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Autologous versus Allogeneic Unrelated Donor Transplantation for Acute Lymphoblastic Leukemia: Comparative Toxicity and Outcomes

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ABSTRACT

For patients with high-risk or relapsed acute lymphoblastic leukemia (ALL) lacking a related histocompatible donor, autologous (Auto) and unrelated donor (URD) transplantation are available options. We compared outcomes and toxicities in 712 patients with ALL (517 URD, 195 Auto) in first complete remission (CR1) or second complete remission (CR2) who underwent transplantation. All patients were <50 years old, although URD patients were younger (median age, 14 versus 18 years, *P* < .002). The proportion of patients in CR1 versus CR2 was similar (36% versus 38%, *P* = .57), but more URD recipients than Auto recipients had high-risk karyotypes (25% versus 13%, *P* = .003) and white blood cell (WBC) counts ≥50 × 10^9/L (33% versus 14%, *P* < .001). Engraftment was similar in URD and Auto recipients. Ex vivo purging delayed but did not prevent engraftment after Auto transplantation. Transplantation-related mortality was higher after URD transplantation (42% ± 8%) than after Auto transplantation (20% ± 12%) in CR1 (*P* = .004) and also in CR2. Conversely, relapse was more frequent after Auto transplantation in CR1 (Auto, 49% ± 12% versus URD, 14% ± 5%) and CR2 (64% ± 8% versus 25% ± 5%) (*P* < .0001). These findings showed net similar outcomes for these 2 transplantation choices. Transplantation in CR1 yielded similar 3-year survival rates for URD (51% ± 7%) and Auto (44% ± 12%), as did transplantation in CR2 (40% ± 6% versus 32% ± 9%, respectively). Multivariate regression analysis identified significantly better disease-free survival after the first 6 months in matched URD versus Auto in younger patients, in those in CR2 with CR1 >1 year, WBC <50 × 10^9/L, performance status ≥90%, and in those who have undergone transplantation since 1995. These comparative data suggest that both matched URD and Auto transplantation can yield extended survival. Although URD transplantation offers substantially better protection against leukemic relapse, improvements in allotransplantation safety and refinements in patient selection are required to better aid treatment decision making for the best overall survival.

KEY WORDS

Bone marrow transplantation • Autologous • Allogeneic unrelated • Acute lymphoblastic leukemia

INTRODUCTION

Acute lymphoblastic leukemia (ALL) can be cured by intensive chemotherapy in most children and a minority of adults. However, high-risk features predict relapse and define a subset of patients for whom bone marrow transplantation (BMT) offers a unique chance for extended leukemia-free survival [1-9]. For patients lacking a related histocompatible donor, autologous (Auto) BMT [10-15], peripheral blood stem cell transplantation, or alternatively, unrelated donor (URD) marrow for allogeneic BMT are available options, along with haploidentical related donor or cord blood transplantation [16-22]. Auto transplantation generally results in less transplantation-related mortality (TRM) but lacks an allogeneic antileukemic effect. High

Table 1. *Patient Characteristics*

	No. Evaluable*	Autologous BMT			Unrelated Donor Allogeneic BMT			
		Total	CR1	CR2	Total	CR1	CR2	*P*†
n		195			517			
Age, median (range), y		18 (1-50)	28 (0-51)	11 (0-50)	14 (1-50)	18 (0-50)	13 (0-51)	.002
No. of patients aged <20 y		111 (57%)	28%	75%	332 (64%)	54%	70%	.07
Male patients, % (M:F, n)		66 (129:66)	68	65	57 (295:222)	56	58	.03
CR1, %		38			36			.57
Time from diagnosis to BMT (CR1), mo			2-40 (7)			3-51 (7)		.42
Duration of CR1 for BMT in CR2, range (median), wk	381/450			7-416 (94)			3-765 (93)	.62
Disease lineage	480/712							
B-lineage, %		78	64	86	82	82	82	.24
T-lineage, %		22	36	14	18	18	18	
WBC at diagnosis $\geq 50 \times 10^9$/L, % (n)	579/712	14 (23)	21	9	33 (136)	44	27	<.001
Karyotype, %								
High risk		13	20	10	25	52	10	.003
t(9;22)		4	8	1	14	31	5	
t(4;11) or 11q32		1.5	4	0	9	18	3	
t(8;14)		3	4	3	<1	0	<1	
t(1:19)		3	4	3	<1	1	1	
Hypodiploid		1.5	0	3	1	2	1	
Other abnormal		22	15	27	16	10	20	
Normal		22	23	22	16	5	23	
Unknown		43	43	43	43	35	47	
Extramedullary leukemia pre-BMT, %		20	17	22	15	17	14	.15
TBI in conditioning, %		65	49	75	90	87	91	<.001
Autologous purged ex vivo, % (n)		57 (111)	45	66	—			
Ex vivo T-cell depletion, % (n)		—			29 (152)	28	30	
Transplantation date 1989-1995 (versus 1996-1998), %		81	71	88	44	41	47	<.001
Recipient CMV positive, %	701/712	42	54	35	35	39	32	<.001
Karnofsky score 90%-100%, %	678/712	80	80	80	80	83	78	.98

*The number of evaluable/eligible patients (if data elements were missing) is shown.
†*P* values represent comparison of patient characteristics between autologous and URD transplantation recipients.

TRM resulting from rejection, graft-versus-host disease (GVHD), and posttransplantation immunodeficiency limit survival after URD allografts, but a potent graft-versus-leukemia (GVL) effect may prevent relapse.

The comparative magnitude of this antileukemic effect versus the life-threatening or morbid complications of transplantation must be balanced to provide patients with the best treatment choices and superior clinical outcomes. We compared the major clinical consequences of Auto and allogeneic URD BMT to assess the differential morbidity, safety, and antileukemic efficacy of these transplantation choices.

PATIENTS AND METHODS

A total of 712 patients with ALL who were ≤50 years of age at the time of transplantation were studied. All received initial transplants during their first complete remission (CR1) or second complete remission (CR2) between January 1989 and December 1998. The patient group included 517 patients receiving BMT from HLA-matched allogeneic URD facilitated by the National Marrow Donor Program using techniques for donor identification, evaluation, marrow collection, processing, and transport as reported previously [23]. All recipient-donor pairs were matched serologically at HLA-A, B and were matched using molecular typing for DRβ1 alleles. Auto BMT recipients (n = 195) underwent transplantation in 49 centers with data reported to the Autologous Blood and Marrow Transplant Registry. Forty-four patients received autologous transplants using blood-derived stem cells; 138 patients received BM; and 13 patients received blood and marrow. All URD recipients received BM grafts. A minority (less than one third) of the patients were included in an earlier analysis [19]. Clinical characteristics of the 2 patient groups are shown in Table 1 with comparisons using the chi-square test (for categorical) or the Wilcoxon rank-sum test (for continuous variables).

Engraftment was defined as the time to recovery of >500 neutrophils/μL for the first of 3 serial measures. Platelet recovery was defined as platelet count $>50 \times 10^9$/L independent of transfusions. GVHD was graded by standard methods and reported to the National Marrow Donor Program in standardized fashion as described [7,19,23]. TRM was defined as death in continuous CR. Survival and disease-free survival (DFS) rates (without posttransplantation relapse) were calculated from the day of transplantation to the last follow-up at which the patient was alive (or alive in remission). Patients with missing relapse status (n = 7) were not included in the outcome analysis of DFS, relapse, or treatment-related mortality. Three patients with missing engraftment status were not evaluated in analyses of posttransplantation engraftment.

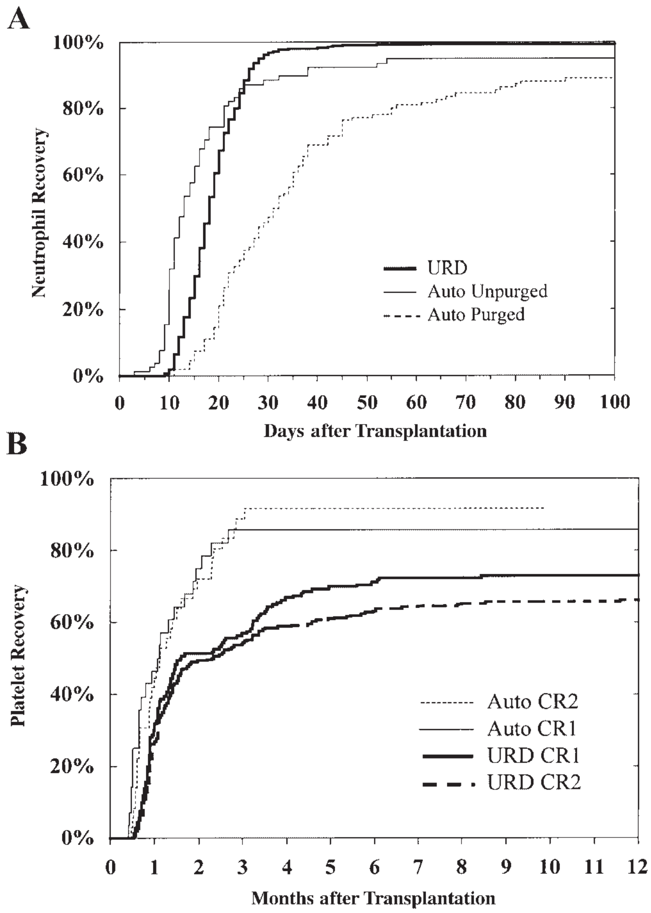

Figure 1. A, The cumulative incidence plots of engraftment (neutrophils >500/µL) in URD (n = 493), purged Auto (n = 110), and unpurged Auto (n = 78) BMT recipients (P < .0001 at day 45; P = .09 at day 100). B, Platelet recovery (to 50 × 10^9/L) was slower and less complete after URD versus Auto BMT: at 12 months, 69% ± 3% of URD recipients and 89% ± 8% of Auto recipients had platelet recovery (CR1, P = .05; CR2, P < .0001). Data for platelet recovery to this level were available in 432 URD recipients (84%) but only 64 Auto recipients (34%).

Time-to-event curves were calculated by the method of Kaplan and Meier [24]. For events (engraftment, relapse, or TRM) in which early competing hazards (death or relapse, as appropriate) would censor patients, the cumulative incidence method was employed [25]. Ninety-five percent confidence limits were calculated from the standard errors using the Greenwood formula (Kaplan and Meier) or an analogous first-order Taylor series for cumulative incidence. Multiple variable analyses were performed using logistic regression for calculations of neutrophil engraftment or the Cox proportional hazards model for other outcomes of interest [26,27]. Patients who died on or before day 21 (2 patients with Auto and 23 patients with URD transplantation) were unevaluable for engraftment, whereas patients without engraftment (13 patients with Auto and 4 patients with URD transplantation) were analyzed as having graft failure in the logistic regression. Forward step-wise regression analyses including testing the proportional hazards assumption and testing for interactions between variables were performed. Variables tested in regression modeling were those listed in Table 1. Regression variables with missing data included an indicator for the missing data elements. As needed, time-dependent covariates (eg, GVHD) were added to explain time-varying effects of relevant covariates as well as stratified analysis for variables not fitting the proportional hazards assumptions. As identified in the regression model for DFS, factors significantly associated with DFS were combined. Kaplan-Meier probabilities of DFS after either transplantation type were calculated for patients with and without the adverse prognostic factors identified in the multivariate analysis.

RESULTS

Patient Characteristics and Transplantation Techniques

Comparison of the 2 cohorts (Table 1) including 195 Auto transplant recipients and 517 URD allogeneic transplant recipients showed that Auto recipients were slightly older (median age, 18 versus 14 years, P = .002) and that a slightly smaller proportion of Auto recipients were younger than 20 years (57% versus 64%, P = .07). A larger fraction of Auto patients were males (66% versus 57%, P = .03).

Characteristics of the leukemia in the 2 groups differed somewhat as well. A smaller percentage of Auto transplant recipients had an elevated leukocyte count (≥50 × 10^9/L) at the time of diagnosis (14% versus 33% of URD recipients, P < .001). High-risk karyotypic features [t(9;22); t(4;11) or 11q32; t(1:19) or hypodiploid] were recognized in 13% of Auto and 25% of URD recipients (P = .003). Auto transplantations were more frequently performed in the earlier years of study, with 81% of Auto transplantations done between 1989 and 1995 versus only 44% of URD transplantations (P < .001). Only 65% of Auto transplantations versus 90% of URD transplantations were performed using total body irradiation (TBI) during pretransplantation conditioning (P < .001). A higher proportion of Auto recipients were cytomegalovirus (CMV) seropositive pre-BMT (40% versus 35% of URD recipients, P < .001).

Engraftment

Neutrophil recovery representing hemopoietic engraftment was observed in 667 evaluable patients (98%). Engraftment was quicker after URD BMT or unpurged Auto transplantation versus purged Auto transplantation (Figure 1A). As shown in Table 2, graft failure was more likely after purged or unpurged Auto transplantation than after URD transplantation (P = .01). Factors not associated with the speed or completeness of engraftment (not shown) were patient age, sex, cytogenetic phenotype, white blood cell (WBC) count at diagnosis, immunophenotype, remission status, or conditioning regimen with or without TBI or T-cell depletion (in URD recipients).

Although delayed neutrophil recovery was more frequent after purged Auto transplantation (P < .0001 at day 45), eventual neutrophil recovery was complete in nearly all patients by day 100 (Figure 1A). Most URD recipients (99% ± 1%), unpurged Auto recipients (95% ± 4%), and ex vivo purged Auto recipients (89% ± 5%) recovered neutrophil production by day 100 (P = .09). In contrast, recovery of

Table 2. *Clinical Outcomes: Multivariate Analysis**

A. Engraftment

	Odds Ratio of Graft Failure	95% CI	*P*
Unpurged autologous	1.0	—	—
Purged autologous	1.72	.51-5.78	.38
URD	.16	.04-.64	.01

B. Platelet recovery

	RR of Platelet Recovery	95% CI	P
Autologous	1.0	—	—
URD (<2 mo post-BMT)	.52	.38-.72	<.0001
URD (≥2 mo post-BMT)	.68	.36-1.28	.23
Age ≤20 y versus >20 y	1.43	1.14-1.79	.002
BMT 1989-1995 versus 1996-1998	.75	.60-.94	.01

C. Transplantation-related mortality

	RR of Death in Remission	95% CI	*P*
URD (versus Auto)	4.1	2.61-6.45	<.0001
Age ≤20 years	.62	.47-.82	.0007
BMT 1989-1995	1.52	1.15-2.02	.004

D. Relapse

	RR of Relapse	95% CI	*P*
WBC $<50 \times 10^9$/L	1.0	—	—
WBC $\geq 50 \times 10^9$/L	2.28	1.46-3.57	.0003
Recipient CMV seropositive	1.50	1.12-2.0	.006
WBC $<50 \times 10^9$/L†			
Autologous	1.0	—	—
URD	.25	.17-.36	.0001
WBC $\geq 50 \times 10^9$/L†			
Autologous	1.0	—	—
URD	.59	.27-1.28	.18

*For engraftment, the odds ratio for graft failure (no neutrophil recovery) in multivariate logistic regression along with the 95% confidence interval (CI) and *P* value are shown. For platelet recovery, Cox multivariate regression–derived RR for platelet recovery to $>50 \times 10^9$/L is shown based on available platelet recovery data for URD (n = 432) and Auto (n = 64) transplantation groups. For transplantation-related mortality, the RR for TRM stratified (because of proportional hazards violations) by sex and by disease status (CR1 ≤7 months to BMT, CR1 >7 months, CR2; 3 groups) is shown. For relapse, the RR for relapse stratified (due to proportional hazards violations) by disease status (CR1, CR2 with CR1 <1 year, and CR2 with CR1 ≥1 year; 3 groups) and disease lineage is shown.

†Risk ratio is shown separately for WBC < or $\geq 50 \times 10^9$/L in URD because of a statistically significant interaction between WBC and transplantation type (*P* = .04). For Auto cases, the RR of relapse of WBC $\geq 50 \times 10^9$/L (compared to WBC $< 50 \times 10^9$/L) is .96 (.46-1.98; *P* = .9).

platelet production to a sustained platelet count $>50 \times 10^9$/L was significantly slower and less frequent after URD BMT. At 12 months post-BMT, 89% ± 8% of Auto recipients but only 69% ± 3% of URD recipients had platelet recovery (Figure 1B, *P* < .0001). Multivariate analysis (Table 2) identified significantly slower and incomplete platelet recovery after URD BMT (within the first 2 months), in older patients, and after transplantations performed from 1989 to 1995. The impact of purging could not be evaluated because too few purged Auto patients (n = 11) had platelet recovery data reported.

Transplantation-Related Mortality

Death during continued posttransplantation remission (TRM) occurred in 217 patients (30%) at a median of 67 days (range, 1-3140 days) following BMT. As shown in Figure 2, for both patients in CR1 and those in CR2, TRM was significantly higher after URD transplantation than after Auto transplantation. By 5 years post-BMT, the incidence of TRM was 42% ± 8% of URD recipients versus 20% ± 12% of Auto recipients (*P* = .004) who received transplants during CR1 and was 40% ± 6% of URD recipients versus 9% ± 5% of Auto recipients (*P* < .0001) who received transplants during CR2. Multivariate analysis (Table 2) demonstrated significantly higher TRM after URD transplantation, in older patients, and after BMT performed from 1989 to 1995. Neither remission number, pretransplantation Karnofsky status, CMV serostatus, use of TBI in conditioning, T-cell depletion, nor other leukemia-specific characteristics (cytogenetics, immunophenotype, WBC at diagnosis) modified the risk of TRM. In the URD recipients, GVHD unfavorably increased TRM. Cox regression analysis demonstrated that patients with acute GVHD (grades II-IV) had a relative risk (RR) of TRM of 2.93 (range, 2.12-4.06, *P* = .0001) and those with chronic GVHD had an RR of TRM of 1.72 (range, 1.07-2.79, *P* = .03) compared to patients without acute or chronic GVHD.

Relapse

Recurrent leukemia developed in only a minority of URD recipients: 14% ± 5% of those receiving transplants in CR1 and 25% ± 5% of those receiving transplants in CR2 at 5 years. In contrast, Auto transplantation was followed by a significantly more frequent risk of relapse compared with URD transplantation (49% ± 12% of those receiving transplants in CR1, 64% ± 8% of those receiving transplants in

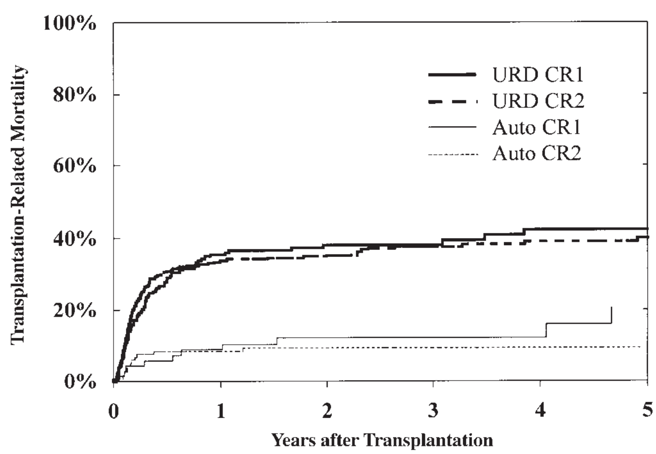

Figure 2. Treatment-related mortality was markedly greater after URD than after Auto BMT. At 5 years, URD BMT resulted in 42% ± 8% TRM for CR1 and 40% ± 6% TRM for CR2 versus 20% ± 12% TRM for CR1 and 9% ± 5% TRM for CR2 after Auto BMT (CR1, *P* = .004; CR2, *P* < .0001).

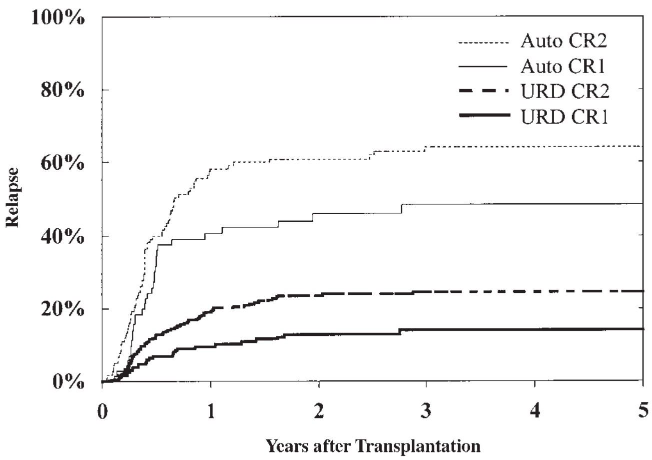

Figure 3. Relapse was less frequent after URD BMT in CR1 (P < .0001) and CR2 (P < .0001) than after Auto BMT.

CR2, both P < .0001 for comparison with URD transplant recipients) (Figure 3). As shown in Table 2, multivariate analysis identified a significantly higher risk of relapse in patients with WBC ≥50 × 10^9/L at diagnosis and a significantly lower risk of relapse after URD versus Auto transplantation. The protection was most notable in patients with WBC <50 × 10^9/L at diagnosis. For patients with higher WBC at diagnosis, URD transplantation, though still superior to autografting, was less effective in preventing relapse. Somewhat unexpectedly, relapse was also more frequent in patients who were CMV seropositive [28].

Other factors, including age (P = .72), high-risk karyotype (P = .42), TBI conditioning (P = .18), purging the autografts, T-cell depletion of the allografts, and the development of acute or chronic GVHD, did not significantly impact the risk of relapse. Among patients receiving transplants during CR2, duration of CR1 was not associated with differences in relapse risk for either Auto or URD patients at 5 years (Auto CR1 <1 year relapse, 61% ± 16% versus CR1 >1 year, 66% ± 10%; URD CR1 <1 year relapse, 32% ± 9% versus CR1 >1 year, 23% ± 6%). URD transplantation led to a significantly lower risk of relapse in both cohorts (P < .002). During the first year post-BMT, the protection against relapse with URD (versus Auto) transplantation was most prominent. URD transplantation led to a lower RR of relapse in B-lineage of .20 (95% CI, .13-.30, P < .0001) and in unknown lineage of .29 (95% CI, .16-.51, P < .0001) but not in T-lineage leukemia, with an RR of .83 (95% CI, .38-1.8, P = .63). This finding was independent of the association between T-lineage ALL and high WBC.

Survival and DFS

These differing influences of higher TRM after URD transplantation yet lower relapse after URD transplantation yielded a DFS rate that was similar using either transplantation technique during CR1 or CR2. As shown in Figure 4, for CR1 patients, the 5-year probability of DFS was 44% ± 8% with URD BMT versus 31% ± 14% with Auto BMT (P = .46). In CR2, transplantations yielded a 5-year DFS after URD transplantation of 36% ± 6% versus 27% ± 8% after Auto transplantations (P = .11). In the univariate analysis, CR2 patients who received transplants after a long (≥1 year) CR had slightly better 5-year DFS rates (URD, 38% ± 8%; Auto, 27% ± 10%). The Cox multiple variable analysis (Table 3) demonstrates a significantly superior DFS rate after URD transplantation than after Auto transplantation among patients who survive the first 6 months posttransplantation. Superior DFS was also observed in CR1 patients and in CR2 patients who underwent transplantation after a ≥1 year initial remission (compared to those with a short CR1), in those with Karnofsky score >90% at transplantation, in patients with WBC <50 × 10^9/L at diagnosis, in patients <20 years of age, and in patients who received transplants between 1996 and 1998. High-risk karyotype, CMV serology, and immunophenotype (T- versus B-lineage) had no additional impact on predicting DFS after transplantation. In the URD transplant recipients, the development of acute GVHD (grades II-IV) was associated with poorer DFS (RR of treatment failure, 1.82 [range, 1.41-2.35], P = .0001). A similar

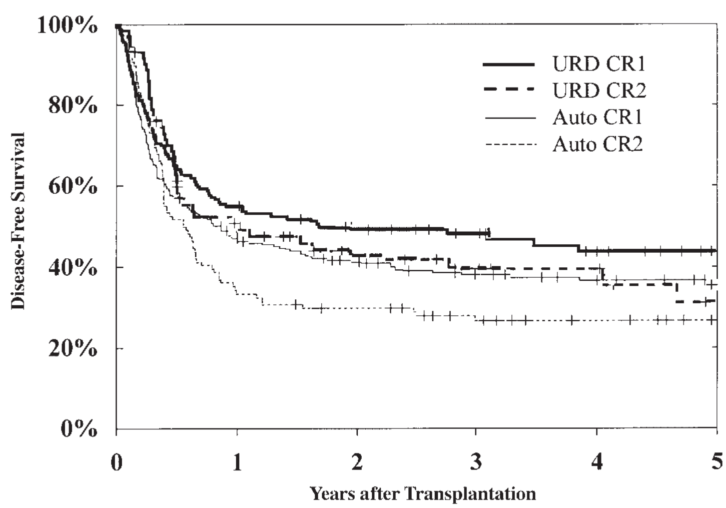

Figure 4. Disease-free survival after URD versus Auto BMT. Outcomes were similar with either approach (CR1, P = .46; CR2, P = .11).

Table 3. *Survival and Disease-Free Survival: Multivariate Analysis**

Disease-Free Survival	RR of Relapse or Death	95% CI	*P*
Autologous	1.0	—	—
URD within first 6 mo post-BMT versus Auto	.99	.75-1.30	.93
URD >6 mo post-BMT versus Auto	.64	.44-.92	.02
Age ≤20 y	.76	.62-.95	.01
Karnofsky score 90%-100%	.77	.61-.98	.03
WBC ≥50 × 10^9/L	1.30	1.02-1.66	.04
BMT from 1989-1995	1.28	1.04-1.59	.02
CR1 ≥1 y (CR2 patients)	1.0	—	—
CR1 <1 year (CR2 patients)	1.37	1.04-1.79	.02
CR1	.72	.56-.91	.007
Survival	**RR of Death**	**95% CI**	***P***
Autologous	1.0	—	—
URD within first 6 mo post-BMT versus Auto	1.79	1.28-2.50	.0006
URD >6 mo post-BMT versus Auto	.56	.41-.77	.0003
Age ≤20 years	.69	.56-.85	.0004
BMT 1989-1995	1.32	1.06-1.64	.01
CR1 ≥1 year (CR2 patients)	1.0	—	—
CR1 <1 year (CR2 patients)	1.53	1.16-2.01	.002
CR1	.78	.61-.99	.04

*Shown are results of Cox multivariate regression models for disease-free survival (stratified by sex and controlled for remission number) and survival (stratified by sex and controlled for remission number). The impact of remission number and duration of CR1 (for transplantations during CR2) are shown adjusted for other significant factors in the regression models.

regression model (Table 3) demonstrated superior survival in Auto transplantation patients within the first 6 months, but beyond the first 6 months, subsequent survival was higher in URD recipients. Additionally, post-BMT survival was significantly better during CR1, in patients with a long initial remission (who received transplants during CR2), in those younger than 20 years, and in patients receiving transplants between 1996 and 1998.

These regression analyses defined risk factors associated with distinctly different DFS rates after transplantation. Using the independently significant factors of initial remission duration of >1 year, WBC <50 × 10^9/L, and Karnofsky score ≥90%, groups with 0, 1, or ≥2 high-risk factors were examined for their outcomes. As shown (Figure 5), patients lacking all of these high-risk factors had 3-year DFS rates of 51% ± 8% after URD and 31% ± 11% after Auto BMT. Patients with 1 risk factor had DFS rates of 42% ± 8% after URD and 41% ± 15% after Auto BMT; ≥2 risk factors led to DFS rates of 25% ± 11% after URD and 20% ± 25% after Auto BMT. Only in the most favorable group (no risk factors) was URD BMT associated with a superior outcome compared to Auto BMT. This association was apparent in both older and younger patients (for no risk factors, URD in patients >20 years [n = 58], 48% ± 13%; URD in patients ≤20 years [n = 117], 53% ± 10%; Auto in patients >20 years [n = 36], 32% ± 17%; Auto in patients ≤20 years [n = 41], 30% ± 14%). Patients with 1 or ≥2 risk factors in either age group had similar outcomes with URD or Auto BMT (not shown).

DISCUSSION

In this study, direct and risk-adjusted comparisons of outcome were performed to define the patients with ALL most likely to benefit from either URD allogeneic or Auto BMT. The superior antileukemic potency of URD transplantation was associated with better protection against leukemia relapse but could not overcome leukemia with certain adverse prognostic factors (particularly extreme leukocytosis), which are markers of highly resistant ALL. Thus, although relapse risks were substantially and significantly lower after URD transplantation, nearly one third of patients with an elevated WBC or short initial remission still relapsed after URD transplantation. In contrast, recurrent

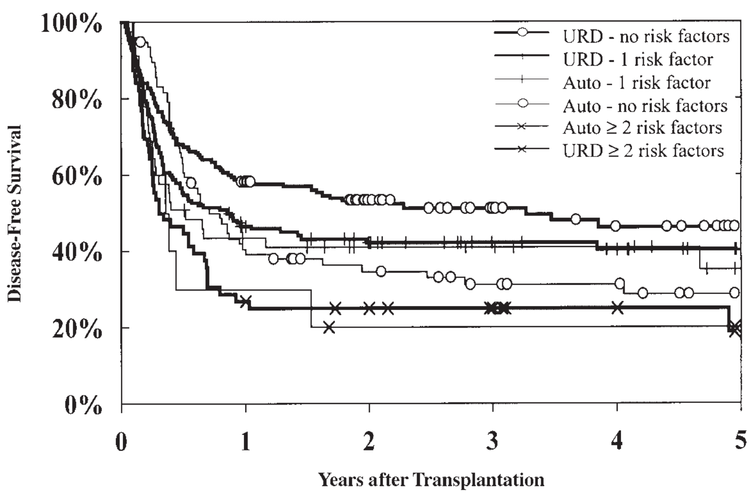

Figure 5. Disease-free survival after either URD or Auto BMT using risk factors of short (<1 year) initial remission, WBC ≥50 × 10^9/L and/or Karnofsky <90% to compare DFS for patients with 0, 1, or ≥2 risk factors. Because of missing data for one or more risk factors, 199 patients were not included.

leukemia was overwhelmingly the major reason for failure after autografting in all patient subsets.

The clinical benefit of URD transplantation is still limited by excessive (approximately 40%) TRM. Encouragingly, TRM was significantly lower in more recent years, but substantial improvements in supportive care plus protection against persistent GVHD and ongoing immunodeficiency will be required before the potent antileukemic benefits of URD transplantation can enhance survival for a larger fraction of patients. Although the highest risk for TRM was apparent in the first 3 months posttransplantation, an additional 15% to 20% of patients died without relapse between 3 and 12 months posttransplantation, which shows the substantial need for greater protection against late lethal transplantation events. Although initial graft failure was uncommon, prolonged thrombocytopenia after URD transplantation was also apparent, with nearly 40% of patients remaining significantly thrombocytopenic by 10 to 12 months posttransplantation.

These distinct causes of treatment failure (relapse after Auto transplantation and TRM after URD transplantation) yielded similar DFS rates for patients choosing either transplantation approach, with an approximately 40% DFS in CR1 and 30% DFS in CR2. However, patients with favorable features (higher Karnofsky scores, longer initial remission, and lower diagnostic WBC) had notably improved DFS rates compared to patients lacking these clinical features. In this favorable group, URD BMT yielded better DFS rates than did Auto transplantation in both older and younger patients.

An earlier analysis of similar data compared multicenter URD transplantation with purged autografts performed at the University of Minnesota and the Dana Farber Cancer Institute [19]. In that report, superior DFS was observed for children, male patients, and patients whose BMT was performed during CR1 or CR2 compared to during more advanced disease. Both regression analyses and recursive partition analyses could suggest only a trend toward an advantage for URD versus Auto transplantation that was apparent only in patients <18 years of age. Either approach yielded only 25% survival in adult patients. A recent expert panel decision analysis also offered no clear consensus about the best choice of transplantation options for ALL patients [29]. Recent French and Medical Research Council–Eastern Cooperative Oncology Group comparative trials of related donor allografting versus autografting or chemotherapy suggest that related donor allografting yields superior outcomes [30,31], but other comparative data regarding URD BMT are unavailable.

Clinical decision making about these 2 options, therefore, must still be guided by features that are suggestively, but not definitively, shown to yield superior outcomes. Features indicating high-risk leukemia (karyotype, extreme leukocytosis, short initial remission) require improved antileukemic effects for both URD and Auto transplantation. Patients with lesser risk factors may benefit from the more potent effects of URD BMT. Conversely, patients with compromised performance status may benefit from alternative nontransplantation approaches or from less intense nonmyeloablative allografting. Intensified conditioning regimens [7], graft purging [11-13], the use of peripheral blood progenitor cells or posttransplantation antileukemic chemotherapy [14], or immunotherapy [32,33] might further enhance the efficacy of autograft approaches. Clinical improvement in both approaches as well as additional study will be needed to define patient subsets displaying a risk-factor phenotype clearly best served by one or the other of these 2 transplantation techniques.

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