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Outcomes of second allogeneic hematopoietic stem cell transplantation (SCT) for patients with acute lymphoblastic leukemia (ALL)

LM Poon[1], **Roland Bassett Jr.**[2], **Gabriela Rondon**[1], **Amir Hamdi**[1], **Muzaffar Qazilbash**[1], **Chitra Hosing**[1], **Roy B Jones**[1], **Elizabeth J Shpall**[1], **Uday R. Popat**[1], **Yago Nieto**[1], **Laura L Worth**[3], **Laurence Cooper**[3], **Marcos De Lima**[1], **Richard E. Champlin**[1], **Partow Kebriaei**[1]

[1]Departments of Stem Cell Transplantation and Cellular Therapy, University of Texas M.D. Anderson Cancer Center, Houston, Texas.

[2]Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, Texas.

[3]Pediatrics, University of Texas M.D. Anderson Cancer Center, Houston, Texas.

Abstract

For patients (pts) with acute lymphoblastic leukemia (ALL) who relapse following allogeneic stem cell transplantation (SCT), only a second SCT provides a realistic chance for long term disease remission. We retrospectively analysed the outcomes of 31 patients (pts) with relapsed ALL after a prior allogeneic SCT, who received a second SCT (SCT2) at our centre. With a median follow-up of 3 years, 1- and 3-year progression-free survival (PFS) was 23% and 11% and 1- and 3 years overall survival (OS) rates were 23% and 11%. Twelve patients (39%) of pts were transplanted with active disease, of which 75% of them attained a complete remission (CR). We found a significant relationship between the time to treatment failure following SCT1 and PFS following SCT 2 (p=0.02, HR=0.93/month). In summary, a second transplant remains a potential treatment option for achieving response in a highly refractory patient population. While long-term survival is limited, a significant proportion of pts remain disease-free for up to one year following SCT2, providing a window of time to administer preventive interventions. Notably, our 4 long-term survivors received novel therapies with their second transplant underscoring the need for a fundamental change with the methods for SCT2 to improve outcome

Keywords

Acute lymphoblastic leukemia; allogeneic transplant; second

INTRODUCTION

One of the major causes of death following allogeneic hematopoietic stem cell transplantation (SCT) for patients with acute lymphoblastic leukemia (ALL) is disease

Correspondence: Partow Kebriaei, M.D., University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 423, Houston TX 77030, 713-745-0663 (T), 713-794-4902 (F), pkebriaei@mdanderson.org.

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relapse. In patients with ALL who relapse following SCT, the prognosis is very poor with long term survival of < 10%[1, 2]. Second allogeneic SCT may be effective salvage for a minority of patients and provide durable long term disease remission. However, current data for second transplantation remain limited, and consists mainly of registry analyses of both acute myeloid and lymphoid leukemias[3, 4]. In one of the largest series, Eapen et al reported data from the CIBMTR, and reported 3 year leukemia-free survival (LFS) and overall survivals(OS) of 30% after second SCT for patients with relapsed ALL[3]. In the largest report of patients with ALL who relapse following an allogeneic transplant, Spyridonidis et al showed that only 6 of 93 patients who underwent a second SCT were alive at a median follow up of 46 months[1]. The limitations of registry data, however, precludes closer look at the individual characteristics of patients reviewed. The objective of our study was to retrospectively analyze outcomes and prognostic factors of patients with ALL receiving a second SCT in our institution.

METHODS

Patients and Data collection:

We reviewed all patients with ALL who underwent a second allograft (SCT2) for relapsed ALL following a first allograft (SCT1) between January 1st 1993 and December 31st 2009 at MD Anderson Cancer Center. Data regarding patient characteristics, disease characteristics at diagnosis, as well as disease status at time of SCT1 and SCT2, source of stem cells (bone marrow versus peripheral blood versus cord blood), type of transplant donor, conditioning regimens, graft-versus-host disease (GVHD) prophylaxis, acute and chronic GVHD data for both the first and second allogeneic transplants were collected. This retrospective analysis received institutional review board approval.

Definitions and clinical outcome variables:

Cytogenetic abnormalities were classified as good, intermediate or poor-risk based on previously published reports [5] Myeloablative and reduced intensity conditioning regimens were defined according to the CIBMTR criteria [6]. Criteria for complete response included normal cytogenetics, the absence of circulating blasts, less than 5% marrow blasts, and a platelet count of 100 × 109/L or higher. Standard morphologic criteria were used to diagnose recurrent disease. The disease stage at transplantation was defined using established criteria. Response was documented as best response occurring after day 30 following SCT. Molecular response measured by quantitative polymerase chain reaction (PCR) analysis for BCR-ABL rearrangement was obtained when possible.

Statistical analysis:

Our study examined the cumulative incidence of acute and chronic GVHD, treatment related mortality (TRM), progression free (PFS) and overall survival (OS) after SCT2 for recurrent leukemia. The outcome data was compiled from the date of SCT2 to the date of last contact or death. The cumulative incidence of grades 2–4 acute GVHD was evaluated in all patients and chronic GVHD was evaluated in patients surviving 90 days or longer after second transplant. The diagnosis of GVHD was confirmed by biopsy when feasible but was ultimately determined by clinical presentation. Acute GVHD was clinically graded as

0 to IV based on standard criteria[7], and chronic GVHD was classified as none, limited, or extensive [8].

TRM was defined as death while in continuous remission; patients who died of other causes and patients who survived were censored at last follow up. The method of Kaplan and Meier was used to estimate the distribution of survival parameters[9]. Cox proportional hazards regression analysis was used to assess the association between survival parameters and covariates of interest. The method of Fine and Gray was used to model the association between acute/chronic GVHD and covariates of interest in a competing risks framework[10].

RESULTS

Patients and Transplant Characteristics:

Between 1993 and 2011, a total of 544 first transplants were performed in our center for patients with acute lymphoblastic leukemia, of which 33.8%of the patients subsequently relapsed (n =184). Among these patients, 31 received a second transplant. Treatment details of the remaining 153 patients were not available, but 148 of these patients have died of either disease or salvage therapy related complications. The five remaining patients have relapsed less than one year ago, and are currently undergoing salvage chemotherapy/ radiotherapy, and remain disease free at the time of this analysis. Patient, disease and transplant characteristics at time of SCT 1 and SCT 2 are presented in Table 1. The 31 patients receiving SCT2 had a median age 26 years at time of SCT 2 (range 7–49 years). At the time of SCT2, 61% of these patients were transplanted in CR (n=19), while 39% (n=12) were transplanted with persistent disease. The salvage therapy the patients received prior to SCT2 could be broadly divided into “intensive chemotherapy” if either a standard induction or salvage protocol for ALL was used or “mild” if combinations of steroids and vincristine, +/− asparaginase, a single cytotoxic drug (eg. clofarabine, nelarabine or liposomal vincristine), tyrosine kinase inhibitors, hypomethylating agents or monoclonal antibody therapies were used.Among the 19 patients who received SCT 2 in CR, 12 received intensive salvage chemotherapy prior to SCT, of which the most frequent regimen used was HyperCVAD[11] (n= 9). Seven patients achieved remission following “mild” chemotherapy (vincristine/ steroids +/− asparaginase (n=3), clofarabine (n=2), nelarabine (n=1)), and anti-CD22 antibody therapy (n=1). Of the 12 patients who were transplanted with refractory disease, three were transplanted without any salvage therapy given, while the six failed up to 2 lines of intensive therapy, and three failed 1–2 lines of milder chemotherapy, with no intensive regimen attempted.

Hematopoietic stem cell sources for SCT2 were matched related donors (n=19), matched unrelated donors (n=10) and mismatched cord blood donors (n=2). Donors for SCT 2 were changed in 48% of cases (n=15). As discussed earlier, at the time of SCT2, 61% of patients were transplanted in CR (n=19), while 39% (n=12) were transplanted with persistent disease.

Conditioning regimens and GVHD prophylaxis were determined by departmental protocols at the time of transplant as well as physician preference. In SCT1, the majority of the transplant preparative regimens were classified as myeloablative (n=24, 80% of all

transplants), of which 14 were TBI based and 10 were not, while for SCT2, 65% (n=20) of the transplants were done utilizing reduced intensity conditioning. The median time to treatment failure from the time of first transplant was 9.5 months (range 2.2 – 32.6 months), and median time between transplants was 12.8 months (range 2.7 −36.8 months).

Additional Therapies

In view of the high risk of relapse in these patients, a number of patients were offered additional unconventional measures in addition to a second transplant, in an attempt to consolidate their responses and reduce the risks of disease relapse. These novel measures were offered either on study protocol or at the discretion of the treating physician, and included the addition of a single umbilical cord blood unit in an attempt to augment the graft versus leukemia (GVL) response (n=6), post-transplant maintenance with azacitidine (n=3), and consolidation with DLI following transplant (n=1). One patient received both azacitidine and umbilical cord blood augmentation.

Remission rates, progression and overall survival:

Out of the twelve patients who were transplanted with active disease, nine achieved a second remission (75% CR rates) following SCT2. All except one of these patients (who died of transplant related complications) subsequently had disease relapse and died of their disease. For the 19 patients who were in remission at the time of SCT2, eleven patients died of treatment related complications while in remission, while four had disease progression, and four remain alive and disease free with characteristics as shown in Table 2. The median time of progression from the second transplant for the patients in the study was 4.3 months. With a median follow up of 3 years among survivors (range 1.0 −8.5yrs), PFS at 1yr and 3yrs was 23% and 11% respectively, and OS at 1yr and 3yrs was 23% and 11%, respectively.

On univariate analysis, only the time to progression from the first transplant had an impact of PFS, with longer progression times from SCT 1 associated with longer time to progression from SCT2. We were not able to identify any risk factors that had an impact on TRM or OS, possibly due to the relatively small numbers of patients. The univariate analyses of factors that may affect PFS, OS and TRM are summarized in Table 3.

Outcomes of patients who received additional therapy:

Among the nine patients who received additional therapies in an attempt to consolidate the responses post SCT2, three remain alive and disease free (See Table 2). Four of six patients receiving the umbilical cord unit for augmentation of the GVL effect have died of disease progression, while one died of transplant related complications and one remains alive and disease free. Two of three patients who received post transplant azacitidine have died of disease progression while one remains alive and disease free. The sole patient who received DLI consolidative treatment remains alive and disease free.

Treatment related mortality:

The most important factors which affected early survival were therapy related toxicities, including regimen related toxicity (RRT), infections and acute GVHD. Twelve patients died of treatment-related complications within the first year after SCT 2 (1 yr.-TRM: 41%), half

of them in the first 3 months. Causes of death included infectious complications (n=9, three of which had associated aGVHD and went on high doses of immunosuppressive therapy), pulmonary RRT (n=2), and one death of unknown cause.

Following SCT2, the incidence of grade 2–4 acute GVHD was 26 % (n=8), cumulative incidence of grade 3–4 GVHD was 16% (n=5) and for the patients who survived 100 days, the incidence of chronic limited GVHD was 17% (n=4) and that of extensive chronic GVHD was 22% (n=5)

DISCUSSION

Relapse of acute leukemia following an allogeneic transplant is associated with a generally dismal outcome. We analyzed long-term follow-up data on patients who underwent SCT2 for ALL at our institution. The primary objective of our study, apart from looking at factors affecting TRM, relapse and OS in a consecutive series of patients treated at a single institution, was also to look in greater depth at the characteristics and disease status of this patient population, and possibly clarify some of the issues which the nature of a registry or population based survey would not allow.

Results from registry and multi-institutional retrospective reviews (as summarized in Table 4) have previously suggested that some of the main factors that appear to affect relapse/leukemia-free survival following SCT2 for acute leukemias include longer duration of remission of the first transplant, as well as disease in remission at the time of second transplant, and possibly the SCT conditioning regimen [3, 4, 12] On univariate analysis in our study, we found that longer time to treatment failure from the first transplant was associated with a longer PFS from the second transplant, a finding that is consistent with that seen with registry data (Table 4). Although persistence of disease at time of transplant showed a trend towards a poorer PFS (hazard ratio 1.69, 95% confidence interval 0.78–3.69), we were not able to demonstrate statistical significance for this factor, which might be attributed to our small patient numbers.

Nevertheless, it is interesting to note that of the 12 patients in our study who were transplanted with active disease (of which 9 were refractory to salvage chemotherapy while 3 were brought directly to transplant without further salvage therapy), 9 were able to be brought to a second remission (75%) following the transplant. Amongst patients who relapse following a first transplant for ALL, only a small percentage may eventually be brought to a second transplant. While reasons such as physician or patient preference may contribute to this, one of the key reasons remains the significant potential treatment related mortality or morbidity associated with salvage chemotherapy, that may prohibit patients from a second transplant. Our data suggests that proceeding to allogeneic transplant without salvage chemotherapy remains a feasible way of getting patients back into another complete remission, and may increase the number of patients who may be brought to SCT2. However, it is clear that despite the initial attainment of CR, the duration of remission following SCT2 (TTP of 4.2 months) remains short.

Of our four long-term survivors, all had received some form of additional therapy with their second transplant which was significantly different from SCT1, in the form of a single umbilical cord blood unit in addition to the PBSC to augment the immune response (n=1), consolidation of remission with donor lymphocyte infusion (n=1), a change in the stem cell source for the SCT from cord to mismatched adult unrelated (n=1), and post SCT maintenance therapy with 5-azacytidine (n=1). The small number of patients receiving each of these interventions however makes it difficult for us to draw any definitive conclusions regarding the efficacy of these novel measures in preventing disease relapse. What is clear from our findings however is that by merely repeating the routine transplant procedure of SCT1 in SCT2, especially in patients with disease relapse within 6 months of SCT1, and in patients with active disease, the chances of attaining any form of long term control is extremely slim. This raises the question of whether the risks of a second transplant (39% TRM in our population), as well as the issue of stem cell donations in this setting (especially from a sibling who has donated previously or from a matched unrelated donor) can be justified.

Given however that a significant proportion of patients remain disease-free for up to one year following SCT 2, the role of a second transplant may be in cytoreduction and allowing disease control, thereby providing a window of time for administration of consolidation/ maintenance therapy. The advent of novel therapeutic agents such as the bispecific T cell engaging antibody blinatumomab[13–15] as well as CD22-directed antibody therapy (inotuzumab ozagamicin) have shown significant responses with minimal toxicity in the salvage setting[16, 17]. Incorporation of these agents as consolidation in the second transplant setting may provide options for further disease control post transplantation without added cytotoxicity. In addition, novel adoptive cellular therapies post transplantation such as with CD19-directed chimeric antigen receptor T cell therapies [18, 19], or genetically modified NK cell therapies may provide other important options for disease control in the future[20].

In conclusion, our findings suggest that a second transplant for acute lymphoblastic leukemia does not result in durable disease remission control for majority of patients. The use of novel therapeutic agents and adoptive cellular therapy may improve the poor prognosis in this setting and further research in this area should be considered.

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Table 1:

Patient Characteristics

	SCT 1 (no, %)	SCT 2 (no, %)
No. of patients	31	31
Median Age (yrs), range	24 (6–48)	26 (7–49)
Disease status at SCT		
Complete remission	22 (71)	19 (61)
Persistent Disease	9 (29)	12 (39)
WBC risk Category at Diagnosis *		
Standard risk	14 (35)	NA
High risk	11 (35)	NA
Uunknown	6 (19)	NA
Cytogenetics Risk category at Diag **		
Good risk (hyperdiploid)	3 (10)	NA
Intermediate risk	9 (29)	NA
High risk (t(9;22), t(4;11), hypodiploid and complex)	15 (48)	NA
Unknown	4 (12)	NA
Conditioning regimen	25 (80)	11 (35)
Myeloablative	6 (19)	20 (65)
RIC		
Donor relation		
Matched sibling	21 (68)	19 (61)
Matched unrelated	7 (23)	8 (26)
Mismatched unrelated	0 (0)	2 (6)
Cord Blood	3 (10)	2 (6)
Stem Cell Source		
Bone Marrow	5 (16)	3 (10)
Peripheral Blood	23 (74)	26 (84)
Cord blood	3 (10)	2 (7)
Donor for SCT2		
Same	NA	16
Different	NA	15
aGVHD 2–4,no (%)	5 (16)	8 (26)
aGVHD 3–4,no (%)	1 (3.2)	5 (16)
cGVHD Limited+extensive	9 (29)	8 (26)
cGVHD extensive	6 (19.4)	5 (16)

SCT= Stem Cell Transplant, RIC= Reduced intensity conditioning, GVHD= Graft versus Host disease

* High risk WBC category: > 30X10(9) for B ALL and > 100X10(9) for T ALL. All others considered standard risk.

** High risk cytogenetics: Defined as t(9;22), t(4;11), hypodiploidy or complex cytogenetics.

Good risk cytogenetics: Defined as hyperdiploidy or t(12;21)

Intermediate risk cytogenetics: Defined as all others.

Table 2:

Characteristics of four long term survivors in our study.

	Disease	Conditioning SCT1	Donor source SCT1	Time to relapse from SCT1	Disease status at SCT2	Conditioning SCT2	Donor Source SCT2	Other intervention	Acute and chronic GVHD Post SCT2	Time of follow up since SCT2/ Disease status
Case 1	Pre B ALL Standard risk Diploid cytogenetics	Flu/Mel/ATG	MUD	3 years	CR3	Flu/Bu/ATG	9/10 MUD	Azacitidine maintenance	No acute GVHD Extensive chronic GVHD	2 yrs and 10mths In remission
Case 2	Pre B ALL Standard risk/Diploid cytogenetics	Cy/TBI/ Campath	MSD	2 years	CR3	Flu/Mel	Same MSD	DLI once.	No aGVHD No chronic GVHD	7yrs and 8 mths In remission
Case 3	B lineage ALL High risk/ t(4;11)	Flu/Mel/ Thiotepa/ ATG	DUCBT	1 year	CR2	Flu/ Bu/ATG	9/10 MUD	Nil	No acute GVHD Limited stage cGVHD	3 yrs and 8 mths In remission
Case 4	Pre B ALL High risk/ Complex cytogenetics	Bu/Clo	MSD	100 days	CR3	Flu/Mel	Same MSD	Addition of single umbilical cord unit to improve graft versus leukemia effect	No acute GVHD No chronic GVHD	1 year and 11 months In remission

Pre-B ALL= precursor B acute lymphoblastic leukemia, MUD=Matched unrelated donor, MSD=Matched sibling, DUCBT=Double UCBT, donorFlu= Fludarabine, Mel= melphalan, ATG= anti thymocyte globulin, Bu=busulphan, Clo=Clofarabine, DLI= Donor lymphocyte infusion, GVHD= graft versus host disease

Table 3.

Factors associated with LFS, OS and TRM following second transplants.

i) Results from Univariate Cox Regression Models for Overall Survival						
Parameter	**Level**	**N Patients**	**N Deaths**	**Hazard Ratio**	**95% Confidence Interval (HR)**	**P-Value**
Donor	Same	16	14	-----	-----	0.72
	Different	15	13	0.87	0.40, 1.88	
Conditioning	Ablative	11	9	-----	-----	0.25
	RIC	20	18	1.59	0.71, 3.59	
Time to Progression From SCT1	Per Month	31	27	0.94	0.89, 1.00	0.05
Disease at 2nd Transplant	No	19	15	-----	-----	0.67
	Yes	12	12	1.18	0.55, 2.54	
Time Between Transplants	Per Month	31	27	0.95	0.90, 1.01	0.08
Age	Per Year	31	27	1.01	0.98, 1.05	0.49
aGVHD	Yes	31	27	1.75	0.71, 4.34	0.22
Chronic Extensive GVHD	Yes	31	27	1.30	0.36, 4.74	0.69
ii) Results from Univariate Cox Regression Models for Progression Free Survival						
Parameter	**Level**	**N Patients**	**N Events (Progression/Death)**	**Hazard Ratio**	**95% Confidence Interval (HR)**	**P-Value**
Donor	Same	16	14	-----	-----	0.84
	Different	15	13	0.93	0.43, 2.00	
Conditioning	Ablative	11	9	-----	-----	0.28
	RIC	20	18	1.58	0.69, 3.60	
Time to Progression From SCT1	Per Month	31	27	0.93	0.88, 0.99	0.02
Disease at 2nd Transplant	No	19	15	-----	-----	0.18
	Yes	12	12	1.69	0.78, 3.69	
Time Between Transplants	Per Month	31	27	0.95	0.90, 0.9998	0.05
Age	Per Year	31	27	1.01	0.97, 1.04	0.72
aGVHD	Yes	31	8	2.19	0.88, 5.46	0.09
Chronic Extensive GVHD	Yes	31	5	2.42	0.32, 18.2	0.39
iii) Results from Univariate Cox Regression Models for Treatment Related Mortality						
Parameter	**Level**	**N Patients**	**N Deaths**	**Hazard Ratio**	**95% Confidence Interval (HR)**	**P-Value**
Sibling/MUD Donor	Sibling	19	8	-----	-----	0.56
	MUD	10	3	0.55	0.14, 2.07	
	Cord	2	1	1.58	0.19, 12.9	
Donor	Same	16	6	-----	-----	0.88
	Different	15	6	1.09	0.35, 3.41	

i) Results from Univariate Cox Regression Models for Overall Survival						
Parameter	**Level**	**N Patients**	**N Deaths**	**Hazard Ratio**	**95% Confidence Interval (HR)**	**P-Value**
Conditioning	Ablative	11	4	-----	-----	0.58
	RIC	20	8	1.41	0.42, 4.78	
Time to Progression From SCT1	Per Month	31	12	0.98	0.91, 1.06	0.65
Time Between Transplants	Per Month	31	12	0.99	0.92, 1.06	0.78
Age	Per Year	31	12	1.03	0.98, 1.09	0.27
aGVHD	Yes	31	12	2.99	0.80, 11.2	0.10
Chronic Extensive GVHD	Yes	31	12	1.03	0.06, 17.0	0.98

RIC= Reduced intensity conditioning, GVHD= Graft versus host disease, MUD: matched unrelated donor.

--- represents reference group

Table 4:

Summary of the large studies which looked at the outcomes of second transplants for acute lymphoblastic leukemia.

Author	Study type	Pt Number/ ALL cases:	Patient population	Leukemia free survival (LFS)	Factors associated with improved LFS
Bosi et al[4] 2001	EBMT Registry data	170 pts ALL pts=83	Pts with (AML/ALL/ABL) (ALL=83 pts)	19%(3yrs)	1) Time from HSCT1 to relapse (≥ median, 292 days) 2) Disease in CR at HSCT2 3) TBI at HSCT2 4) Acute GVHD at HSCT1 and 2
Kishi et al 1997[21]	Multi-institutional Survey (Japan)	66 pts ALL pts=27	Pts with AML/ALL/CML/ MDS	19% (1yr) 9% (4yrs)	1) Time from HSCT1 to relapse (>6mths) 2)Time between BMT1 and BMT2 (>6mths) 3) Disease in CR at the time of HSCT2. Presence/ Absence of GVHD did not affect outcomes
Bosi et al 1997[12]	Multi-institutional Survey (Italy)	38 pts ALL pts=17	Pts with AML and ALL	17% EFS (3yrs)	No identified factors affecting leukemia free survival. (Time from transplant to relapse/ time between transplant/ disease status at time of transplant/ GVHD rates did not affect outcomes)
Eapen et al 2004[3]	CIBMTR Registry Data	279 pts ALL=72 pts	Pts with AML/ALL/CML	30% (3yrs)	1) Time from HSCT1 to relapse (>6 mths) 2) Disease in CR at the time of relapse. 3) Age ≤ 20

EBMT=European group for Blood and Marrow Transplantation, CIBMTR= Center for International Blood and Marrow Transplant Research, ALL= Acute lymphoblastic leukemia, AML=Acute myeloid leukemia, ABL= acute biphenotypic leukemia, CML= chronic lymphocytic leukemia, MDS=Myelodysplastic syndrome, EFS= event free survival, HSCT= hematopoietic stem cell transplantation, CR= Complete remission, TBI= Total body irradiation, GVHD= Graft versus host disease.