (n = 248)	1.0		
Autologous (n = 209)	1.3	1.0 to 1.6	.06
Well-matched URD (n = 19)	0.9	0.5 to 1.7	.76
Partially matched URD (n = 23)	1.1	0.6 to 2.0	.77
Mismatched URD (n = 58)	1.5	1.0 to 2.1	.05
Umbilical cord blood (n = 66)	0.9	0.6 to 1.5	.73
Disease status at HCT			
CR1	1.0		
CR2	1.4	1.1 to 1.8	.01
CR3+	1.9	1.4 to 2.6	< .01
Relapse	1.8	1.2 to 2.7	< .01
CMV serostatus			
Negative/negative	1.0		
Either positive	1.3	1.0 to 1.6	.02
WBC at diagnosis			
< 30 × 10 ⁹ /L	1.0		
≥ 30 × 10 ⁹ /L	1.4	1.1 to 1.7	< .01
Leukemia-free survival			
Age			
< 18	1.0		
18-40	1.5	1.2 to 1.9	< .01
> 40	1.8	1.3 to 2.5	< .01
Donor type			
Related (n = 248)	1.0		
Autologous (n = 209)	1.4	1.1 to 1.8	.07
Well-matched URD (n = 19)	0.8	0.4 to 1.5	.50
Partially matched URD (n = 23)	1.1	0.6 to 2.0	.67
Mismatched URD (n = 58)	1.4	1.0 to 2.0	.07
Umbilical cord blood (n = 66)	0.9	0.5 to 1.4	.49
Disease status at HCT			
CR1	1.0		
CR2	1.4	1.1 to 1.8	.02
CR3+	1.8	1.3 to 2.5	< .01
Relapse	1.8	1.2 to 2.6	< .01
CMV serostatus			
Negative/negative	1.0		
Either positive	1.3	1.1 to 1.6	.01
WBC at diagnosis			
< 30 × 10 ⁹ /L	1.0		
≥ 30 × 10 ⁹ /L	1.4	1.1 to 1.7	< .01
Treatment-related mortality			
Age			
< 18	1.0		
18-40	2.6	1.8 to 3.6	< .01
> 40	2.8	1.7 to 4.6	< .01
Donor type			
Related (n = 248)	1.0		
Autologous (n = 209)	0.6	0.4 to 1.0	.05
Well-matched URD (n = 19)	0.9	0.4 to 2.2	.88
Partially matched URD (n = 23)	1.4	0.6 to 3.0	.41
Mismatched URD (n = 58)	2.2	1.4 to 3.5	< .01
Umbilical cord blood (n = 66)	1.5	0.8 to 3.1	.23

(continued in next column)

Table 2. Outcomes for Patients Undergoing Myeloablative HCT for Acute Lymphoblastic Leukemia: Multivariate Analyses (n = 623) (continued)

Variable	Relative Risk	95% CI	P
Disease status at HCT			
CR1	1.0		
CR2	1.1	0.8 to 1.6	.55
CR3+	1.9	1.2 to 3.0	< .01
Relapse	1.2	0.7 to 2.2	.45
CMV serostatus			
Negative/negative	1.0		
Either positive	1.5	1.1 to 2.0	.02
Grade III-IV acute GVHD			
No	1.0		
Yes	1.7	1.1 to 2.5	.01
Relapse			
Sex			
Male	1.0		
Female	1.4	1.0 to 1.8	.02
Donor type			
Related (n = 248)	1.0		
Autologous (n = 209)	2.2	1.6 to 3.1	< .01
Well-matched URD (n = 19)	0.5	0.2 to 1.5	.24
Partially matched URD (n = 23)	1.0	0.4 to 2.5	.93
Mismatched URD (n = 58)	0.4	0.2 to 1.0	.06
Umbilical cord blood (n = 66)	0.6	0.3 to 1.1	.13
Disease status at HCT			
CR1	1.0		
CR2	1.8	1.3 to 2.6	< .01
CR3+	2.1	1.3 to 3.3	< .01
Relapse	3.0	1.8 to 5.1	< .01
Immunophenotype			
B lineage/other	1.0		
T lineage	1.5	1.2 to 2.2	.02
Grade II-IV acute GVHD			
No	1.0		
Yes	0.6	0.4 to 0.9	< .01

NOTE. Cox multivariate analyses for overall survival, leukemia-free survival at 10 years; competing hazards regression for treatment-related mortality at 2 years and relapse at 10 years. Bold font indicates statistical significance.

Abbreviations: CMV, cytomegalovirus; CR, complete remission; GVHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; CR1, first complete response; CR2, second complete response; CR3, third complete response; URD, unrelated.

transplants than for other donor sources ($P < .01$). In multivariate regression, there was a strong trend ($P = .06$) for a lower risk of relapse with MM-URD graft recipients while other URD and UCB recipients had relapse risk similar to RD HCT. Other factors significantly associated with relapse included female sex, transplant in CR2 or later, and T-lineage ALL. Augmented conditioning with agents in addition to CyTBI (n = 217) had no significant protective impact on either relapse or TRM. The development of grade 2 to 4 acute GVHD was associated with a significantly lower RR of relapse (RR, 0.6; 95% CI, 0.4 to 0.9; $P < .01$; Table 2). There was no significant interaction between the protective antileukemic effect of GVHD and either disease status at HCT or donor source.

Allogeneic HCT in CR1 and CR2 (1990 to 2005)

In order to examine a more contemporary population of patients undergoing allogeneic HCT, we restricted the analysis to include only patients in CR1 and CR2 who received transplants between 1990 and 2005. The patient demographics for this cohort were similar to the

larger population, except that a larger proportion of patients received transplantation in CR1 and a larger proportion had UCB transplants (Table 1). B-lineage ALL was noted in 70%, T-lineage in 10%, 44% had WBC higher than 30,000/ μ L, and 18% had Philadelphia chromosome-positive ALL. Of the 141 CR2 patients, 31 (22%) had a CR1 duration shorter than 1 year. In this more recent cohort, the median follow-up of survivors was 5.8 years (range, 1 to 14.5 years).

As shown in Figure 2A, at 5 years post-HCT overall survival was 42% for RD (33% to 51%), 42% for WM-URD (95% CI, 14% to

70%), 38% for PM-URD (95% CI, 18% to 58%), 31% for MM-URD (95% CI, 17% to 45%), and 51% for UCB (95% CI, 46% to 66%; $P = .12$). Compared to transplantation in CR1, patients who received transplantation in CR2 with shorter CR1 (< 1 year) had significantly poorer OS, while longer CR1 followed by HCT in CR2 had a similar OS as in CR1 (Table 3). Multivariate regression showed that MM-URD, older age, and WBC $\geq 30,000/\mu$ L at diagnosis were associated with significantly poorer OS while HCT during more recent years (2000 to 2005 v earlier) led to significantly better OS.

LFS at 5 years yielded similar results, ranging from 27% for MM-URD (95% CI, 14% to 40%) to 49% for UCB recipients (95% CI, 34% to 64%; $P = .09$; Fig 2B). As with OS, LFS was inferior using MM-URD, while LFS after allogeneic HCT from all other donor sources was approximately equivalent. LFS was significantly better for younger patients, those with WBC counts lower than 30,000/ μ L at diagnosis and was improved in more recent years (2000 to 2005 v earlier; Table 3). Patients who received transplantation either in CR1 or in CR2 with long CR1 had significantly better LFS than CR2 after a short CR1.

The cumulative incidence of TRM at 2 years was 62% for patients who received transplantation with MM-URD sources, versus 26% for RD, 33% for WM-URD, 38% for PM-URD, and 24% for UCB ($P < .01$, Fig 2C). Predictors of higher TRM include older age, WBC higher than 30,000/ μ L, grade 3 to 4 acute GVHD, and transplant in CR2 after short CR1 (Table 3). TRM was progressively and significantly lower since 1995 for recipients of RD, WM-URD, PM-URD, or UCB donor sources.

Relapse incidence in these CR1 and CR2 HCT recipients were similar across all allogeneic donor sources ($P = .33$). Multivariate analyses showed a trend to greater relapse in CR2 after brief CR1, but no reduction in relapse rates over the period of the study. Patients with grade 2 to 4 acute GVHD had a significantly lower RR of relapse (Table 3).

Analysis of the 91 adult patients undergoing HCT for ALL in CR1 or CR2 between 1990 and 2005 showed no differences between the allogeneic donor sources for OS, LFS, or TRM. There were trends toward improved OS (RR, 0.4; 95% CI, 0.1 to 1.1; $P = .08$) and LFS (RR, 0.4; 95% CI, 0.2 to 1.1; $P = .09$) for UCB donor sources compared to matched sibling HCT. There was also a trend toward poorer TRM for MM-URD sources (RR, 2.1; 95% CI, 0.9 to 3.6; $P = .07$). In these adults, UCB donor grafts were associated with significantly lower risk of relapse (RR, 0.1; 95% CI, 0.02 to 1.0; $P = .05$).

Acute and Chronic GVHD

Among the CR1 and CR2 allograft recipients, the cumulative incidence of acute GVHD at 100 days was 45% for grade 2 to 4 (95% CI, 39% to 51%) and 16% for grade 3 to 4 (95% CI, 12% to 20%). As presented in Table 4, there was no difference in the incidence of grade 2 to 4 acute GVHD between RD and WM-URD sources while PM-URD, MM-URD, and UCB grafts were all associated with a significantly higher, but similar RR. No change in the incidence of acute GVHD was noted by year of transplant. As expected, older patients had a higher RR of grade 2 to 4 acute GVHD (Table 4). Grade 3 to 4 acute GVHD occurred most frequently with 29% for MM-URD (95% CI, 16% to 42%) compared to 11% (95% CI, 6% to 16%), 0%, 24% (95% CI, 6% to 42%), and 16% (95% CI, 6% to 26%) after RD, WM-URD, PM-URD, and UCB, respectively ($P = .01$).

Fig 2. Transplant outcomes by donor group for 242 acute lymphoblastic leukemia patients who underwent myeloablative hematopoietic cell transplantation from 1990 to 2005. (A) Overall survival; (B) leukemia-free survival; (C) treatment-related mortality. MM, mismatched; URD, unrelated donor; PM, partially matched; WM, well matched; RD, related donor; UCB, umbilical cord blood.

Table 3. Outcomes for Acute Lymphoblastic Leukemia Patients in CR1 or CR2 Undergoing Myeloablative Allogeneic HCT From 1990-2005: Multivariate Analyses (n = 242)

Variable	Relative Risk	95% CI	P
Overall survival			
Age			
< 18	1.0		
18-40	2.7	1.8 to 4.0	< .01
> 40	4.0	2.2 to 7.1	< .01
Donor type			
Related (n = 113)	1.0		
Well-matched URD (n = 12)	1.1	0.5 to 2.6	.75
Partially matched URD (n = 21)	1.5	0.8 to 2.7	.24
Mismatched URD (n = 45)	1.7	1.1 to 2.7	.01
Umbilical cord blood (n = 51)	1.1	0.6 to 2.0	.66
Disease status at HCT			
CR1	1.0		
CR2 (CR1 duration < 1 year)	2.0	1.2 to 3.3	< .01
CR2 (CR1 duration ≥ 1 year)	1.1	0.6 to 2.0	.70
WBC at diagnosis			
< 30 × 10 ⁹ /L	1.0		
≥ 30 × 10 ⁹ /L	1.7	1.2 to 2.4	< .01
Year of transplant			
1990-1994	1.0		
1995-1999	0.6	0.4 to 1.0	.03
2000-2005	0.4	0.2 to 0.8	< .01
Leukemia-free survival			
Age			
< 18	1.0		
18-40	2.4	1.6 to 3.6	< .01
> 40	3.5	1.9 to 6.2	< .01
Donor type			
Related (n = 113)	1.0		
Well-matched URD (n = 12)	1.1	0.5 to 2.4	.88
Partially matched URD (n = 21)	1.5	0.8 to 2.8	.36
Mismatched URD (n = 45)	1.7	1.1 to 2.7	.02
Umbilical cord blood (n = 51)	1.0	0.6 to 1.8	.99
Disease status at HCT			
CR1	1.0		
CR2 (CR1 duration < 1 year)	1.9	1.2 to 3.2	.01
CR2 (CR1 duration ≥ 1 year)	1.0	0.7 to 1.5	.86
WBC at diagnosis			
< 30 × 10 ⁹ /L	1.0		
≥ 30 × 10 ⁹ /L	1.6	1.1 to 2.3	< .01
Year of transplant			
1990-1994	1.0		
1995-1999	0.7	0.4 to 1.0	.04
2000-2005	0.5	0.3 to 0.9	.02
Treatment-related mortality			
Age			
< 18	1.0		
18-40	3.2	1.9 to 5.5	< .01
> 40	4.2	2.0 to 8.9	< .01
Donor type			
Related (n = 113)	1.0		
Well-matched URD (n = 12)	1.7	0.6 to 5.1	.34
Partially matched URD (n = 21)	1.8	0.8 to 4.1	.19
Mismatched URD (n = 45)	3.0	1.7 to 5.4	< .01
Umbilical cord blood (n = 51)	1.5	0.6 to 3.7	.35
Disease status at HCT			
CR1	1.0		
CR2 (CR1 duration < 1 year)	2.3	1.2 to 4.4	.02
CR2 (CR1 duration ≥ 1 year)	1.0	0.6 to 1.8	.89

(continued in next column)

Table 3. Outcomes for Acute Lymphoblastic Leukemia Patients in CR1 or CR2 Undergoing Myeloablative Allogeneic HCT From 1990-2005: Multivariate Analyses (n = 242) (continued)

Variable	Relative Risk	95% CI	P
WBC at diagnosis			
< 30 × 10 ⁹ /L	1.0		
≥ 30 × 10 ⁹ /L	1.7	1.1 to 2.8	.03
Grade III-IV acute GVHD			
No	1.0		
Yes	1.7	1.0 to 3.0	.05
Year of transplant			
1990-1994	1.0		
1995-1999	0.5	0.3 to 0.9	.02
2000-2005	0.3	0.1 to 0.7	< .01
Relapse			
Donor type			
Related (n = 113)	1.0		
Well-matched URD (n = 12)	0.6	0.1 to 2.6	.49
Partially matched URD (n = 21)	1.1	0.4 to 2.9	.87
Mismatched URD (n = 45)	0.5	0.2 to 1.5	.21
Umbilical cord blood (n = 51)	0.7	0.3 to 1.6	.42
Disease status at HCT			
CR1	1.0		
CR2 (CR1 duration < 1 year)	2.1	1.0 to 4.8	.06
CR2 (CR1 duration ≥ 1 year)	1.1	0.6 to 1.9	.84
Grade II-IV acute GVHD			
No	1.0		
Yes	0.5	0.3 to 0.9	.03
Year of transplant			
1990-1994	1.0		
1995-1999	1.1	0.6 to 2.1	.77
2000-2005	1.3	0.6 to 2.7	.56

NOTE. Cox multivariate analyses for overall survival and leukemia-free survival at 10 years; competing hazards regression for treatment-related mortality at 2 years and relapse at 10 years. Bold font indicates statistical significance.

Abbreviations: HCT, hematopoietic cell transplantation; CR1, first complete response; CR2, second complete response; GVHD, graft-versus-host disease; URD, unrelated.

Chronic GVHD at 2 years developed in only 18% (95% CI, 13% to 23%) of patients. The risk was significantly (> three-fold) higher in MM-URD compared to all other donor sources. RD and UCB recipients had similar risks of chronic GVHD. WM-URD and PM-URD also had apparently higher RRs (1.9 and 2.1, respectively) of chronic GVHD though the differences were not statistically significant. Older recipients also developed more frequent chronic GVHD. No difference in chronic GVHD was noted by year of transplant. Somewhat surprisingly, patients with WBC of ≥ 30,000/μL at diagnosis had a lower RR of chronic GVHD.

DISCUSSION

This large series of ALL patients received myeloablative HCT at a single institution using consistent preparative and supportive care regimens. These data indicate that allogeneic HCT for patients with ALL can result in a durable LFS, between 40% and 49% at 5 years with either RD, WM-URD, PM-URD, or UCB sources. OS was similar, with RD, WM-URD, PM-URD, and UCB HCT yielding nearly 50% OS at 5 years. Two-year TRM was below 35% for RD, WM-URD,

Table 4. Acute and Chronic GVHD for Acute Lymphoblastic Leukemia Patients in First Complete Response or Second Complete Response Undergoing Myeloablative Allogeneic Hematopoietic Cell Transplantation From 1990-2005: Multivariate Analyses (n = 242)

Variable	Relative Risk	95% CI	P
Grade II-IV acute GVHD			
Age			
< 18	1.0		
18-40	1.9	1.3 to 2.9	< .01
> 40	1.8	0.9 to 3.6	.09
Donor type			
Related	1.0		
Well-matched URD	1.5	0.7 to 3.3	.35
Partially matched URD	3.3	1.7 to 6.5	< .01
Mismatched URD	2.9	1.7 to 6.5	< .01
Umbilical cord blood	2.2	1.2 to 3.9	.01
Year of transplant			
1990-1994	1.0		
1995-1999	0.6	0.4 to 1.1	.08
2000-2005	0.8	0.4 to 1.5	.46
Chronic GVHD			
Age			
< 18	1.0		
18-40	2.1	1.0 to 4.4	.04
> 40	4.0	1.8 to 9.0	< .01
Donor type			
Related	1.0		
Well-matched URD	1.9	0.7 to 5.8	.24
Partially matched URD	2.1	0.6 to 7.3	.24
Mismatched URD	3.1	1.3 to 7.3	.01
Umbilical cord blood	1.1	0.4 to 2.8	.86
WBC at diagnosis			
< 30 × 10 ⁹ /L	1.0		
≥ 30 × 10 ⁹ /L	0.5	0.2 to 1.0	.05
Year of transplant			
1990-1994	1.0		
1995-1999	0.7	0.4 to 1.5	.40
2000-2005	0.8	0.4 to 1.9	.65

NOTE. Cox multivariate analyses for grade II-IV acute GVHD at 100 days and chronic GVHD at 2 years. Bold font indicates statistical significance. Abbreviations: GVHD, graft-versus-host disease; URD, unrelated.

PM-URD, and UCB transplants. This compares favorably with previously published series from a national registry.⁹ Autologous transplants were associated with high rates of relapse, nearly 70% at 5 years, consistent with previous reports¹² and consequently yielding inferior LFS (14%) and OS (17%) at 5 years. Similar to other reports, patients who received transplantation beyond CR2 had a significantly worse OS, LFS, and relapse rates compared to patients who received transplantation in CR1.¹⁸

In the more recent (1990 to 2005, CR1/CR2) allogeneic cohort, patients achieved a promising and durable response to allogeneic HCT, with an OS and LFS up to 50% at 5 years for RD, WM-URD, PM-URD, and UCB graft sources. TRM at 2 years was lowest for UCB (24%) and highest for MM-URD (62%). The allogeneic antileukemia effect of all graft types appeared potent and similar as there was no difference in relapse between any of the donor sources, with rates comparable to other reported series.⁹ The majority of patients who received transplantation in CR2 in this cohort had a CR1 duration longer than 1 year, perhaps indicating better-risk patients. In addition,

the development of acute GVHD was associated with significantly less relapse using all allogeneic donor sources. Remissions were durable and in all groups, relapse was rare beyond 2 years.

Despite significant advances in the supportive care and management of GVHD, we found similar trends in both the overall and more recent cohorts. Patient age, disease status at transplant, degree of HLA mismatch, and leukocyte count at diagnosis were important prognostic variables in all allograft recipients. Autologous HCT, despite an associated lower risk of TRM, remains an inferior graft option due to the higher risk of relapse compared to allogeneic HCT. MM-URD leads to unacceptably high TRM.

We also analyzed major transplant outcomes by year of transplant: 1990 to 1994 versus 1995 to 1999 versus 2000 to 2005. Encouragingly, we observed significant improvements over time for OS, LFS, and TRM. This may be due to improvements in supportive care over time with better management of CMV and fungal infections, but may also be explained by the recognition of critical factors in HLA matching and the availability of UCB units as an alternative to poorly matched URD donors.

This long-term analysis demonstrates that outcomes are similar for transplantation using RD, WM-URD, PM-URD, or UCB sources, and these may be considered equivalent options for patients with ALL. Autologous HCT should no longer be used for high-risk or relapsed ALL due to the unacceptably high relapse and poor long-term survival. Perhaps most importantly, as TRM has significantly declined in recent years, availability of better matched URD or UCB has improved survival for patients with ALL undergoing HCT. Patients with ALL lacking a sibling donor can seek UCB (which yielded the best OS and LFS in our series), or a well-matched URD and have a good chance at long-term LFS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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