Outcomes of patients undergoing third hematopoietic cell transplantation for hematologic malignancies

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Abstract

With advancements in novel therapeutics, it is unclear whether third hematopoietic cell transplantation (HCT3) has a place in the treatment of recurrent hematopoietic malignancies. We evaluated patients with hematologic malignancies who underwent HCT3 between 2000–2020. Nine patients, with a median age of 18 (9—68) years at HCT3 with acute myelogenous leukemia ($n=5$), acute lymphoblastic leukemia ($n=2$), myelodysplastic syndrome ($n=1$), or undifferentiated acute leukemia ($n=1$), were identified. The median time between first HCT and HCT3 was 3.9 (0.7—13.6) years. Indication for HCT3 was relapse ($n=8$) or graft failure ($n=1$) after second HCT. At HCT3, seven of nine patients were in complete remission by flow cytometry. All experienced robust donor engraftment by one month after HCT3 ($\geq 90\%$ CD3) while one died at day + 24 of multi-organ failure and was not evaluable for chimerism. In total, eight patients died from relapse ($n=4$), non-relapse, ($n=3$) or unknown ($n=1$) causes at a median of 0.6 (range, 0.1 – 9.9) years after HCT3. After HCT3, estimated overall survival at 6 months, 1 year, and 5 years was 88%, 63%, and 22%, respectively. In this highly selected group, HCT3 provided a treatment option although long-term survival was still dismal.

Introduction

For some patients with high-risk leukemia, treatment consolidation with hematopoietic cell transplantation (HCT) can often lead to long-term cure. While advances have been made in reducing non-relapse mortality (NRM), relapse continues to be a barrier and limits long-term survival after HCT. Multiple options are available to treat relapse after HCT, including withdrawal of immune suppression, donor

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lymphocyte infusions (DLI), natural killer (NK) cell infusions, chimeric antigen receptor T-cell therapy, and other targeted drugs and immunomodulatory therapies to either augment graft-versus-leukemia effects or directly eradicate disease [1–8]. However, once remission has been achieved, many groups aim to re-attempt disease consolidation with a second HCT (HCT2) [9–11]. To that effect, relapse after first HCT (HCT1) is the leading indication for second allogeneic HCT (HCT2) [12]. However, if this relapse occurs within 6 months following HCT1, it is associated with early relapse after HCT2 and overall worse survival compared to transplants in first complete remission [9–11]. While HCT2 is a potentially curative treatment, relapse after HCT2 is often considered incurable. Third HCTs (HCT3) have not been prospectively studied, and few retrospective studies have been reported to guide clinical decision making about the role of this treatment [13, 14]. Furthermore, little is known about the utility of HCT3 in this current era of immunotherapy and directed molecular therapy. Here, we report our institution's experience and outcomes of patients undergoing HCT3.

Materials and methods

Data collection and analysis

Pediatric and adult patients with acute leukemias or myelo-dysplastic syndrome (MDS) who underwent HCT3 from an allogeneic donor between January 1, 2000 through October 1, 2020 from the Fred Hutchinson Cancer Center (FHCC) were included in this study. Patients who received an autologous graft for HCT1 were included. Two patients who received an autologous graft for HCT2 or HCT3 were excluded. Data was collected retrospectively via chart review within the electronic medical record of each patient. The retrospective study was approved by the FHCC Institutional Review Board.

Definitions

Pediatric patients were defined as those < 18 years old, while adults were ≥ 18 years old. Conditioning intensity was defined as either reduced-intensity (RIC; including non-myeloablative regimens) or myeloablative based on previous definitions [15, 16]. Acute and chronic graft-versus-host-disease (GVHD) were defined as previously described [17, 18]. HCT comorbidity index (HCT-CI) scores were calculated using previously published criteria [19]. Neutrophil recovery was defined as the first of three consecutive days of absolute neutrophil count ≥ 500 cells/microliter. Platelet recovery was defined as the first of seven consecutive days of platelet count ≥ 50 000 without platelet transfusions. Relapse was defined as any evidence of disease detection based on either bone marrow morphology and/or flow cytometry. Non-relapse mortality (NRM) was defined as any death after HCT caused by events not due to relapse.

Statistical analysis

Patient outcomes were captured from the date of HCT until death or end of follow-up. For incomplete dates, the first day of the month was used. Data cut-off date was December 31, 2020. Overall survival (OS) was calculated using Kaplan–Meier method. Probabilities of NRM and relapse rate were calculated using cumulative incidence estimates to accommodate competing risks. Descriptive statistics were summarized, and categorical variables were presented as percentages. Median value and range were used for continuous variables with non-normal distribution.

Results

Of the 3,795 total allogeneic HCTs performed, a total of nine patients who received HCT3 between 2000 – 2020 were identified (pediatric, $n = 5$ and adult, $n = 4$). Of note, all

patients were reported to be of White, non-Hispanic/Latino background. Most patients had a diagnosis of acute myeloid leukemia (AML; $n = 5$) or acute lymphoid leukemia (ALL; $n = 2$). One patient had MDS and one had acute undifferentiated leukemia (Table 1).

First HCT

First transplants frequently occurred at outside centers ($n = 6$). Median age at HCT1 was 12 (range 5—56) years. Disease status data was only available for seven patients, all of whom were in a complete morphologic remission. A majority ($n = 7$) of patients received HCT from 10/10 human leukocyte antigen (HLA)-matched related donors and Patient 1 received an autologous HCT. Five patients received bone marrow (BM) grafts, and four patients received peripheral blood stem cell (PBSC) grafts. Most ($n = 8$) patients received myeloablative conditioning regimens. All but one relapsed after HCT1 at a median of 1.3 (range, 0.2 – 3.3) years. Patient 2 with MDS experienced graft rejection (Fig. 1).

Second HCT

The median time between HCT1 and HCT2 was 1.6 (range, 0.6—3.7) years, with the median time from relapse to HCT2 of 4.6 (range, 1.9—9.6) months. The median age at HCT2 was 16 (range, 7—57) years. Patient 2 with MDS who experienced graft rejection following HCT1 received DLI as an unsuccessful attempt to improve donor engraftment before proceeding to HCT2. Four patients received HCT2 at outside centers. Most patients received HCT (PBSC, $n = 5$ and marrow, $n = 1$) from 10/10 HLA-matched related donors ($n = 4$, two of which were the same donor as HCT1) or 10/10 HLA-matched unrelated donors ($n = 2$). Two pediatric patients received cord blood transplants that were HLA-matched 5/6 or 6/6. Patient 9 was transplanted outside of our center and received an HLA-haploidentical donor with unknown stem cell source. Four patients (44%) received myeloablative conditioning regimens. Eight patients relapsed after HCT2 at a median of 0.97 years (range, 0.39 – 11.78; Fig. 1), while Patient 3 with AML experienced de novo graft failure.

Third HCT

All patients received HCT3 at our center. Median time between HCT2 and HCT3 was 1.9 (range, 0.1 – 12.6) years, with median time from relapse to HCT3 of 6.8 (range, 3.8 – 20.6) months. The median age at HCT3 was 18 (range, 9 – 68) years. Details regarding HCT3 characteristics are described in Table 1. Patient 3 underwent HCT3 with the same 10/10 HLA-matched related donor as used in HCT2.

Table 1 Patient demographics and HCT3 characteristics (*n* = 9)

Age at HCT3, years	
Median (range)	18 (9−68)
Sex, n	
Female	3
Male	6
Race, n	
White	9
Ethnicity, n	
Not hispanic or latino	9
Disease, n	
Acute myelogenous leukemia	5
Acute lymphoblastic leukemia	2
Myelodysplastic syndrome	1
Acute undifferentiated leukemia	1
Karnofsky/Lansky score at HCT3, n	
100	2
90	2
80	4
70	0
60	1
HCT-CI Score at HCT3, n	
0	2
1	0
2	2
3	4
4	0
5	0
6	1
Disease status at HCT3, n	
Complete remission	7
Residual disease[1]	2
Donor source at HCT3, n	
HLA-haploidentical	3
Cord Blood	3
10/10 HLA-matched related PBSC	1
10/10 HLA-matched unrelated PBSC	1
9/10 HLA-matched unrelated PBSC	1
Conditioning Regimen at HCT3, n	
Non-myeloablative/reduced-intensity	
Fludarabine and TBI 3 or 4 Gy	3
Fludarabine, Cytarabine, and TBI 2 Gy	3
Myeloablative	
Busulfan and Clofarabine	1
Treosulfan, Fludarabine, and TBI 2 Gy	1
Fludarabine, Cytarabine, and TBI 12 Gy	1
GVHD Prophylaxis at HCT3, n	
Cyclosporine + MMF	4
Cyclosporine + MMF + Sirolimus	1
Tacrolimus + MMF	1
Tacrolimus + MMF + Cyclophosphamide	3

[1]Residual disease is defined as having any presence of disease by flow cytometry

Abbreviations: *Gy* gray *HCT3* third hematopoietic cell transplantation *MMF* mycophenolate mofetil *PBSC* peripheral blood stem cell *TBI* total-body irradiation

Three patients received HLA-haploidentical transplantation, and all three received post-HCT infusions of donor-derived natural killer (NK) cells on a clinical trial. All cord blood recipients (*n* = 3) underwent myeloablative conditioning while all other patients (*n* = 6) received RIC conditioning (Table 1). Five patients had HCT-CI scores of ≥ 3, and two patients had HCT-CI scores of 2, while two patients had HCT-CI scores of 0. For the seven patients who had comorbidities contributing to HCT-CI scores, all had moderate (*n* n = 6) or severe (*n* = 1) pulmonary involvement. One patient had moderate to severe hepatic and psychiatric comorbidities. Two patients had an infection preceding transplant, and one patient had cardiac dysfunction. Seven of the patients were in complete remission by flow cytometry at time of HCT3. Patient 6 had refractory AML and was transplanted after clearance of peripheral blasts (marrow was not checked), and Patient 7 had 0.07% residual marrow disease at time of HCT3.

Engraftment after HCT3

All patients (*n* = 9) achieved neutrophil engraftment at a median of 16 (range, 13−48) days following HCT3. Eight patients were evaluable for donor chimerism at one month and all achieved CD3 engraftment (≥ 90%). Seven patients achieved platelet engraftment at a median of 17 (range, 10 − 33) days following HCT3. Two patients did not achieve platelet engraftment before death. In those evaluable, there were no primary or secondary graft rejections or failures after HCT3.

GVHD after HCT3

Following HCT3, eight patients were evaluable for the development of acute and chronic GVHD. Six patients had a maximum acute GVHD grade of II, and one patient had maximum acute GVHD score of III. This latter patient received an HLA-haploidentical marrow graft. For chronic GVHD, one patient developed limited chronic GVHD and had received a 10/10 HLA-matched related PBSC graft. One patient developed extensive chronic GVHD and had received a 9/10 HLA-mismatched unrelated PBSC graft.

Relapse and survival outcomes after HCT3

Five patients relapsed following HCT3. Median time to relapse after HCT3 was 5.2 (range, 1.8−5.9) months. After HCT3, estimated relapse rates at 6 months, 1 year, and 5 years post-HCT3 were 63% (Fig. 2a). Estimated overall survival at 6 months, 1 year, 2 years, and 5 years post-HCT3 was 88%, 63%, 33%, and 22% respectively (Fig. 2b). Overall, eight patients died at a median time of 0.6 (range, 0.1−2.9) years after HCT3. Four deaths were due to relapse, three

Fig. 1 Swimmer plots depicting clinical events and outcomes of nine patients following (**A**) first hematopoietic cell transplant (HCT), (**B**) second HCT and (**C**) third HCT until death or date of last follow-up
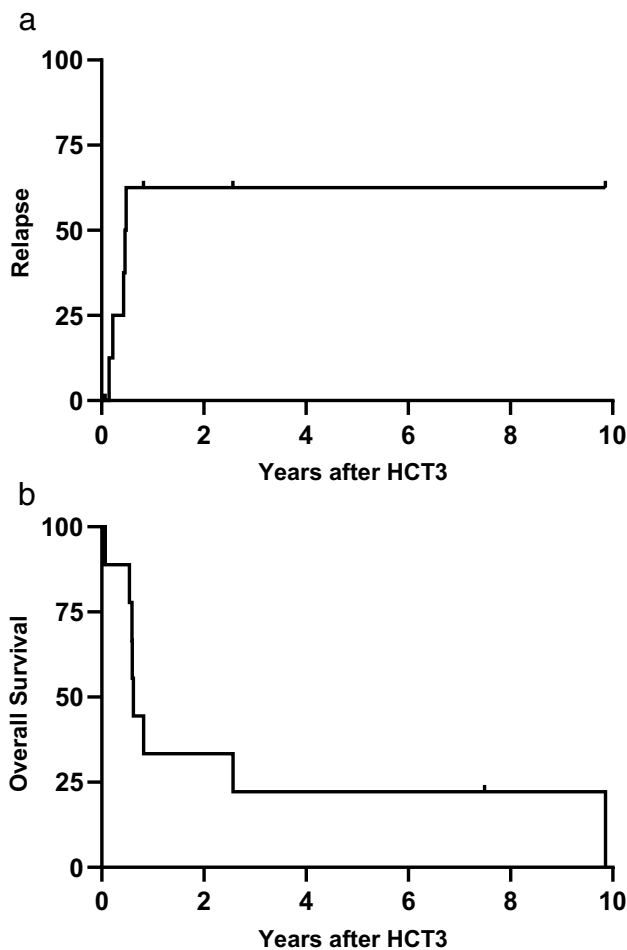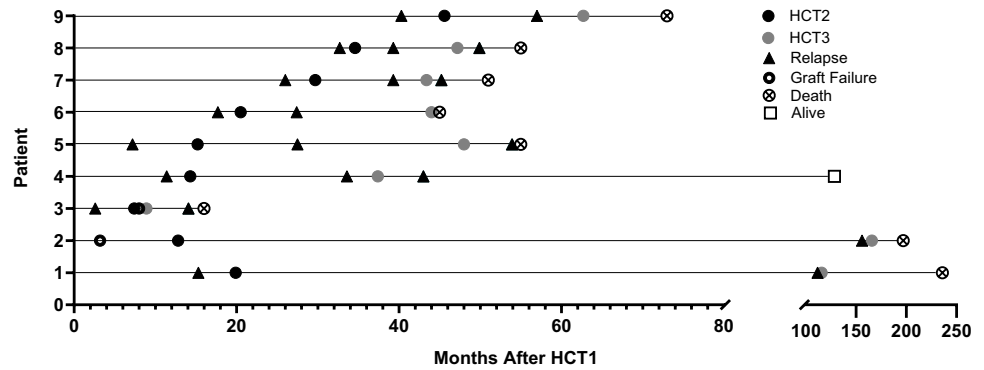

Fig. 2 Cumulative incidence of relapse (**A**) and probability of overall survival (**B**) for nine patients following third hematopoietic cell transplant (HCT3)

were due to NRM, and one was unknown (Table 2). NRM causes of death included veno-occlusive disease with intraperitoneal and intrapleural hemorrhages, multi-system organ failure (acute lung injury, renal failure, and septic shock), and chronic GVHD. Out of the eight deaths, two (Patients 3 and 6) occurred early at 0.1- and 0.5-years after HCT3 and occurred

in patients with HCT-CI scores of 2 and 3, respectively. The three patients with the longest overall survival (Patients 1, 2, and 4) had scores of 0, 0, and 2, with moderate/severe lung disease contributing to the HCT-CI score of 2. Patient 1 survived until 9.9 years after HCT3 and died of unknown causes, and Patient 4 was treated for post-HCT relapse and is currently alive at 7.5 years following HCT3 (Table 2).

Discussion

This study aimed to explore the characteristics of patients who underwent HCT3 and their outcomes at a single center. Our experience suggests that HCT3 is rarely used (0.2% of HCTs conducted at FHCC during the time period studied) but it is possible to have long-term survival in rare cases. Three patients were alive at two years, and of these three, two patients remained alive at five years after HCT3. Factors previously reported to be associated with improved OS after HCT3 included high performance status, robust remission status at time of transplant, and longer length of time from HCT2 to relapse [13, 14]. In our small study, we had a single long-term survivor who was able to maintain durable remission after CAR-T therapy.

The European Society for Blood and Marrow Transplantation reported on a cohort of 45 adult patients who underwent HCT3 from 2001−2018. They included only patients who underwent HCT3 for relapse or disease progression. The 1- and 2-year OS was 20% and 7% and progression-free survival was 11% and 2%, respectively. On univariate analysis, an improved OS was noted when the Karnofsky score was > 80, an unrelated donor was used, and there was at least one donor change between HCT1 to HCT3. Authors further speculated that patients with AML may be better candidates for HCT3 [13]. In our study, the only patient who survived after HCT3 had ALL; however, this patient received salvage CAR-T treatment for recurrent disease after HCT3 and is now alive more than 7 years after HCT3. The role that disease type plays in determining potential HCT3 benefit remains unclear.

Table 2 Transplant course by patient

Pt #	Disease	HCT#	Age at HCT	Year of HCT	Disease status at HCT	HCT-CI	Conditioning intensity	Donor	HCT outcome	Time to death or last follow-up after HCT3 (years)
1	AML	1	56	2001	CR	–	MAC	Auto PBSC	Relapse	
		2	57	2002	CR	–	RIC	10/10 MRD PBSC	Relapse	
		3	65	2010	CR	0	RIC	10/10 URD PBSC	Unknown cause of death	9.9
2	MDS	1	54	2003	–	–	RIC	10/10 MRD PBSC	Graft failure	
		2	56	2004	–	–	MAC	10/10 MRD PBSC[1]	Relapse	
		3	68	2016	CR	0	RIC	9/10 URD PBSC	NRM death	2.6
3	AML	1	32	2008	CR	0	MAC	10/10 MRD PBSC	Relapse	
		2	33	2009	CR	2	RIC	10/10 MRD PBSC	Graft Failure	
		3	33	2009	CR	2	RIC	10/10 MRD PBSC[2]	Relapse, death	0.6
4	ALL	1	9	2010	CR	0	MAC	10/10 URD BM	Relapse	
		2	11	2011	CR	2	RIC	10/10 URD PBSC	Relapse	
		3	13	2013	CR	2	RIC	Haplo BM	Relapse, alive	7.5
5	ALL	1	9	2011	CR	0	MAC	10/10 MRD BM	Relapse	
		2	10	2013	CR	2	MAC	5/6 UCB	Relapse	
		3	13	2015	CR	3	RIC	Haplo BM	Relapse, death	0.5
6	AML	1	5	2010	CR	–	MAC	10/10 MRD BM	Relapse	
		2	7	2012	CR	–	MAC	10/10 URD BM	Relapse	
		3	9	2014	RD	3	MAC	5/6 and 4/6 UCB	NRM death	0.1
7	AML	1	12	2010	CR	–	MAC	10/10 MRD BM	Relapse	
		2	15	2013	CR	–	MAC	6/6 UCB	Relapse	
		3	16	2014	RD	3	RIC	Haplo BM	Relapse, death	0.6
8	AML	1	23	2012	CR	1	MAC	10/10 MRD PBSC	Relapse	
		2	26	2015	CR	0	RIC	10/10 MRD PBSC[1]	Relapse	
		3	26	2016	CR	3	MAC	4/6 and 4/6 UCB	Relapse, death	0.6
9	Undiff	1	12	2013	–	0	MAC	10/10 MRD BM	Relapse	
		2	16	2017	–	5	RIC	Haplo[3]	Relapse	
		3	18	2018	CR	6	MAC	4/6 UCB	NRM death	0.8

[1]same donor as 1st HCT, [2]same donor as 2nd HCT, [3]Unknown stem cell source

"–" indicates missing data

Abbreviations: *BM* bone marrow *CR* complete remission haplo, haploidentical *MAC* myeloablative conditioning *MRD* matched related donor *NRM* non-relapse mortality, *PBSC* peripheral blood stem cells, *RD* residual disease, *RIC* reduced-intensity conditioning, *UCB* umbilical cord blood, *URD* unrelated donor

A retrospective study by Kobayashi et al. reported patients from the Japanese national HCT database [14]. In this study, the outcomes of 253 adults undergoing HCT3 for relapsed or refractory acute leukemia between the years of 1994 and 2017 were described. Of the 253 patients, only 20% were in remission at the time of HCT3. OS was 17% and 11% at 2 and 3 years respectively, with median OS of 4.9 months. The authors concluded that remission status and longer duration of remission after HCT2 were the strongest predictors of improved OS. Multivariate analysis revealed that having grade 1 GVHD after HCT2, being > 2 years from HCT2 to relapse, and having ECOG performance score < 2 at time of HCT3 were all associated with improved OS. However, even for patients in CR, a poor performance status was associated with earlier mortality.

Pretransplant comorbidities play an important role in predicting OS after transplant. Sorror et al. previously established that HCT-CI scores ≥ 3 conferred increased risk of death from non-relapse causes [20]. In our study, five of the nine patients had HCT-CI scores ≥ 3 prior to third HCT. It has also been well-established that achievement of deep remission prior to HCT1 provided the most optimal chance for prevention of relapse, and it has been inferred that this remains important for any subsequent HCTs. In our cohort, seven patients were in complete remission by flow cytometry while two had presence of disease (0.07% and refractory disease with resolution of peripheral blasts) at HCT3. The EBMT and Japanese cohorts included approximately 76−80% of patients undergoing HCT3 with refractory or active disease, with 2-year OS of the entire cohort of 7% and 17%, respectively, after HCT3 [13, 14]. In the Japanese registry, a multivariate analysis was performed demonstrating that not being in a CR at time of HCT3 was associated with an increased risk of relapse following HCT3 (HR: 1.89 and 95% CI: 1.15−3.09; $p = 0.012$). Kobayashi et al. also found that > 2 years from HCT2 to time of relapse was associated with improved OS [14].

Cord blood and haploidentical grafts comprised most donor grafts for HCT3 in our study. It has been suggested that alternative donor sources could offer improved outcomes for subsequent transplants [10, 14, 21–24]. Rank et al. did find benefit in progression-free and OS with at least one donor change over the course of HCT1 to HCT3 [13]. While our numbers are too small to evaluate any associations with outcomes, all patients in our cohort underwent at least one donor change over the course of three HCTs.

While single center data can be advantageous in providing a study population that has received similar clinical care, our study has several limitations including small sample size, retrospective data collection, and limited data from HCT1 and HCT2 which were performed at outside transplant centers. Additionally, we noted that all patients were of White, non-Hispanic/non-Latino race and ethnicity. As HCT3 is a rare treatment, efforts relating to resource utilization and access of treatments for all patients need to be considered and appropriately offered. However, our small sample size is also indicative of the rarity that third HCTs are performed. This small sample size did not allow the opportunity to perform additional analyses regarding factors predictive of improved survival; however, our results are in line with previously reported outcomes for HCT3.

Though HCT3 may prolong survival in rare cases, we do not know how HCT3 compares to other treatment options including cellular immune therapies or chemotherapy including tyrosine kinase inhibitors, hypomethylating agents, and novel regimens when considering long-term efficacy and quality of life. Additionally, the use of maintenance therapies after HCT3 should be studied and considered for individual patients to sustain a durable remission induced or consolidated by HCT [25, 26].

In summary, HCT3 may prolong survival in rare patients who have relapsed after HCT2. Further longitudinal studies evaluating duration of remission status and quality of life following HCT3 are needed to understand the benefit of this treatment option for patients in this unique situation.

Author contributions ERC was responsible for acquisition, analysis or interpretation of data and drafting of the manuscript and critical revisions. CS was responsible for study concept and design and acquisition, analysis or interpretation of data. FM, AD, MB & BMS were responsible for the drafting of the manuscript and critical revisions. MST was responsible for study concept and design, acquisition, analysis or interpretation of data, and drafting of the manuscript and critical revisions.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate The retrospective study was approved by the Fred Hutchinson Cancer Center Institutional Review Board in accordance with the Declaration of Helsinki.

Competing interests The authors declare no competing interests.

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