A Retrospective Review of the Outcome after Second or Subsequent Allogeneic Transplantation

Meirav Kedmi,1 Igor B. Resnick,1 Liliane Dray,1 Memet Aker,2 Simcha Samuel,1 Benjamin Gesundheit,1 Shimon Slavin,1 Reuven Or,1 Michael Y. Shapira1

The failure of allogeneic stem cell transplant (allo-SCT) is cumbersome. We analyzed our experience in a second allo-SCT. Between the years 1981 and 2007, 144 patients underwent 2 or more allo-SCT. The first to second transplant interval ranged from 18 days to 13.25 years (median 98 days). The most frequent indications for the second SCT were activity of the basic disease (78), rejection (37), and engraftment failure (25). Twenty-nine of the 144 (20%) patients transplanted survived more than a year with treatment-related mortality of 45.5% as the leading cause of death. Interestingly, despite the low rate of graft-versus-host disease (GVHD) prophylaxis used, only 51 and 16 of the patients developed acute and chronic GVHD (aGVHD, cGVHD), respectively. Factors indicating higher likelihood for survival were nonmalignant disease, a nonrelapse indication for the second SCT, full HLA-matching, and the use of reduced-intensity conditioning (RIC). Age at transplantation, time interval between transplants, the development of GVHD, conditioning regimen, GVHD prophylaxis, or graft source were not shown to influence the prognosis. With a median follow-up of 4.5 years, 25 patients (17.2%) are alive, and 18 are disease-free. We conclude that although toxic, a second allo-SCT can lead to long-term survival.


KEY WORDS: Allogeneic bone marrow transplantation, Toxicity, GVHD, Graft rejection, Engraftment failure, Relapse

INTRODUCTION

Patients who undergo allogeneic bone-marrow or blood stem cell transplantation (allo-SCT) may suffer from graft rejection, engraftment failure, or relapse of their primary disease. The only therapeutic option may be second allo-SCT. Very little is known about the outcome of those patients. Acute leukemia patients, who relapse after first allo-SCT, were shown to have poor outcome in the second [1]. There is, however, some evidence that the outcome of the second allo-SCT is better if the disease burden is low [2] or if the first SCT was autologous [3]. Kobayashi et al. [4] found that some acute myelogenous leukemia (AML) patients achieved prolonged remission after allogeneic immunotherapy-based interventions, but these procedures carried a high risk [4]. In children with AML there seems to be better results, but there are not much data [5]. Greater success has been reported with chronic myelogenous leukemia (CML) patients undergoing repeated allo-SCT [6].

In nonmalignant diseases, however, the data is even vaguer. There is 1 case report in the literature about a severe aplastic anemia (SAA) patient who underwent 3 allo-SCTs because of engraftment failure; the last of which was successful [7]. Additionally, we found 3 other case reports about patients with genetic diseases undergoing SCT [8-10]; in each of these reports, 1 of the patients underwent a successful second or higher allo-SCT. Recently, Ayas et al. [11] documented their experience in 4 patients with Fanconi’s anemia who were reconditioned with antithymocyte globulin (ATG).

Because the major advantage of allo-SCT is because of the graft-versus-leukemia (GVL) effect mediated by alloreactive donor lymphocytes administered at the time of transplant [12] or donor leukocyte infusions (DLI) administered posttransplantation [13,14], availability of reduced-intensity conditioning (RIC) [15], lower dose, or earlier withdrawal of posttransplant immunosuppression [16], more aggressive

From the 1Department of Bone Marrow Transplantation & Cancer Immunotherapy; and 2Pediatric Hemato-oncology, Hadassah, Hebrew University Medical Center, Jerusalem, Israel.

Financial disclosure: See Acknowledgments on page 488.
Correspondence and reprint requests: Michael Shapira, MD, Department of Bone Marrow Transplantation & Cancer Immunotherapy, Hadassah, Hebrew University Medical Center, P.O. Box 12000, Jerusalem 91120, Israel (e-mail: shapiram@hadassah.org.il).

Received August 18, 2008; accepted January 8, 2009
© 2009 American Society for Blood and Marrow Transplantation
1083-8791/09/154-0001$36.00/0
doi:10.1016/j.bbmt.2009.01.009
cell-mediated immunotherapy [17] or more effective alloreactivity induced by another donor may improve the efficacy of a subsequent transplant procedure. To achieve better understanding of the course of the second allo-SCT, to have better future selection of the target patient population, and to provide patients with enough data to get an informed consent, we analyzed the outcome of all the patients who underwent 2 or more allo-SCTs in our institution.

**METHODS**

**Patients’ Characteristics**

Between the years 1981 and 2007, 1533 allo-SCTs were performed in our department. One hundred forty-four patients (92 males) underwent more than 1 allo-SCT (10 underwent 3 allo-SCTs). The median age at the second SCT was 20.7 years, with a range of 8 months to 68.4 years. The indications for the first allo-SCT were acute leukemia/myelodysplastic syndromes (MDS) (92), chronic leukemia (17), lymphoma (3), other malignancies (3) and nonmalignant (29) (Table 1).

**Conditioning Regimen and Graft-versus-Host Disease (GVHD) Prophylaxis**

GVHD prophylaxis (when given) consisted of short-term cyclosporine (CsA) starting on day 2 or 21. In some of the patients with partially matched donors (2-3 HLA mismatches), T cell depletion was done using positive stem cell selection (CD34 immunomagnetic beads (Miltenyi biotec, Germany) or Campath-1G and later on alemtuzumab introduced “in the bag” (mabcampath, Bayer Schering pharma, UK).

**Donors**

Donors were fully matched siblings (n = 83), matched unrelated donors (MUD, n = 8), and 1-locus mismatched unrelated donors (n = 2). Mismatched family member donors with 2-3 mismatches were used in 51 transplants. Peripheral blood stem cells (PBSCs) (n = 79) were mobilized by granulocyte-colony stimulating factor (G-CSF) (Neupogen) and stem cells were collected on days 5 and 6. Bone marrow aspiration was done under anesthesia using standard aspiration needles (n = 65).

**Supportive Care**

Prior to transplantation, all patients received trimethoprim/sulfamethoxazole until day −2, acyclovir from the initiation of therapy at least until day +120, and allopurinol until day −1. Trimethoprim/sulfamethoxazole was re instituted after recovery from neutropenia for 6 months. Febrile neutropenia was treated according to the hospital’s protocols.

Starting on day −8, cytomegalovirus (CMV) was monitored with a DNA-polymerase charin reaction (PCR) test or pp65 antigenemia on a weekly basis. CMV reactivation indicated replacing acyclovir with ganciclovir until a minimum of 2 negative tests were obtained. Patients were treated with reverse isolation HEPA-filtered rooms, and received a regular diet. Additional supportive measures, such as parenteral nutrition and blood component transfusion, were administered as necessary.

Acute and chronic GVHD (aGVHD, cGVHD) were graded according to the International Bone Marrow Transplantation Registry (IBMTR) severity indices [11,18]. Immediately upon the appearance of signs and symptoms of GVHD, i.v. methylprednisolone (2 mg/kg) and CSA were administered.

To assess engraftment, degree of chimerism, minimal residual disease, and early relapse, patients were monitored at regular intervals by cytogenetic analysis, by male/female amelogenine gene PCR bands [12,19], and by variable-number tandem repeat (VNTR)-PCR assay [13,20]. All patients or their guardians signed an informed consent prior to the procedure.

**Table 1. Disease Distribution among Patients Who Underwent More than 1 Allogeneic SCT in Our Center**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients Number</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignant</strong></td>
<td></td>
</tr>
<tr>
<td>Acute myelogenous leukemia/myelodysplastic syndrome</td>
<td>70</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>22</td>
</tr>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>17</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>1</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Testicular carcinoma</td>
<td>1</td>
</tr>
<tr>
<td><strong>Nonmalignant</strong></td>
<td></td>
</tr>
<tr>
<td>Severe aplastic anemia</td>
<td>9</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>5</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>4</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>2</td>
</tr>
<tr>
<td>Leukocyte adhesion deficiency</td>
<td>1</td>
</tr>
<tr>
<td>Chediak Higashi syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>1</td>
</tr>
<tr>
<td>Fanconi’s anemia</td>
<td>1</td>
</tr>
<tr>
<td>Hyper IgM syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Wolman’s disease</td>
<td>1</td>
</tr>
<tr>
<td>Wiskott Aldrich syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Kostmann’s syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>1</td>
</tr>
</tbody>
</table>

SCT indicates stem cell transplantation.
(NRM), engraftment, disease response, relapse, and incidence/severity of GVHD. Preengraftment death excluded from aGVHD analysis; death before day 100 excluded from cGVHD analysis. Engraftment failure was defined as peripheral blood aplasia and marrow hypoplasia >21 days posttransplant, with no evidence of donor markers revealed by cytogenetic and molecular techniques, whereas graft rejection was defined as peripheral blood aplasia and marrow hypoplasia >21 days posttransplant, with evidence of donor markers that appeared and then disappeared. Overall survival (OS) was defined as time from the day of transplantation to death from any cause, or last follow-up. Relapse was defined as the recurrence of the malignancy, after the initial achievement of complete remission. Disease-free survival (DFS) was defined as time from the day of transplant until relapse or death from any cause. In patients who did not achieve remission of the disease post transplant, day 0 was considered for DFS analysis as the day of relapse. Treatment-related morbidity and TRM was defined as morbidity or mortality because of any cause other than disease progression within 100 days of transplantation. NRM was defined as mortality because of any cause other than disease progression within 1 year of transplantation.

Data were analyzed using Microsoft excel and Medcalc (Medcalc Inc., Belgium). The probabilities of OS and DFS were plotted using the Kaplan-Meier method. The significance was estimated by log-rank test and logistic regression analysis. Chi-square was used to analyze some survival predictors.

RESULTS

One hundred forty-four patients underwent 298 allogeneic transplant procedures.

The first to second SCT time interval ranged between 18 days and 13.25 years (median 89 days). The most frequent indications for the second SCT were relapse/resistant basic disease (79), rejection (37), and engraftment failure (25) (Table 2).

Engraftment

Neutrophils and platelet engraftment at the second transplant occurred in 97 (67%) and 48 patients (33%), respectively. The median time to white blood cell (WBC) (>1 × 10⁹/L) and absolute neutrophil count (ANC) (>0.5 × 10⁹/L) engraftment was 15 days (range: 1-135) and 17 days (range: 1-125), respectively. The range of time to platelets recovery was 1-131 days (median: 14 days). In the subgroup of patients that underwent 3 allogeneic SCTs, there was no difference in the rate or time of engraftment within transplants. The median time for WBC and ANC engraftment was 20 and 16 days and 21, and 18 days for the second and third SCT, respectively (nonsignificant). Likewise, the median time for platelets engraftment was 31, and 56 days for the second and third SCT, respectively (nonsignificant).

Incidence and Severity of GVHD

Fifty-one of the 97 patients who engrafted (51%) developed aGVHD, with a median onset time at 23 days. Ten patients had grade I aGVHD, whereas 41 had grade II-IV. With a median time of 101 days 16 of 55 (29.1%) of the evaluable patients developed cGVHD; most of them evolved from aGVHD. Seven patients had severe cGVHD, 2 had moderate, and the rest had mild cGVHD.

NRM

Eighty-four patients (58%) died within the first 100 days of second transplant. Eighteen (12.5%) died of relapse/progression of their basic disease and 66 (45.5%) from transplant-related complications. Among them, 28 died of different infections, 15 of treatment-related organ toxicities, 8 of engraftment failure, 5 of rejection, 9 from aGVHD, and 1 patient committed suicide.

Transplant Outcome

Twenty-nine patients (20%) survived at least a year after the second procedure (Figure 1). The median survival from the second SCT was 70 days (range: 1 day to 23.7 years). Median DFS was 59 days (range: 1 day to 23.7 years). Twenty-five patients (17.2%) are alive at the time of this report with a median follow-up of 4.5 years; of them 18 are disease-free. Ten patients underwent 3 allogeneic SCTs, of these, 3 survived at least 1 year from the third SCT. Four patients are alive at the time of this report (1 with 7 months follow-up), all are disease free. Causes of death were relapse (3), infection (2), and cGVHD (1).

The factors that were associated with higher chance of survival were: basic disease (malignant versus nonmalignant), indication for the second SCT (relapse versus nonrelapse), donor matching (full match versus mismatched), and conditioning regimen (RIC versus myeloablative).

Table 2. Indications for the Second SCT

<table>
<thead>
<tr>
<th>Indication</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse/resistant basic disease</td>
<td>78</td>
</tr>
<tr>
<td>Rejection</td>
<td>37</td>
</tr>
<tr>
<td>Engraftment failure</td>
<td>25</td>
</tr>
<tr>
<td>Donor type leukemia</td>
<td>1</td>
</tr>
<tr>
<td>Allogeneic SAA (graft versus graft)</td>
<td>1</td>
</tr>
</tbody>
</table>

SCT indicates stem cell transplant, SAA, severe aplastic anemia.
malignancy (n = 115) only 14 survived at 1 year (Figure 2; P = .0009).

Seventy-nine patients had the second transplant because of relapse or refractory disease, and 65 because of other indications; the number of survivors at 1 year was 8 and 21, respectively (Figure 3A; P = .013).

Only 4 of 53 patients who were transplanted from a mismatched donor survived a year. In contrast to that, 25 of 91 patients (27.5%) who were transplanted from a full-matched donor were alive at 1 year (Figure 3B; P = .029).

RIC regimen in the second SCT (Figure 4) was associated with higher probability of survival at 1 year (23 of 80) compared with myeloablative regimen (6 of 64) (P = .03).

The factors that were not significant as predictors of survival at 1 year from the second transplant were age, the development of aGVHD, chemotherapy versus radiotherapy-based conditioning, stem cell origin

Figure 2. OS of patients according to basic disease. It is clear that patients who underwent the second allogeneic SCT because of a nonmalignant condition survived better than patients with malignant diseases.

Figure 3. (A) Survival according to the indication for the second SCT. Patients who were transplanted because of persistent/relapse of their basic disease survived significantly less than those who were transplanted for other reasons. (B) Survival according to donor matching in the second SCT—patients who had the second transplant from a matched donor survived significantly more than those who were transplanted from a mismatched donor.

Figure 4. OS from second SCT according to conditioning regimen. Patients who underwent RIC survived significantly better than those who underwent myeloablative conditioning.
(bone marrow [BM] versus PBSC), the interval between SCTs and the use of GVHD prophylaxis (pharmacologic or T cell depletion).

Subgroup analysis of the patients with malignant diseases (n = 115), demonstrated that the only predictor of 1-year survival was donor matching. Patients who were transplanted from a fully matched donor survived significantly more than those that were not (P=.034). All the other parameters that were checked (including age at transplantation, time between transplants, conditioning regimen, second transplant’s indication, GVHD prophylaxis, aGVHD occurrence, and cells’ source), did not significantly differ between the groups.

DISCUSSION

The failure of allo-SCT is mostly fatal. For these patients, the only curative alternative is to consider another allo-SCT. So far, there is very little information in the literature regarding such a cohort of patients. To develop better understanding of the fate of patients failing allo-SCT and have better idea about the indications and future selection of the target patient population in need, to provide justification for consideration of a second or third transplant procedure, and to offer patients enough data to get an informed consent, we retrospectively analyzed the medical records of all patients that underwent more than 1 allo-SCT procedure for any indication in our center between the years 1981 and 2007. We then compared and analyzed the data of patients who survived at least a year after second allo-SCT to those who did not survive, using different parameters.

The most significant factor that we found as a predictor of prolonged survival was the basic disease for which the first allo-SCT was performed. More patients with nonmalignant diseases (Figure 2) survived compared with patients with malignant diseases. To date, most of the data in the literature deals with patients who underwent 2 allo-SCTs for malignant diseases, mostly AML, acute lymphoblastic leukemia (ALL), and CML. Frassoni et al. [1] analyzed retrospectively the European Blood and Marrow Transplant (EBMT) registry for the outcome of 117 patients with either AML or ALL, who relapsed after allogeneic SCT. Nine of the 117 patients (7.7%) underwent another allo-SCT; of them, only 1 had prolonged survival (11%). Radich et al. [6] published the Seattle experience with a second allo-SCT. Seventy-seven patients with AML, ALL, or CML, aged 2-51 years, who relapsed after allogeneic transplant with TBI containing regimens, were transplanted again from the same donor with intensive chemotherapy conditioning. As may be expected, veno-occlusive disease (VOD) was the most common cause of severe treatment-related toxicity and TRM. TRM was high (36%), and the risk for relapse was even higher (relapse probability was 70%). The risk of relapse was inversely related with GVHD. DFS rate was 14% with different DFS rates for ALL, AML, and CML (8%, 10%, and 25%, respectively). The authors demonstrated that young patients and CML patients were the most likely to succeed in a second SCT. In the subgroup analysis we did for patients with malignant diseases, we found the only predictor for survival was full donor matching; all the other parameters were not significantly different between the groups.

There is no comprehensive data in the literature regarding second allo-SCT in genetic/nonmalignant diseases. There are only reports on 3 patients with chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome, or Diamond-Blakfan anemia undergoing SCT, in which 1 of the reported patients underwent more than 1 allogeneic SCT [8-10]. We had 29 patients with different nonmalignant diseases (Table 1) who underwent 2 allo-SCTs. Of them, 15 survived at least a year after the procedure. This finding might reflect the greater success of allo-SCT reported in genetic diseases [21].

In patients who were transplanted because of relapse, the survival rates were considerably lower. Patients with resistant malignancies who did not respond to chemotherapy had lower chances to respond to a second transplant procedure. However, 8 of 70 (11.4%) of patients who had a second transplant did benefit a long-term DFS. Hosing et al. [2] also found that patients with AML/MDS have better outcome in a second transplant if they start it with low disease burden (absence or <5% blasts in the peripheral blood). Despite that, we found 14 patients with resistant malignant diseases (AML, ALL, and CML) surviving longer than a year after second SCT.

Another interesting finding in our analysis was that the use of RIC was associated with significantly better outcome compared with myeloablative conditioning. One would be predisposed to use myeloablative conditioning in many types of transplant failure (eg, relapse, rejection, engraftment failure, etc.). However, in view of the high incidence of transplant associated toxicity and TRM expected in second allo-SCT [6], which may be linked to cumulative damage because of past exposure to high doses of chemoradiotherapy on the 1 hand, and higher resistance to future anticancer chemotherapy, treating physicians should prepare to choose RIC for the second SCT.

In our cohort, HLA matching was also an important factor predicting prolonged survival both in the whole patient group and in the subgroup of patients with malignant diseases. Patients who underwent second allo-SCT from a matched donor (either family or MUD) survived more than those who received the graft from a haploidentical or mismatched donor.
This is not surprising if we consider the higher TRM in haploidentical and mismatched transplantations [22], and that the most common cause of death in our cohort was indeed TRM.

Among the factors that did not have an effect on survival the most surprising 1 was the age at second SCT. As mentioned before [5], there is some evidence that children and young adults are more likely to succeed in second allo-SCT. Chewning et al. [23] recently reported 16 patients who underwent second allo-SCT because of graft failure. They found that the outcome was superior in patients who were younger than 20 years. Eapen et al. [24] also reported that patients younger than 20 are more likely to succeed in second allo-SCT. Platzbecker et al. [25] reported that patients younger than 50 years and those with graft failure as the etiology for second transplant did better. Our findings were not limited by the number of patients, as 67 of 144 patients in our group were children and young adults under the age of 18 years at the time of the second transplant and the median age of the whole group was 20.7 years. Moreover, we might have had a selection bias, because reduced performance status in this clinical situation is more common in older patients who were accordingly not offered a second SCT. Therefore, our interpretations might not be relevant to older patients.

It would be reasonable to assume that patients who maintained remission longer after first allo-SCT will be more likely to succeed in the second procedure. Indeed, the time interval between transplants was previously reported as an important factor predicting survival after second transplant [24]. We could not reproduce such an effect in our analysis.

Another interesting finding was that the use of GVHD prophylaxis or T cell depletion did not affect survival. This finding is further supported by the lack of impact of aGVHD on survival. The expected GVL (especially in patients with no relapse after the second SCT) may have been counterbalanced by transplant-related toxicity.

A remarkable group that deserves a separate discussion was the 10 patients who underwent 3 allo-SCT procedures. Of these patients (median ages 12.4 and 13.3 years at the second and third SCT, respectively), including 7 with malignant diseases, 3 patients are long-term survivors, and all are disease free. The repeated conditioning procedures did not seem to harm the engraftment processes and the rate and time to engraftment was the same in the first, second, and third SCTs.

Despite the long period of time that is represented in our cohort with all its disadvantages in terms of differences in supportive care quality, conditioning regimens, and immunosuppressive therapy, we believe there are some important conclusions that can be made.

Our data supports the notion that a second allo-SCT should be seriously considered especially for patients with nonmalignant disorders, but also for a selected group of patients with malignant diseases failing the first allogeneic SCT, especially if they have responded to conventional chemotherapy to minimize the risk of early relapse, or if transplant failure occurred while in remission. Some patients with refractory disease may even benefit from a third transplant procedure and remain disease free with good quality of life. A larger number of patients and longer observations are needed to confirm the benefit and cost-effectiveness of allo-SCT for patients who failed the first transplant procedure because availability of RIC supported by posttransplant immunotherapy may increase the probability of a successful second, and in rare cases, even a third transplant procedure.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

We deeply thank Mrs. Pantel-Bakst Sharon for her ongoing assistance in data management, and Mrs. Sara Farkash for the secretarial support and patience.

REFERENCES


