Favorable outcomes with alemtuzumab-conditioned unrelated donor stem cell transplantation in adults with high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in first complete remission

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ABSTRACT

Background

Approximately 40% of adults with Philadelphia chromosome-negative acute lymphoblastic leukemia achieve long-term survival following unrelated donor hematopoietic stem cell transplantation in first complete remission but severe graft-versus-host disease remains a problem affecting survival. Although T-cell depletion abrogates graft-versus-host disease, the impact on disease-free survival in acute lymphoblastic leukemia is not known.

Design and Methods

We analyzed the outcome of 48 adults (median age 26 years) with high-risk, Philadelphia-chromosome-negative acute lymphoblastic leukemia undergoing T-cell depleted unrelated donor-hematopoietic stem cell transplantation (67% 10 of 10 loci matched) in first complete remission reported to the British Society of Blood and Marrow Transplantation Registry from 1993 to 2005.

Results

T-cell depletion was carried out by *in vivo* alemtuzumab administration. Additional, *ex vivo* T-cell depletion was performed in 21% of patients. Overall survival, disease-free survival and non-relapse mortality rates at 5 years were 61% (95% CI 46-75), 59% (95% CI 45-74) and 13% (95% CI 3-25), respectively. The incidences of grades II-IV and III-IV acute graft-versus-host disease were 27% (95% CI 16-44) and 10% (95% CI 4-25), respectively. The actuarial estimate of extensive chronic graft-versus-host disease at 5 years was 22% (95%CI 13-38). High-risk cytogenetics at diagnosis was associated with a lower 5-year overall survival (47% (95% CI 27-71) *vs.* 68% (95% CI 44-84), p=0.045).

Conclusions

T-cell depleted hematopoietic stem cell transplantation from unrelated donors can result in good overall survival and low non-relapse mortality for adults with high-risk acute lymphoblastic leukemia in first complete remission and merits prospective evaluation.

Key words: adult acute lymphoblastic leukemia, stem cell transplantation, T-cell depletion.

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Introduction

In adult acute lymphoblastic leukemia despite high initial rates of complete remission the majority of adult patients relapse.[1] Hematopoietic stem cell transplantation (HSCT) from a sibling donor, carried out while the recipient is in first complete remission, extends disease-free survival in certain populations of patients. In high-risk acute lymphoblastic leukemia, sibling allografting results in a 22-35% survival advantage over alternative therapies.[2-6] A donor versus no donor analysis in the UKALL/XII/ECOG2993 collaborative study of 1929 participants showed significantly prolonged overall survival with sibling allografting compared to chemotherapy in standard risk ALL in first complete remission.[1] In high-risk patients, although relapse was significantly reduced, a high non-relapse mortality resulted in no overall survival advantage, a finding which was largely attributed to the inclusion of older (>35 years) patients within the high-risk group.

The greater curative potential of allogeneic HSCT and a better understanding of risk factors for treatment failure with chemotherapy[7] have inevitably led to the investigation of alternative sources of donor stem cells for HSCT in poor-risk ALL. For patients with Philadelphia chromosome (Ph)-positive disease, unrelated donor (URD) HSCT in first complete remission is an accepted strategy resulting in superior outcomes to those achieved with chemotherapy.[8] Comparative studies previously[9,10] found equivalent transplant-related mortality and disease-free survival rates between adults undergoing matched URD or sibling HSCT for high-risk ALL. A detailed analysis of URD-HSCT for Ph-negative ALL in first complete remission was recently presented by Marks *et al*.[11] This CIBMTR registry study of largely T-cell replete URD HSCT reported a 5-year overall survival rate of 39% in 169 patients. However, procedural-related mortality was a major cause of treatment failure, occurring in 42% of patients, with graft-versus-host disease (GVHD) reported as the second most common cause of death.

T-cell depletion is the most effective method of preventing GVHD after allogeneic HSCT, a substantial cause of transplant-associated morbidity and mortality.[12,13] However, this can be at the cost of impaired immune reconstitution[14] and a reduced graft-versus- *vs.* leukemia effect[15] due to a loss of antigen- and tumor-specific T cells. Whether there is a role for T-cell depletion in the setting of transplants from URD for poor-risk Ph-negative ALL is not known.

In the UK, most URD grafts are T-cell depleted (TCD). We, therefore, used the British Society of Blood and Marrow Transplantation (BSBMT) data registry to identify adult recipients of URD transplants for Ph-negative ALL. Here we report the outcome of 48 consecutive patients undergoing TCD URD transplantation for high-risk Ph-negative ALL in first complete remission.

Design and Methods

Study patients were identified through the BSBMT registry database. All transplant centers in the United Kingdom and Republic of Ireland are required to report outcomes of consecutive transplants to the BSBMT registry. Search criteria included: (i) age between 15 and 55 years old, inclusive, (ii) a diagnosis of *de novo* ALL between 1993–2005, (iii) a TCD-URD transplant performed in first complete remission. One hundred and seven patients fulfilled these criteria in 21 transplant centers. Ph status was checked with all the centers and Ph-positive patients excluded. Forty-eight patients from 16 transplant centres were finally confirmed as having high-risk Ph-negative ALL and constituted the study population.

Definition of high risk

Patients were defined as having high-risk ALL if they were over 35 years old, had a high white blood cell count (>30×10^9/L in B- cell disease /immunophenotype unknown, >100×10^9/L in T-cell disease), had adverse cytogenetics including t(4;11) with or without other abnormalities, a complex karyotype (≥5 abnormalities) or low hypodiploidy/near triploidy at diagnosis and took more than 8 weeks to achieve first complete remission. Two further patients were considered to have high-risk ALL because of persistent extramedullary disease in first complete remission.

Typing of human leukocyte antigens

Matching status of human leukocyte antigens (HLA) was assigned based on the data available. In all but three cases, matching status was entered for five HLA loci (HLA-A,-B,-C,-DRB1,-DQB1). In three cases the matching status for HLA-C was unknown. When possible, actual HLA types were obtained and verified (51% of cases).

In 18 cases the HLA matching status was defined as *definite*, i.e. the actual tissue types had been reviewed and the result obtained with high resolution typing. The matching status of the remaining pairs was designated as either *probable* (tissue typing reviewed and of medium resolution or transplantation after 01/01/2000 when HLA class I and II typing was routinely performed by molecular techniques, n = 21) or *possible* (tissue typing reviewed and serological typing or transplant performed before 2000, n=9).

Statistical analysis

Probabilities of overall survival and disease-free survival were calculated by the Kaplan-Meier method. Comparisons between groups were made using the log-rank test. Probabilities of non-relapse mortality, relapse, acute and chronic GVHD disease were calculated as cumulative incidences using competing risks analysis with group comparisons made using Gray's test.[16] The competing risks considered were relapse for non-relapse mortality, non-relapse death for relapse and death from any cause for chronic GVHD.

Results

Patient-related, disease and transplant characteristics

Patient-related, disease and transplant characteristics of the 48 patients are shown in Table 1. The median age of the patients at diagnosis was 26.2 years (range, 16 - 50), and the median follow-up of surviving patients was 56 months (range, 18-160). Adverse karyotype was present in 17/48 (35%) of patients, 22/40 (55%) of evaluable patients had a high presenting white blood cell count and 14/48 (29%) were aged over 35 years. Multiple poor

Table 1. Patient, disease and transplant characteristics.

Characteristic	N. of patients
Total n. of patients	48
Gender (%)	
male	38 (79%)
female	10 (21%)
Median age at diagnosis, years (range)	26 (16 -50)
Median age at time of transplant, years (range)	27 (17 -51)
15-20	11 (23%)
21-30	19 (40%)
31-40	12 (25%)
>40	6 (12%)
Median WBC ($\times 10^9$/L) at diagnosis (range)	50 (2-607.9)
<30	13 (33%)
30-100	11 (27%)
100-200	5 (13%)
>200	11 (27%)
missing	8
Cytogenetics (%)	
Normal	15 (31%)
t(4;11) ± others	12 (25%)
hyperdiploidy	1 (2%)
other cytogenetic abnormality	15 (31%)
complex karyotype	5 (10%)
Immunophenotype (%)	
B lineage	27 (61%)
T lineage	12 (27%)
other	5 (11%)
missing	4
Median time from diagnosis to CR1, weeks (range)	7.7 (1.3-52.6)
<4 weeks	2 (5%)
4-8 weeks	17 (40%)
> 8 weeks	23 (50%)
missing	6
Median time from CR1 to transplantation, months (range)	5 (0.1-15)
< 3 months	22 (52%)
3-6 months	8 (19%)
>6 months	12 (29%)
missing	6
Median time from diagnosis to transplantation, months (range)	7 (4-15)
Number of induction courses to CR1	
1 cycle	27 (71%)
2 cycles	8 (21%)
3 cycles	1 (3%)
4 cycles	2 (5%)
missing	10
CMV recipient / donor	
- / -	19 (40%)
+ / -	12 (26%)
- / +	2 (4%)
+ / +	14 (30%)
missing	1
Hematopoetic stem cell source	
bone marrow	29 (60%)
peripheral blood	19 (40%)

Characteristic	N. of patients
Regimen	
cyclophosphamide + TBI	32 (67%)
cyclophosphamide + TBI + [a]other	7 (15%)
etoposide + TBI	8 (17%)
busulpan + etoposide (no TBI)	1 (2%)
TBI dose cGy	
≥1300	34 (76%)
<1300	10 (22%)
none	1 (2%)
missing	3
Median n. of cells ($\times 10^8$/kg)	3.8 (0.97-28.6)
missing	6
Donor HLA (%)	
10/10 match	32 (67%)
definite	9
probable	15
possible	8
9/10 match	13 (27%)
definite	6
probable	6
possible	1
8/10 match	3 (6%)
definite	3 (6%)
probable	0
possible	0
Karnofsky performance score at transplantation (%)	
10 (good)	43 (96%)
20 (poor)	2 (4%)
missing	3
Alemtuzumab (%)	
in vivo	48 (100%)
additional *ex vivo*	10 (21%)
GVHD prophylaxis	
cyclosporine A + methotrexate	31 (67%)
cyclosporine alone	10 (22%)
cyclosporine +methotrexate+ steroids	3 (7%)
cyclosporine and steroids	1 (2%)
mycophenolate mofetil	1 (2%)
missing	2
Donor age, years (range)	33 (21-51)
≤20	0 (0%)
21-30	17 (46%)
31-40	20 (54%)
missing	11
Donor- recipient gender match	
male-male	25 (53%)
male-female	6 (13%)
female-male	12 (26%)
female-female	4 (9%)
missing	1
Median (range) follow-up of survivors, months	56.3 (17.8-160)

[a]*Other conditioning agents were stated as thiotepa (n=3), methylprednisolone (n=1), busulphan (n=1),and fludarabine (n= 2). CR1: first complete remission; CMV: cytomegalovirus; TBI: total body irradiation.*

prognostic features were present in 40% (19/48) of the patients. Of these 12/48 (25%) had two adverse risk factors present at diagnosis and 7/48 (15%) had three. Forty-seven of the 48 (98%) patients received conditiong regimes containing total body irradiation. All patients received a TCD transplant with *in vivo* administration of alemtuzumab. In ten patients additional T-cell depletion was performed using alemtuzumab *in vitro*. Details of *in vivo* alemtuzumab treatment were available for 41 of the 48 recipients of a TCD transplant. Alemtuzumab -1G (60–100 mg) was used in nine patients, alemtuzumab -1H (50–100 mg) in 31 patients and alemtuzumab -1M, at an unknown dose, in one case. Donor lymphocyte infusions were given to four patients following transplantation.

Engraftment

Neutrophil engraftment to a level of 0.5×10^9/L occurred in all patients at a median of 16.5 days (range, 11-35) after transplantation with 46/48 (96%) evaluable patients engrafting before day 28. The median time to engraftment was 18 days in patients receiving bone marrow grafts and 16 days in patients receiving peripheral blood stem cells grafts (p=0.16). Platelet engraftment occurred in 41 evaluable patients at a median of 21 days (range, 11-209), and was achieved by day 28 in 28 (66%) of these patients.

Table 2. Univariate analysis of overall survival and disease-free survival.

Variable	N.	Disease-free survival at 5 years (95% CI)	p	Overall survival at 5 years (95% CI)	p
Patient-related variables					
Cytomegalovirus positive					
neither	21	67% (45-85)	0.42	71% (49-86)	0.29
donor or recipient	27	52% (33-72)		51% (31-71)	
HLA disparity					
no mismatches	32	62% (44-78)	0.70	64% (46-79)	0.58
1-2 mismatches	16	48% (26-71)		55% (31-77)	
Age at diagnosis					
≤26 (median)	23	64% (43-81)	0.53	67% (44-84)	0.32
>26	25	55% (37-72)		55% (34-77)	
Disease-related variables					
Cytogenetics					
normal or other abnormalities	31	65% (45-83)	0.065	68% (44-84)	0.045
adverse cytogenetics	17	47% (27-71)		47% (26-69)	
Presenting white cell count					
low	18	52% (35-71)	0.45	52% (31-71)	0.46
high	22	68% (52-86)		68% (48-84)	
Age					
≤35 years	34	61% (44-77)	0.86	63% (45-78)	0.70
>35 years	14	54% (30-79)		56% (29-80)	
Time to first complete remission					
≤8 weeks	19	60% (39-79)	0.99	60% (39-78)	0.82
>8 weeks	23	53% (34-73)		57% (36-76)	
Treatment-related variables					
Dose of total body irradiation					
<13Gy	10	80% (51-96)	0.17	80% (48-95)	0.20
>13Gy	34	53% (36-69)		56% (39-72)	
Alemtuzumab					
in vivo and *ex vivo*	10	50% (33-67)	0.45	55% (23-78)	0.46
in vivo only	38	61% (44-76)		58% (41-72)	
Source of stem cells					
bone marrow	29	59% (42-75)	0.85	57% (38-72)	0.95
peripheral blood	19	57% (31-79)		58% (31-78)	
Year of transplant					
1993-2000	20	60% (40-79)	0.98	63% (39-80)	0.73
>2000	28	58% (39-75)		55% (35-71)	
Acute graft-versus-host disease					
0-I	34	64% (45-79)	0.44	49% (26-69)	0.38
II-IV	12	39% (22-59)		63% (44-77)	
Chronic graft-versus-host disease					
none	22	58% (38-77)	0.41	60% (37%-77%)	0.24
limited/extensive	23	67% (44-83)		68% (46%-83%)	

Overall survival and disease-free survival

With a median follow-up of 56 months (range 18-160) 30 of 48 patients were alive and of these 27 were free of leukemia. The Kaplan-Meier estimates for overall survival of all patients at 3 and 5 years were 64% (95% CI 48-76) and 61% (95% CI 45-74), respectively (Figure 1). The disease-free survival rate was 59% at 3 years and unchanged at 5 years. Factors influencing disease-free survival and overall survival were examined by univariate analysis and are shown in Table 2. The only factor that had a significant effect on overall survival was adverse cytogenetics which was associated with a significantly shorter survival (p=0.045).

Relapse

Recurrent leukemia occurred in 13 (27%) patients at a median time of 8 months (0.8-30) following transplantation. The median survival after relapse was 2.5 months with only two patients surviving at 6 months. The 3- and 5- year cumulative relapse rates were 28% (95% CI 20-42) for all patients (Figure 1). Four of the 13 relapsed patients had received donor lymphocyte infusions, one was reported to be in complete remission at last follow-up and three subsequently died in continued relapse. Various factors were investigated for their effect on relapse risk and are shown in Table 3. Delayed achievement of complete remission or development of acute GVHD did not significantly affect relapse rate following URD transplantation.

Graft-versus-host disease

Acute GVHD occurred in 65% of patients and was grade I in 18 patients (39%), grade II in eight (17%), and grades III-IV in four (9%). Cumulative incidences of grades II-IV and grades III-IV acute GVHD were 27% (95%CI 16-44) and 10% (95% CI 4-25), respectively (Figure 2A). The probability of limited or extensive chronic GVHD was 44% (95% CI 30-61) at 5 years (22 of 45 evaluable patients) while that of extensive disease was 22% (95% CI 13-38) (Figure 2B). Ten patients had

Table 3. Univariate analysis of relapse.

Relapse	N.	Relapse at 5 years (95%CI)	p
White blood cell at diagnosis			
high	22	14% (5-39)	0.19
low	18	33% (17-64)	
Age at diagnosis			
≤35 years	34	30% (18-51)	0.61
>35 years	14	21% (8-58)	
Graft-versus-host-disease			
acute: grades 0-I	34	24% (13-44)	0.57
acute: grades II-IV	12	33% (15-74)	
chronic: none	22	28% (14-55)	0.75
chronic: limited/extensive	23	26% (13-52)	
Cytogenetic findings			
normal or other abnormalities	31	27% (15-49)	0.36
adverse cytogenetics	17	29% (14-61)	
HLA disparity			
none	32	29% (17-50)	0.90
1-2 mismatches	16	25% (11-58)	
Time from diagnosis to first complete remission			
<8 weeks	19	25% (12-53)	0.86
≥8 weeks	23	32% (18-59)	

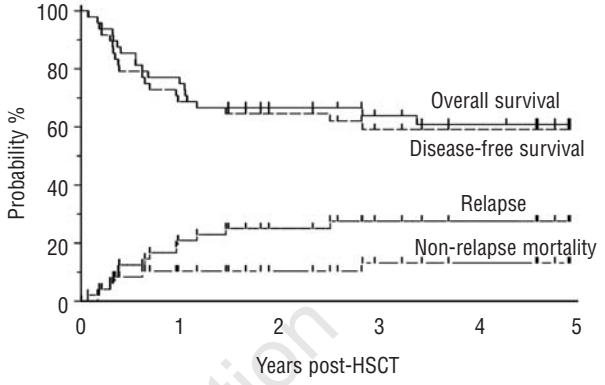

Figure 1. Primary outcomes of 48 high-risk ALL patients who underwent TCD URD-HSCT.

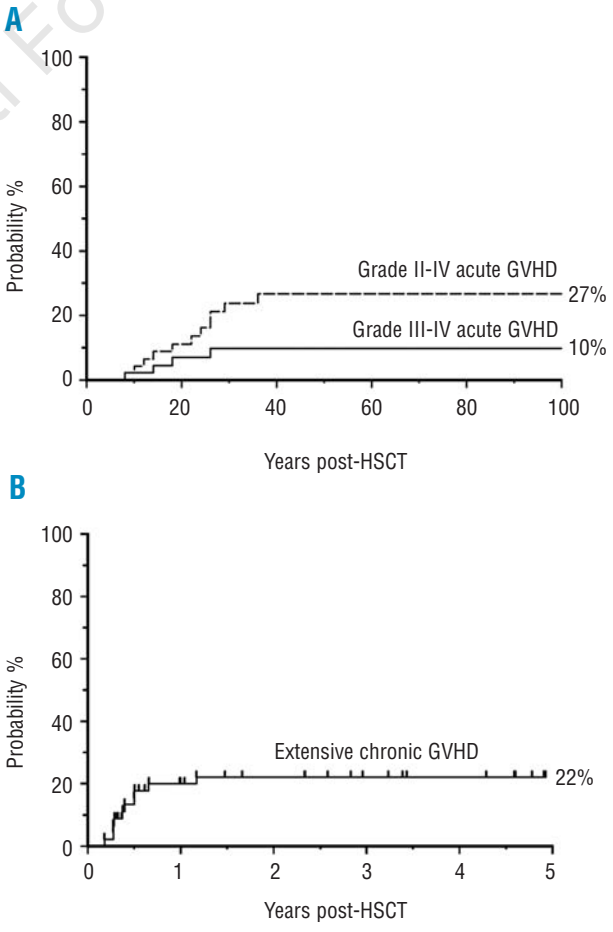

Figure 2. Cumulative incidences of GVHD after TCD URD-HSCT for high-risk ALL. (A) Acute grades II-IV and III-IV. (B) Chronic extensive.

Table 4. Univariate analysis of non-relapse mortality.

Non-relapse mortality	N.	Non-relapse mortality at 5 years (95%CI)	p
Age at diagnosis			
≤35 years	34	9% (3-26)	0.28
> 35 years	14	26% (9-70)	
Median age at diagnosis			
≤25.5 years	23	9% (2-33)	0.48
>25.5 years	25	18% (7-43)	
Donor-recipient sex			
male recipient	38	14% (6-32)	0.82
female recipient	10	10% (2-64)	
Stem cell source			
bone marrow	29	14% (6-32)	0.82
peripheral blood	19	17% (4-64)	
HLA disparity			
none	32	9% (3-27)	0.37
1-2 mismatches	16	21% (7-57)	
Graft-versus-host disease			
acute: grades 0-I	34	12% (5-31)	0.62
acute: grades II-IV	12	28% (8-96)	
chronic: none	22	14% (5-39)	0.28
chronic: limited/extensive	23	7% (1-45)	
Time from diagnosis to transplantation			
<7 months	25	8% (2-30)	0.36
≥7 months	23	19% (8-45)	
Positivity for cytomegalovirus			
neither	21	10% (3-35)	0.50
donor or recipient	27	17% (7-43)	

extensive chronic GVHD and 12 limited involvement. The incidence of chronic GVHD was significantly higher in recipients of peripheral blood stem cell grafts than in recipients of bone marrow grafts (78% *vs.* 24%; at 5 years p=0.001). Additional *ex vivo* T-cell depletion did not affect the incidence of acute or chronic GVHD.

Non-relapse mortality

Death occurred for reasons other than relapse in six patients at a median of 117 days (range, 60–1033) following transplantation. The causes of death were infection (n=2), graft failure (n=1), neurological toxicity (n=1), secondary malignancy (n=1) and unknown (n=1). Importantly, GVHD-related deaths were not reported. Late non-relapse mortality occurred in one patient at 34 months due to adenocarcinoma of the lung.

The estimated cumulative incidence of non-relapse deaths in first complete remission at 3 years, in plateau, was 13% (95% CI 3-25) (Figure 1). The probabilities of non-relapse mortality at day 100 and day 365 were 4.2% (95% CI 3-16) and 10.4 % (95% CI 4-24), respectively. Various factors were investigated for an association with a significantly increased non-relapse mortality but none was found to be statistically significant by univariate analysis (Table 4).

Discussion

This study is the first to report the longer term outcome of TCD URD transplantation for adults with poor risk Ph-negative ALL in first complete remission. With this approach the multicenter non-relapse mortality rate was 13% (95% CI 3-25) and the disease-free survival rate an encouraging 59% (95% CI 45-74) at 5 years. There is considerable evidence for a potent graft-versus-leukemia effect in allografting for ALL, with nearly all randomized studies demonstrating a significantly lower incidence of relapse with this therapy[1,17] The finding of durable leukemia-free remissions in more than 50% of patients undergoing TCD allografting for high-risk ALL in this study suggests that a graft-versus-ALL effect might be preserved with this treatment approach. Such an interpretation lends support to the rationale for partial T-cell depletion, which is to reduce severe (grade III-IV) GVHD whilst still allowing for some graft-versus-leukemia effect and mild acute or chronic GVHD. Indeed, nearly 40% of patients experienced grade I acute GVHD and this could also have been protective against relapse.

Notably, the probability of relapse in this series of patients with poor-risk ALL undergoing TCD URD-HSCT compares favorably with that reported for T-cell replete sibling allografting in high-risk patients on the MRC/ECOG study[1] (28% *vs.* 39% at 5 years, respectively). Furthermore, the predicted 5-year survival in high-risk subgroups (high WBC: 68%, >8 weeks to first complete remission: 57%) in this analysis contrasts well with an approximately 30% 5-year overall survival in comparable groups receiving mostly T-replete URD transplants reported by the CIBMTR study.[11] Thus, the finding of higher rates of disease relapse with TCD allotransplantation reported by some authors[18] does not appear to be recapitulated in this series of high-risk ALL. Reports in childhood ALL[19] showing comparable disease-free survival rates in patients undergoing HLA-matched sibling donor transplants and in those undergoing T-cell-modified URD-HSCT for ALL in first or subsequent complete remission provide further support for retention of a graft-versus-leukemia effect with a TCD approach.

Patients with adverse cytogenetics had a significantly worse overall survival (47 *vs.* 68%, p=0.045) and a trend towards a lower disease-free survival (47% *vs.* 65%, p=0.065) in this study. Their outcomes are, however, similar to those reported by the CIBMTR[11] for patients with ALL with adverse karyotype using a T-replete transplantation approach (overall survival: 38% at 5 years). The optimal conditioning approach in this ALL subgroup is, therefore, yet to be determined and further study is clearly warranted.

CD52 is expressed on 66-78% of ALL cells.[20] We, therefore, recognize the possibility that alemtuzumab may have contributed to an antileukemic effect which may have partly offset a reduced graft-versus-leukemia effect. However, since all patients were in first complete remission and information on minimal residual disease at transplant is lacking, the magnitude of such a contribution is impossible to assess. Whether TCD URD transplantation is effective in those entering transplant with detectable minimal residual disease requires specific study, a matter which is likely to be addressed in the next UK-US ALL trial.

In agreement with results of previous studies we found TCD allotransplantation effective in preventing GVHD and graft rejection after URD-HSCT.[21-24] The very low (10%) overall incidence of grade III to IV acute GVHD in our study population, together with only a single case of secondary graft failure, is consistent with this. However, chronic GVHD did occur in approximately half of the patients. The interpretation of this finding is confounded by the variation in alemtuzumab antibody, dosing and scheduling in our series which may have resulted in suboptimal prophylaxis of chronic GVHD in some cases. However, the finding of a reduction in acute GVHD but not always chronic GVHD after TCD URD-HSCT is well described[24-27] and may reflect differing pathogenic mechanisms between these GVHD syndromes.[28]

A major drawback of T-cell depletion is slow immune reconstitution and post-transplant infection but only a third of transplant-related deaths in this series were due to infection. Pharmacokinetic studies have shown clinically significant differences in the type of CD52 antibody with rat antibodies, alemtuzumab -1G, having a shorter half-life (12–13 hours) than that of the humanized form, alemtuzumab-IH (15–21days), resulting in persistent lympholytic concentrations with the latter and a higher incidence of infections.[14] A formal comparison between these agents and non-relapse mortality did not reveal any significant association.

There are very few studies addressing the utility of URD transplantation in Ph-negative ALL and none specifically examining the impact of T-cell depletion in this setting. Significant heterogeneity in selection of patients and transplant characteristics between studies limits an adequate comparison. Nonetheless, the finding of a higher rate of non-relapse mortality (RR 2.67; CI 1.42–4.99) in 16 patients who had received a TCD transplant by a variety of methods reported in the CIBMTR study is not corroborated in this larger series of TCD transplants. Importantly, the lack of GVHD-attributable deaths in this BSBMT series contrasts sharply with the findings of CIBMTR study in which GVHD was the second commonest cause of death.[11] The cautions applicable to analysis of all retrospective registry data are also relevant here: in particular, the selection bias for surviving patients, which may result in improved outcomes being reported. For this reason considerable caution should be applied in comparing the overall survival rate of 60% with the 30–40% survival of adult ALL patients undergoing URD-HSCT reported by other studies. However, prospective randomized studies in this area are difficult to perform. Hence, retrospective data analysis is a pragmatic basis for initial investigation in this setting. Increasing age confers the highest risk of treatment-related mortality. The median age of our population was lower (26 years) than that of other published series (23-33 years), which might have contributed to the low observed non-relapse mortality although it is of note that older age did not increase non-relapse mortality or negatively influence overall outcome in the series reported. It is also recognized that the adolescent population (15–20 years) included in the study are now treated according to pediatric protocols, although it is important to note that randomized controlled evidence supporting the efficacy of this approach is still awaited.

The grim outlook of relapsed ALL in adults is indicated by the report by Fielding *et al.* which described a 5-year survival rate of 7% in 609 patients following initial recurrence.[29] Prevention of relapse through primary application of the most effective therapies is, therefore, vital. In this study we demonstrate the potential efficacy of TCD URD transplantation for high-risk ALL and show that durable leukemia- free remissions can be achieved with this approach. These results support the prospective study of TCD URD transplantation in Ph-negative ALL to further define the role of this strategy.

Authorship and Disclosures

BP and DIM designed the study; RP and RS performed the statistical analysis; KK, collected data; BP prepared the manuscript; BES collected and analyzed HLA typing data; all authors participated in the interpretation of data and approved the final version of the manuscript.

The authors reported no potential conflicts of interest.

References

1. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood 2008;111: 1827-33.
2. Sebban C, Lepage E, Vernant JP, Gluckman E, Attal M, Reiffers J, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. J Clin Oncol 1994;12:2580-7.
3. Takeuchi J, Kyo T, Naito K, Sao H, Takahashi M, Miyawaki S, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. Leukemia 2002;16:1259-66.
4. Hunault M, Harousseau JL, Delain M Truchan-Graczyk M, Cahn JY, Witz F, et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. Blood 2004;104:3028-37.
5. Labar B, Suciu S, Zittoun R, Muus P, Marie JP, Fillet G, et al. Allogeneic stem cell transplantation in acute lymphoblastic leukemia and non-Hodgkin's lymphoma for patients <or=50 years old in first complete remission: results of the EORTC ALL-3 trial. Haematologica 2004;89: 809-17.
6. Thomas X, Boiron JM, Huguet F,

Dombret H, Bradstock K, Vey N, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. J Clin Oncol 2004;22:4075-86.
7. Rowe JM, Buck G, Burnett AK, Chopra R, Wiernik PH, Richards SM, et al. Induction therapy for adults with acute lymphoblastic leukemia: results of more than 1500 patients from the international ALL trial: MRC UKALL XII/ECOG E2993. Blood 2005;106:3760-7.
8. Marks DI, Bird JM, Cornish JM, Goulden NJ, Jones CG, Knechtli CJ, et al. Unrelated donor bone marrow transplantation for children and adolescents with Philadelphia-positive acute lymphoblastic leukemia. J Clin Oncol 1998;16:931-6.
9. Kiehl MG, Kraut L, Schwerdtfeger R, Hertenstein B, Remberger M, Kroeger N, et al. Outcome of allogeneic hematopoietic stem-cell transplantation in adult patients with acute lymphoblastic leukemia: no difference in related compared with unrelated transplant in first complete remission. J Clin Oncol 2004;22: 2816-25.
10. Dahlke J, Kröger N, Zabelina T, Ayuk F, Fehse N, Wolschke C, et al. Comparable results in patients with acute lymphoblastic leukemia after related and unrelated stem cell transplantation. Bone Marrow Transplant 2006;37:155-63.
11. Marks DI, Pérez WS, He W, Zhang MJ, Bishop MR, Bolwell BJ, et al. Unrelated donor transplants in adults with Philadelphia-negative acute lymphoblastic leukemia in first complete remission. Blood 2008;112:426-34.
12. Hale G, Jacobs P, Wood L, Fibbe WE, Barge R, Novitzky N, et al. CD52 antibodies for prevention of graft-versus-host disease and graft rejection following transplantation of allogeneic peripheral blood stem cells. Bone Marrow Transplant 2000;26:69-76.
13. Hale G, Waldmann H. Recent results using CAMPATH-1 antibodies to control GVHD and graft rejection. Bone Marrow Transplant 1996;17: 305-8.
14. Morris EC, Rebello P, Thomson KJ, Peggs KS, Kyriakou C, Goldstone AH, et al. Pharmacokinetics of alemtuzumab used for in vivo and in vitro T-cell depletion in allogeneic transplantations: relevance for early adoptive immunotherapy and infectious complications. Blood 2003;102:404-6.
15. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood 1990;75:555-62.
16. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Annals Of Statistics 1988;16:1141-54.
17. Yanada M, Matsuo K, Suzuki T, Naoe T. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. Cancer 2006;106: 2657-63.
18. Marmont AM, Horowitz MM, Gale RP, Sobocinski K, Ash RC, van Bekkum DW, et al. T-cell depletion of HLA-identical transplants in leukemia. Blood 1991;78:2120-30.
19. Kennedy-Nasser AA, Bollard CM, Myers GD, Leung KS, Gottschalk S, Zhang Y, et al. Comparable outcome of alternative donor and matched sibling donor hematopoietic stem cell transplant for children with acute lymphoblastic leukemia in first or second remission using alemtuzumab in a myeloablative conditioning regimen. Biol Blood Marrow Transplant 2008;14:1245-52.
20. Gokbuget N, Hoelzer D. Treatment with monoclonal antibodies in acute lymphoblastic leukemia: current knowledge and future prospects. Ann Hematol 2004;83:201-5.
21. Byrne JL, Stainer C, Cull G, Haynes AP, Bessell EM, Hale G, et al. The effect of the serotherapy regimen used and the marrow cell dose received on rejection, graft-versus-host disease and outcome following unrelated donor bone marrow transplantation for leukaemia. Bone Marrow Transplant 2000;25:411-7.
22. Kernan NA, Bartsch G, Ash RC, Beatty PG, Champlin R, Filipovich A, et al. Analysis of 462 transplantations from unrelated donors facilitated by the National Marrow Donor Program. N Engl J Med 1993;328: 593-602.
23. Kottaridis PD, Milligan DW, Chopra R, Chakraverty RK, Chakrabarti S, Robinson S, et al. In vivo CAMPATH-1H prevents GvHD following nonmyeloablative stem-cell transplantation. Cytotherapy 2001;3:197-201.
24. Maraninchi D, Gluckman E, Blaise D, Guyotat D, Rio B, Pico JL, et al. Impact of T-cell depletion on outcome of allogeneic bone-marrow transplantation for standard-risk leukaemias. Lancet 1987;2:175-8.
25. Champlin RE, Passweg JR, Zhang MJ, Rowlings PA, Pelz CJ, Atkinson KA, et al. T-cell depletion of bone marrow transplants for leukemia from donors other than HLA-identical siblings: advantage of T-cell antibodies with narrow specificities. Blood 2000;95:3996-4003.
26. Pavletic SZ, Carter SL, Kernan NA, Henslee-Downey J, Mendizabal AM, Papadopoulos E, et al. Influence of T-cell depletion on chronic graft-versus-host disease: results of a multicenter randomized trial in unrelated marrow donor transplantation. National Heart, Lung, and Blood Institute Unrelated Donor Marrow Transplantation Trial. Blood 2005; 106:3308-13.
27. Ringdén O, Remberger M, Aschan J, Lungman P, Lönnqvist B, Markling L. Long-term follow-up of a randomized trial comparing T cell depletion with a combination of methotrexate and cyclosporine in adult leukemic marrow transplant recipients. Transplantation 1994;58:887-91.
28. Yamashita K, Choi U, Woltz PC, Foster SF, Sneller MC, Hakim FT, et al. Severe chronic graft-versus-host disease is characterized by a preponderance of CD4(+) effector memory cells relative to central memory cells. Blood 2004;103:3986-8.
29. Fielding AK, Richards SM, Chopra R Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Medical Research Council of the United Kingdom Adult ALL Working Party; Eastern Cooperative Oncology Group. Blood 2007;109: 944-50.