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Second Allogeneic Hematopoietic Cell Transplantation for Relapse After First Allografts

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Abstract

We analyzed outcomes of 126 patients with hematologic malignancies, who relapsed after first allogeneic hematopoietic cell transplantation (HCT) and received subsequent allografts. In 17 cases, the original donors were utilized, while in 109 cases different donors were identified. The 2-year overall survival (OS), relapse, and non-relapse mortality (NRM) rates were 33%, 42%, and 33%, respectively. Patients with early relapse after first allogeneic HCT (within 100 days vs. 100 days to 12 months vs. >12 months) had higher relapse rates (50% vs. 47% vs. 34%, respectively; $p=0.01$) and worse OS (15% vs. 25% vs. 45%, respectively, $p=0.005$) at 2 years after second allogeneic HCT. In conclusion, second allogeneic HCT should be considered in patients who relapse after first allografts, especially in those who relapse after more than a year. Utilizing a different donor for the second allotransplant including umbilical cord blood or HLA-haploidentical, related donors did not adversely impact outcomes.

Keywords

allogeneic hematopoietic cell transplantation; post-transplant relapse; 2nd allotransplant

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INTRODUCTION

Advances in the field of allogeneic hematopoietic cell transplantation (HCT) have resulted in the reduction of treatment-related mortality over the past two decades, but relapse has remained the leading cause of failure for most hematologic malignancies [1], especially in patients receiving reduced-intensity or nonmyeloablative conditioning regimens. The prognosis of patients who experience post-transplant relapse is generally poor. Currently there is no consensus regarding the treatment of patients with post-transplant relapse. Salvage chemotherapy (with or without molecularly targeted therapy when available), withdrawal of immunosuppression, and donor lymphocyte infusions (DLI) have been used as interventions with moderate success, resulting in 2-year overall survivals of 3% to 19%, depending on timing of post-transplant relapse [2].

A second allogeneic HCT has been described as a potential salvage procedure that could lead to long-term disease control. Several retrospective reports, including a large EBMT analysis [3] with likely overlapping subgroup analyses [4, 5, 6] have described the experience with second allogeneic HCT for relapse after first allografts. Similar to non-transplant interventions, a relatively consistent finding in these studies was that duration of remission after the first allograft was the most important factor influencing disease free (DFS) and overall survivals (OS) after a second HCT. Another important factor was the remission status at the time of second allografts. While most analyses attempted to determine whether conditioning regimen intensity, graft source, or other patient or disease-related factors had any effect on long-term outcomes, there is no current consensus on these variables, likely due to the retrospective nature of these studies in highly selected patient populations.

An interesting question is whether switching to a different donor for the second allograft will result in improved outcomes. Several groups of investigators have addressed this question without conclusive answers, likely owing to insufficient statistical power in these retrospective analyses [7, 8]. Emerging data on the use of easily accessible, alternative donor sources, such as umbilical cord blood units [9, 10] or HLA-haploidentical family members [11, 12], may promote the practice of switching donors for second allotransplants.

Here, we summarize our single-institution experience of second allogeneic HCT in patients who experienced relapse after their first allografts. What differentiates our experience from other retrospective analyses of second allogeneic HCT is that, as a general practice, when available, a different donor was used for patients who experienced both disease relapse and acute or chronic graft-versus-host disease (GVHD) after first allogeneic HCT, which represents the majority (87%) of patients. In addition, unlike in other previously reported series, T-cell replete marrow or peripheral blood stem cell (PBSC) grafts were utilized for second HCT, without incorporating anti-thymocyte globulin (ATG) in the conditioning regimen (with one exception). We also examined the effect of treosulfan-based conditioning regimens on outcomes after second allogeneic HCT after this drug became available at our institution in 2005.

PATIENTS AND METHODS

Study Design

This retrospective analysis included 126 consecutive patients with hematologic malignancies who experienced disease relapse after an allogeneic HCT and who underwent a second/salvage allogeneic HCT between March 1998 and December 2014 at the Fred Hutchinson Cancer Research Center (Fred Hutch). A retrospective chart review and waiver of informed consent for chart review were approved by the institutional review boards of the FHCRC. The main objectives were to assess feasibility, efficacy, and safety, using overall OS, relapse rate, and non-relapse mortality (NRM) as objectives. Results were analyzed as of October 1, 2015. Of note, early outcomes of 20 patients included in the current cohort were previously reported by Salit et al. in a separate publication [10].

Definitions

Second allogeneic HCT was defined as a conditioning regimen followed by infusion of allografts and administration of GVHD prophylaxis. Remission, relapse [13], persistent disease [14], CML in chronic and accelerated phases [15, 16], blast crisis, conditioning regimen intensity [17, 18], and HCT-specific comorbidity index (HCT-CI) [19] were defined as previously described. Acute and chronic GVHD were graded as previously described [20, 21]. As a general practice at our institution, when available, a different donor was utilized for patients who experienced both disease relapse and acute or chronic GVHD after first allogeneic HCT.

Causes of Death

In patients who relapsed or progressed, relapse or progression was listed as primary cause of death regardless of other associated events. All deaths occurring in the absence of relapse/progression were considered non-relapse mortality (NRM).

Statistical Analysis

Summary statistics were reported using standard measures as appropriate for categorical and continuous data. The primary endpoint of this retrospective analysis was overall survival. Secondary endpoints included: relapse/progression, NRM, and acute and chronic GVHD.

Overall survival was estimated using the Kaplan-Meier method. Cumulative incidence estimates were used for relapse/progression, acute and chronic GVHD, and NRM, treating death prior to the event of interest as a competing risk for relapse and acute GVHD, and relapse as a competing risk event for NRM [22]. Comparisons between hazards of time to event outcomes were analyzed using Cox regression. All reported p-values are two-sided.

RESULTS

Patient, First and Second Transplant Characteristics

Patient characteristics are summarized in Table 1. Of the 126 patients, two relapsed after their second allogeneic HCT and underwent a third allotransplant; in these cases the two most recent HCTs were included in the analysis. Four patients underwent second allogeneic

HCTs to treat donor-derived MDS (n=2) or AML (n=2) after their first allografts. Three patients had autologous HCTs before their first allogeneic HCTs. There were 67 males and 59 females. Median age of patients was 32 (range 3 to 69) years. Diagnoses included acute myeloid leukemia (AML), n=66; acute lymphoid leukemia (ALL), n=26; myelodysplastic syndrome (MDS), n=13; chronic myeloid leukemia (CML), n=5; non-Hodgkin lymphoma (NHL), n=4; Hodgkin lymphoma, n=3; myelofibrosis, n=5; chronic lymphoid leukemia (CLL), n=3; and multiple myeloma, n=1.

Characteristics of the first allogeneic HCT are summarized in Table 2. At the time of their first allogeneic HCT, 78 patients were in remission, including three patients with CML in chronic phase. Thirty-four patients experienced relapse or persistent disease, and one patient with CML was in accelerated phase. The disease stage of 13 patients at the time of first allotransplant is unknown. A total of 90 patients received high-dose conditioning with total body irradiation (TBI, n=56) or busulfan-based regimens (n=34). The conditioning regimen of six patients consisted of treosulfan (14 g/m²/day × 3 days) and fludarabine only; in five patients, low-dose (2 Gy) TBI was added to the treosulfan and fludarabine regimen. Sixteen patients received nonmyeloablative conditioning with 2 or 3 Gy TBI with (n=13) or without (n=3) fludarabine. Additional details of conditioning regimens for first allotransplants are described in Table 2. Grafts were from HLA-identical siblings (n=64), single HLA-antigen mismatched siblings (n=2), HLA-matched unrelated donors (n=35) and HLA-mismatched unrelated donors (n=7, including 2 patients who received double unrelated umbilical cord blood (UCB) grafts). The stem cell sources were granulocyte colony-stimulating factor-mobilized peripheral blood stem cell (PBSC; n=62), marrow (n=53), or UCB (n=2).

Characteristics of the second allogeneic HCT are also summarized in Table 2. Second HCTs were performed at a median of 23 (range 2 to 186) months after the first or preceding HCT. At the time of second allotransplants, 85 patients were in remission, while 41 patients were in relapse or had persistent disease, including two CML patients in accelerated phase and two CML patients in blast crisis. Pre-transplantation comorbidities prior second HCT were determined retrospectively using the HCT-CI. The HCT-CI was 0 or 1 in 36 patients, 2 or 3 in 43 patients, and 4 or higher in 47 patients. Data on performance state at the time of second allogeneic HCT were available on 93 patients, the median Karnofsky score (range) was 90 (60–100; n=77) and the median (range) Lansky score was 90 (80–100; n=16).

Fifty-one patients received a low-dose TBI-based conditioning regimen. Twenty-four patients received high-dose conditioning regimens (TBI-based, n=16; or busulfan-based, n=10). Twenty-five patients underwent treosulfan-based conditioning regimens (treosulfan 14 g/m²/day × 3 days), with (n=16) or without (n=9) low-dose TBI (2 Gy). Additional details of conditioning regimens for second/salvage HCTs can be found in Table 2.

Donors for second/salvage HCT were the same as for the first HCT in 17 (13%) cases and different for 109 (87%) patients. Donors were HLA-identical siblings (n=25), single HLA-antigen mismatched siblings (n=2), HLA-matched unrelated donors (n=59, including an HLA-matched UCB unit), HLA-mismatched unrelated donors (n=9) or HLA-haploidentical family members (n=11), while 20 patients received mismatched UCB. The stem cell sources were PBSC (n=85), marrow (n=20), or UCB (n=21).

GVHD

All patients were assessed for acute GVHD. The cumulative incidences of acute GVHD, grades II–IV and III–IV, were 67% and 17%, respectively (Figure 1(A)). The cumulative incidence of chronic GVHD was 30% and 34% at 2 and 4 years after second HCT, respectively (Figure 1(B)).

Survival, Relapse, and Non-relapse Mortality

The median follow-up among surviving patients was 48 (range 2 to 186) months. The estimated overall OS was 33% at 2 years and 27% at 4 years after a second HCT (Figure 2). The cumulative incidence of relapse was 42% both at 2 years and 4 years after second allogeneic HCT, while the cumulative incidences of NRM were 33% and 35% at 2 and 4 years after second allografts, respectively (Figure 2(A)).

When the analysis was restricted to patients with AML, who represented 52% of the study population, 2-year OS, relapse rate, and NRM were 28%, 43%, and 32%, respectively (Figure 2(B)).

Among four patients who underwent second allogeneic HCTs to treat donor-derived MDS (n=2) or AML (n=2) after their first allografts, two were alive at last follow up, one patient died of relapse on post-transplant day 136, and one patient died of infections on post-transplant day 40 (in the absence of GVHD).

Prognostic Factors

Within the limitations of the small number of patients studied, in univariate analyses the only factor with a statistically significant impact on OS was the time interval between first HCT and relapse after first HCT, i.e. the duration of remission after first allogeneic HCT. The 2-year OS was 45% in patients who experienced disease relapse more than one year after their first allografts vs. 25% and 15% in those who relapsed between day +100 and 1-year after first HCT or those who relapsed in less than 100 days after their first allografts, respectively (P=0.005; Figure 3(A)). This outcome was mostly driven by a statistically significant difference in relapse incidence after the second allogeneic HCT. Patients who relapsed within 100 days after their first allografts had a higher relapse incidence after second allogeneic HCT than those who experienced relapse within the range of day +100 through 1 year, or at >1 year after second HCT: 50% vs. 47% vs. 34%, respectively (P=0.01; Figure 3(B)). There was a slight trend toward increased NRM after second allogeneic HCT in the group of patients with early relapse after first allografts; however, this did not reach statistical significance (35%, 34%, and 31%, respectively, in patients experiencing relapse less than 100 days, between 100 days and 1 year, and >1 year after first allografts; P=0.14). Within the group of patients with longer intervals between first and second HCTs, 30 patients had their second allotransplant within 1–3 years following their first HCT, and 29 patients had more than 3 years between their two allotransplants. There were no statistically significant differences between these groups for any of the endpoints, which may reflect a limitation of the small sample size.

There was a strong association between performance state at the time of second HCT and NRM in univariate analyses, which translated into a statistically significant difference in OS, although performance state data were available only on 93 patients (Karnofsky, n=77; Lansky, n=16). Patients with a Karnofsky or Lansky performance score > 80 had statistically significantly improved NRM and OS than those with Karnofsky or Lansky performance 80, 26% vs. 43% and 43% vs. 13%, respectively. As expected, there was no association between performance state and relapse rates.

Additional patient-, disease- and transplant-related factors, such as recipient age, lymphoid vs. myeloid malignancy, HCT-CI, conditioning intensity, donor type, utilizing the same vs. different donors for first and second allogeneic HCT, or transplant era (1998–2004 vs. 2005–2009 vs. 2010–2014) did not have statistically significant impacts on OS, relapse, or NRM (Figure 4). Remission status at the time of a second HCT in this cohort did not have an effect on relapse incidence after the second HCT, but did have a statistically significant impact on NRM (28% vs. 42%, respectively, in patients in remission vs. with relapsed disease; $P=0.02$), which translated into a trend towards improved 2-year OS (35% vs. 26%, respectively, $P=0.07$), in patients in remission vs. with relapsed disease at the time of the second allogeneic HCT. When comparing patients with acute leukemia (myeloid and lymphoid) to those with other diagnoses, we observed trends for increased risk of relapse (47% vs. 25% in patients with acute leukemia vs. other diagnoses, respectively, at 2 years; $P=0.09$) and for decreased NRM (29% vs. 45%, respectively, at 2 years; $P=0.47$), resulting in similar 2-year OS in patients with acute leukemia vs. other diagnoses (34% vs. 30%, respectively; $P=0.47$).

Finally, due to previously observed improved outcomes with treosulfan-based conditioning regimens [23, 24], we explored the possible impact of these regimens in this setting. While limited by small numbers (only 25 patients in this cohort received treosulfan-based conditioning in preparation of their second allografts), we observed a trend toward improved NRM (20% vs. 36%, respectively, at 2 years in patients receiving treosulfan vs. non-treosulfan based regimens; $P=0.09$), which translated into improved OS (51% vs. 29%, respectively, at 2 years in patients receiving treosulfan vs. non-treosulfan based regimens; $P=0.06$).

DISCUSSION

Based on our retrospective review, we conclude that giving a second allogeneic HCT for relapse after first allografts is feasible and can be carried out safely in patients with hematologic malignancies, regardless of the underlying diagnosis (i.e. acute leukemias, NHL, etc.). Graft-versus-host disease rates (acute, grades II-IV, and III-IV, 67% and 17%, respectively, and chronic GVHD of 34%), were similar to those observed after first allografts. While we recognize the intrinsic selection bias hidden in all retrospective studies, our 2-year OS and NRM rates of 33% each compared well to large, registry-based studies of second allografts performed for relapsed hematologic malignancies (OS of 15% to 28% at 2–5 years) [3, 7, 8]. When the analysis was restricted to patients with AML, who represented 52% of the study population, outcomes were similar to those of the whole cohort.

As in other reports [7, 8], relapse was the leading cause of treatment failure after second allografts, having a 42% 2-year relapse rate. We also found in univariate analyses that a longer duration of remission after first allografts predicted a lower risk of relapse compared to patients who relapsed earlier, which translated into an improved long-term survival rate. Interestingly, remission status at the second HCT did not affect the relapse incidence after the second HCT. Equally puzzling, patients who were not in remission had a statistically significantly increased risk for NRM and a trend towards increased overall mortality. This finding could be a reflection of an overall greater fragility of this patient population having decreased tolerance to more aggressive interventions. As expected, patients with higher Karnofsky or Lansky performance scores at the time of second HCT had improved outcomes, due to decreased NRM. Unlike large retrospective analyses, in our single-institution study we were able to calculate HCT-CI scores to account for existing comorbidities at the time of second HCTs. In this highly selected patient population, however, we did not observe a statistically significant association between HCT-CI and NRM, although there was a non-significant trend of worse OS in patients with an HCT-CI of 4 or more. Furthermore, in our univariate analyses, patient age, disease category (myeloid vs. lymphoid), regimen intensity, and donor type did not have statistically significant impacts on outcomes. These findings again, are likely owing to the inherent selection bias present in most retrospective analyses. In addition, there was a non-significant trend towards decreased relapse and NRM rates observed with treosulfan-based conditioning regimens, which resulted in an improved OS with borderline statistical significance in this patient population, raising the possibility of a role for treosulfan-based regimens in this scenario. Future studies to test this observation may be warranted based on our analysis.

The question whether to use the same or different donors for second allogeneic HCT has been addressed in numerous previous analyses [3, 7, 8]. With a few exceptions [8], the majority of the large registry-based studies reported that the same donors were utilized for first and second allotransplants in a large proportion of patients [3, 7]. The majority of current patients (87%) received second allografts from different donors, and outcomes were comparable to those with received grafts from the same donor, demonstrating no adverse effect of switching the donor in this retrospective analysis. Emerging data on the use of alternative donor sources that may be more easily accessible, such as umbilical cord blood units [9, 10] or HLA-haploidentical family members [11, 12], may shift future practice towards switching donors for second allotransplants.

In summary, a second allogeneic HCT should be considered in patients whose malignant hematologic disease relapsed after a first allograft, with outcome rates remaining similar for OS and NRM to those reported after first allogeneic HCT. Patients who experience relapse more than a year after their first allogeneic HCT seem to benefit most from this approach. Similarly to first allotransplants, relapse remains the leading cause of treatment failure after second allogeneic HCT. Currently published retrospective data by others and us show no benefit of utilizing the same vs. different donors for second allogeneic HCT, although there is emerging evidence that HCT from readily available alternative donor sources, such as umbilical cord blood units or HLA-haploidentical family donors can lead to long-term survival. The incorporation of treosulfan into the conditioning regimen of second allotransplants may be beneficial.

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Figure 1. Cumulative incidences of (A) acute and (B) chronic GVHD following second HCT.

Figure 2. Overall survival, relapse/progression, and non-relapse mortality following 2nd HCT in (A) the whole cohort, n=126; and (B) in AML patients, n=66.

Figure 3. The impact of the time between 1st HCT and 1st post-transplant relapse on (A) relapse and (B) overall survival after 2nd HCT.

Figure 4.

The impact of (A) age, (B) diagnosis, (C) HCT-CI, (D) conditioning regimen, (E) donor type, and (F) same vs. different donor on overall survival after 2nd HCT.

Table 1.

Patient characteristics.

Characteristics	<i>n</i>
Patients	126
Median age (range) in years	32 (3 to 69)
Sex	
Female	59
Male	67
Diagnosis	
AML	66
ALL	26
MDS	13
CML	5
NHL	4
Hodgkin lymphoma	3
Myelofibrosis	5
CLL	3
Multiple Myeloma	1

AML: acute myeloid leukemia; ALL: acute lymphoid leukemia; CLL: chronic lymphoid leukemia; CML: chronic myeloid leukemia; MDS: myelodysplastic syndrome; NHL: non-Hodgkin lymphoma.

Table 2.

Characteristics of first and second allogeneic HCT.

<u>First HCT</u>	<i>n</i>
Disease Status	
Remission (chronic phase, n=3)	78
Relapse/persistent disease (accelerated phase, n=1)	35
Unknown	13
Conditioning:	
CY, TBI (12 Gy; + ATG, n=1; + RIT, n=2; + FLU, n=5; + TEPA, n=2; + VP-16, n=2)	56
BU, CY (+ ATG, n=4; + RIT, n=2; CY, BU, n=1)	34
TREO, FLU (+ TBI 2 Gy, n=5)	6
TBI (2–3 Gy; + FLU, n=10; + CY + FLU, n=2; + FLU + RIT, n=1)	16
BU, FLU	5
Other ^a	9
Donor	
HLA-Identical, related (single HLA-antigen mismatched, n=2)	66
HLA-matched, unrelated (single HLA-allele mismatched, n=5; UCB, n=2)	42
HLA-mismatched, unrelated	7
HLA-mismatched, UCB	9
HLA-haploidentical, related	2
Stem Cell Source	
PBSC	62
Marrow	53
UCB	11
<u>Second HCT</u>	<i>n</i>
Disease Status	
Remission	85
Relapse/persistent disease (accelerated phase, n=2; blast crisis, n=2)	41
HCT-CI	
0,1	36
2,3	43
4 to 9	47
Conditioning	
TBI (2–4.5 Gy; + FLU, n=40; + CLO, n=4; + FLU + RIT, n=3)	51
TREO, FLU (+ TBI 2 Gy, n=16)	25
CY, TBI (12 Gy; + FLU, n=3)	16
CY, FLU, TBI (2–4 Gy; + RIT, n=4; +ATG, n=1)	16
BU, CY (Cy, BU, n=1)	8
Other ^b	10
Donor	
HLA-Identical, related (single HLA-antigen mismatched, n=2)	27
HLA-matched, unrelated (single HLA-allele mismatched, n=3; double UCB, n=1)	59

HLA-mismatched, unrelated	9
HLA-mismatched, UCB	20
HLA-haploidentical, related	11
Same	17
Different	109
Stem Cell Source	
PBSC	85
Marrow	20
UCB	21
Median time between HCTs (range) in months	23 (2 to 186)
Remission duration after 1st HCT (range) in months	11 (0.7 to 180)

^aOther: CLO, MEL, THIO, n=1; CY, FLU, n=1; FLU, MEL, n=2; FLU, MEL, THIO, n=1; TLI, ATG, n=1; Samarium, n=1; Unknown, n=1; FLU, TBI (450), n=1.

^bOther: BU, CLO, n=2; BU, FLU, n=3; BU, TEPA, n=2; CY, TEPA, FLU, TBI 4 Gy, n=2; FLU, TBI 8 Gy, n=1

ATG, anti thymocyte globulin; BU, busulfan; CLO, clofarabine; CY, cyclophosphamide; FLU, fludarabine; HCT-CI, HCT-specific comorbidity index; HLA, human leukocyte antigen; PBSC, peripheral blood stem cells; RIT, radioimmunotherapy; TBI, total body irradiation; TEPA, thiotepa; TREO, treosulfan; UCB, umbilical cord blood; VP-16, etoposide.