ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR NEUROBLASTOMA: THE CIBMTR EXPERIENCE

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Abstract

While the role of auto-HCT is well established in neuroblastoma, the role of allo-HCT is controversial. The CIBMTR conducted a retrospective review of 143 allo-HCT for NBL reported in 1990-2007. Patients were categorized into two different groups: those who had not (Group 1) and had (Group 2) undergone a prior auto HCT (n=46 and 97, respectively). One-year and five-year overall survival (OS) were 59% and 29% for Group 1 and 50% and 7% for Group 2. Amongst donor types, disease free survival (DFS) and OS were significantly lower for unrelated transplants at 1 and 3 years but not 5 years post-HCT. Patients in complete response (CR) or very good partial response (VGPR) at transplant had lower relapse rates and better DFS and OS, compared to those not in CR or VGPR. Our analysis indicates that allo-HCT can cure some neuroblastoma patients, with lower relapse rates and improved survival in patients without a history of prior auto-HCT as compared to those patients who had previously undergone auto-HCT. Although the data do not address why either strategy was chosen for patients, allo-HCT after a

prior auto-HCT appears to offer minimal benefit. Disease recurrence remains the most common cause of treatment failure.

Keywords

neuroblastoma; allogeneic HCT; autologous HCT; CIBMTR

INTRODUCTION

Neuroblastoma is the most common extracranial solid tumor of childhood. Most children have metastatic disease at diagnosis, and require aggressive therapy including chemotherapy, surgery and radiation, with autologous hematopoietic cell transplantation (auto-HCT) as consolidation [1, 2]. In a randomized clinical trial conducted by the Children's Cancer Group, auto-HCT resulted in better event-free survival than standard chemotherapy, which was confirmed on long-term follow-up of this cohort [3, 4]. Neuroblastoma is one of the most common indications for auto-HCT in pediatrics; however, disease recurrence remains the main cause of treatment failure. Even when post-transplant anti-GD2 antibody therapy is incorporated, the 3-year disease-free survival rate from transplant is 65% at best[5]. Allo-HCT has been utilized as treatment for neuroblastoma. However, limited comparisons of autologous vs. allogeneic HCT have not shown an advantage for allo-HCT [6, 7], and a retrospective review by the EBMT suggested that successful outcomes after allo-HCT have been limited by unacceptably high rates of regimen- related mortality and disease recurrence [8]. More recently, with improvements in supportive care, improved HLA typing and the advent of reduced intensity conditioning regimens, physicians have been re-exploring allo-HCT [9-12]. We therefore performed a retrospective study to describe the use of allo-HCT for neuroblastoma and to evaluate the outcomes of recipients of allo-HCT for neuroblastoma among patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR).

METHODS

Data collection

CIBMTR is a research affiliation of the International Bone Marrow Transplant Registry (IBMTR), the Autologous Blood and Marrow Transplant Registry (ABMTR) and the National Marrow Donor Program (NMDP) that comprises a voluntary working group of more than 500 transplantation centers worldwide that contribute data on consecutive HCT to a Statistical Center at the Medical College of Wisconsin and the NMDP. Participating centers are required to report all consecutive transplants; compliance is monitored by on-site audits. Computerized checks for errors, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are done with a waiver of informed consent and in compliance with HIPAA regulations as determined by the Institutional Review Board (IRB) and the Privacy Officer of the Medical College of Wisconsin.

Study population

There were 3528 transplants (autologous or allogeneic) registered to the CIBMTR between 1990 and 2007 for neuroblastoma. This study was restricted to subjects with neuroblastoma undergoing a first allo-HCT from 1990 to 2007. All surviving recipients who received transplants from unrelated donors (URD) included in this analysis were retrospectively contacted and provided informed consent for participation in the NMDP research program. Informed consent for retrospective data analysis was waived by the NMDP IRB for all deceased patients. Surviving patients who did not provide signed informed consent to allow analysis of their clinical data were excluded. To adjust for potential bias introduced by exclusion of non-consenting surviving patients, a corrective action plan (CAP)–modeling process randomly excluded approximately the same percentage of deceased patients using a biased coin randomization with exclusion probabilities based on characteristics associated with not providing consent for use of data in survivors. The classification of degree of HLA-match was based on the model proposed by Weisdorf et al [13]. In this schema "well-matched" category included those with no defined mismatches and no untested HLA locus; partially-matched included those with only one untested or mismatched locus; and mismatched included those with two or more known or mismatched or untested HLA-loci.

The study population included 143 subjects with neuroblastoma (4% of all transplants for neuroblastoma performed during this time period). We categorized patients into 2 groups, based on whether they had a history of a prior auto-HCT, with 97 patients not having a prior autograft and 46 patients having a prior autograft, registered with CIBMTR. A subset of these patients had more detailed report forms available (n=66) and are described in Table 2. Definitions and categorization of donor recipient HLA-matching and conditioning regimens were assigned according to published CIBMTR criteria[14, 15]. Patient-, disease-, and transplant-related characteristics are listed in Table 1 for the entire group and in Table 2 for the subgroup that had report forms available.

Endpoints and Definitions

The primary objective was to describe the overall (OS) and disease-free survival (DFS) after allo-HCT for neuroblastoma and to describe the usage of this modality. In addition, we analyzed time to engraftment, incidence of acute and chronic GVHD, relapse or disease progression and transplant related mortality (TRM). Neutrophil engraftment was defined as the first of three consecutive days with an absolute neutrophil count of 0.5×10^9/L; platelet engraftment was defined as platelet count 20×10^9/L for seven consecutive days without transfusion support. TRM was defined as death from any cause in the first 28 days or death without evidence of disease progression/relapse. Relapse was defined as recurrence of neuroblastoma after a complete response (CR) or progression of disease at existing sites, or new sites of disease. For calculating DFS, patients were considered treatment failures at relapse or progression, or death. The OS interval variable was defined as the time from date of transplant to date of death or last contact. Acute GVHD was defined and graded based on the pattern and severity of organ involvement using established criteria[16]. Chronic GVHD was defined as the development of any chronic GVHD based on clinical criteria[17].

Statistical analysis

Patient-, disease-, and transplant-related variables (Table 1) were described with median and range for continuous variables, and percent of total for categorical variables. Occurrence of acute and chronic GVHD, TRM, and disease recurrence/progression were calculated using cumulative incidence estimates, taking into account the competing risks. Probabilities of DFS and OS were estimated from the time of HCT using the Kaplan-Meier estimator. When possible, univariate analysis was performed to compare outcomes among the two groups of patients: patients without a prior auto-HCT (Group 1) and those with a prior auto-HCT (Group 2). All p-values were two-sided. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Subjects, disease, transplant characteristics

Median age was 5 years (range, <1-55 years) in Group 1 and 7 years (range, 2-32 years) in group 2 (table 1). 40% of subjects in Group 1 and 61% of subjects in Group 2 had a Karnofsky/Lansky performance score > 90. The median time to allo-HCT from auto-HCT was 20 months (range, 1-68 months). A subgroup of 66 patients (35 in Group 1, 31 in Group 2) had more extensive data collected and was available for additional analysis (Table 2).

Graft-versus-host disease

The incidence of grade II-IV acute GVHD was 28% (95% CI 20-37%) by 100 days post HCT. The incidence of chronic GVHD was 14% (95% CI 8-21%) at 1 year (Table 3a). In an analysis of relapse evaluating the impact of GVHD, no effect of acute GVHD (p=0.6738) on relapse was observed. Effect of chronic GVHD could not be estimated because of the low incidence of chronic GVHD (14%). There was no difference in the cumulative incidence of acute or chronic GVHD between the two patient cohorts studied (Table 3b).

Relapse

Cumulative incidences of neuroblastoma progression or relapse at 1 and 5 years post-HCT were 38% (95% CI 29-47%) and 55% (95% CI 45-64%), respectively, for all subjects (Table 3a). GVHD did not correlate with disease progression or relapse. Disease recurrence at 1 year post allo-HCT was observed more often in patients in Group 2 compared to Group 1 (Table 3b) (57% versus 27% at 1year, p=0.0012). This observation persisted at 3 and 5 years post-allo-HCT.

Treatment-related mortality

TRM at 100 days post-HCT was 18% (95% CI 12-26%) for the entire study population. TRM was stable over the first 5 years after transplant: from 25% (95% CI 17-33%) at 1 year to 25% (95% CI 18-34%) at 3 years, to 25% (95% CI; 18-34%) at 5 years post-HCT. There was no difference in the cumulative incidence of TRM between the two patient cohorts studied (Table 3b).

Disease-free survival (DFS)

For the entire cohort, DFS was 37% (95% CI 28-46%) at 1 year post-HCT and 20% (95% CI 13-27%) at 5 years post-HCT (Table 3a). Neither acute nor chronic GVHD correlated with DFS. DFS was higher for patients in Group 1 compared to Group 2 (Table 3b) (48% versus 19% at 1 year, p=0.0006).

Overall Survival (OS)

Survival at 1 year post HCT was 56% (95% CI 47-64%) and 22% (95% CI 15-30%) at 5 years post-HCT for all patients (Table 3a). Survival was higher for patients in Group 1 compared to Group 2 (Table 3b) (36% versus 16% at 3 years, p=0.0086).

Cause of death

The most common cause of death among transplant recipients was disease recurrence (n=72, 68%). Other common causes included organ failure (n=8, 8%), infection (n=9, 8%), and GVHD (n=4, 4%) (Table 5). Of patients in Group 2, 87% died. Of patients in Group 1, 68% died.

Outcome by donor type

Time to neutrophil engraftment, platelet engraftment, acute GVHD, chronic GVHD, and TRM were unaffected by donor type (Table 3c). Relapse was consistently higher for recipients of URD grafts compared to other hematopoietic graft sources. Similarly, early DFS (at 1 year) and OS (at 1 and 3 years) was lower for URD grafts. A separate analysis of the 33 patients undergoing cord blood transplantation was performed (Table 6); 16 did not undergo prior auto-HCT. In this subgroup, the day 100 TRM was 19%, plateauing at 23% from 1 year to 5 year post-HCT. One-year DFS was 20%.

Outcome by disease status at allogeneic HCT

Time to neutrophil engraftment, platelet engraftment, acute GVHD, chronic GVHD, and TRM were unaffected by disease status at allo-HCT (Table 3d). The incidence of relapse at one year was significantly lower for patients in complete response (CR) or very good partial response (VGPR) at allo-HCT, but this effect was not statistically significant at 3 and 5 years after allo-HCT. However, DFS and OS were consistently significantly higher for patients transplanted in CR or VGPR compared to patients with more advanced disease. This observation held throughout the first 5 years following allo-HCT.

Outcome for patients without prior auto-HCT in CR, VGPR, or PR

For the patients proceeding directly to allo-HCT (with no prior history of auto-HCT) in CR, VGPR, or PR, the treatment-related mortality was 15%, with no occurrences after the first 100 days post-HCT (Table 4). DFS declined from 59% at 1-year post –HCT to 37% at 5-years post-HCT. Disease recurrence rates at 1-year post-HCT were 26%, rising to 48% at 5-years post-HCT.

Outcome by conditioning regimen

The majority of patients received a myeloablative conditioning regimen (67%). Of the 96 patients receiving an ablative regimen, only 19 had undergone prior auto-HCT. Of the 35 receiving a reduced intensity or non-myeloablative regimen (RIC), 20 had undergone a prior auto-HCT. TRM was significantly lower at 100 days post-HCT for those receiving a reduced intensity regimen (9% versus 23%, p-0.0437) but was not statistically significant thereafter. Recipients of RIC regimens had higher relapse rates at all time points post-HCT. DFS at one-year and OS at 3 years post-HCT (Table 7), were lower for recipients of RIC regimens.

DISCUSSION

This study demonstrates that allo-HCT for neuroblastoma is uncommon, accounting for 4% of all transplants for neuroblastoma in this publication and 3% (124 of 4098) reported by EBMT (8). In this cohort of patients with high-risk neuroblastoma, 20% (95% CI 13-27%) of subjects were alive without disease recurrence at five years after allo-HCT. Reflecting improvements in HCT practice, in this cohort graft failure and TRM were not significant causes of treatment failure; however, disease recurrence remained the most common barrier to transplant success. It is important to recognize that this study population included only first allogeneic transplants, and excluded those who had undergone prior allo-HCT. However, as expected for patients with high-risk neuroblastoma, a significant proportion of patients had undergone prior autologous transplantation, which is the standard treatment for these patients. However, it was surprising that 68% of the patients had not undergone prior autologous transplantation, receiving allogeneic transplant as their initial transplant consolidative therapy. Therefore, a portion of this patient population is unique in that the treating physicians proceeded directly to allo-HCT rather than auto-HCT.

Most series of auto-HCT report DFS rates approximating 45% from diagnosis with relapse being the most common cause of patient mortality[3, 4], although two phase 2 trials utilizing multiple cycles of HCT have reported DFS rates of ~55% [18-20]. Persistent disease may cause relapse, although it has also been hypothesized that disease contamination in infused stem cells may also contribute to recurrence [3, 4, 21]. However, tumor cell contamination in PBSC is low, even when the cells are collected from a patient with residual tumor in the marrow[22], and a recent trial from the Children's Oncology Group failed to detect an impact of tumor cell purging of PBSC used for auto-HCT[23]. Using allogeneic marrow certainly avoids the possibility of infusing contaminating tumor in the PBSC product, but at the expense of the complications of allogenicity such as graft failure, GVHD and delayed immune reconstitution. In this series the authors cannot comment on why some patients proceeded directly to allo-HCT and did not undergo auto-HCT. This decision was made by the treating physician and the registry does not collect this information. It is conceivable that patients were unable to have adequate numbers of autologous hematopoietic progenitor cells collected, were unable to have tumor-free grafts obtained, or had progressive disease making auto-HCT impractical. Certainly patients who had a matched related donor seemed to be more common in our series than other allogeneic donor types.

Recently, with the addition of the post-transplant immunotherapy with the chimeric anti-GD2 antibody, the Children's Oncology Group has reported DFS rates approaching 65% from the point of auto-HCT for neuroblastoma [5]. There are no large series of outcomes for allo-HCT in neuroblastoma, with the present report being the largest series collected to date. Recently, at the 2012 EBMT meeting, a group from Japan reported on retrospective outcomes after allo UCBT for neuroblastoma[24]. In a cohort of 75 patients, differences were again seen between those in a first CR/VGPR vs. other patients (51.5% 3 year EFS vs. 38.5%, respectively). Although a direct comparison is not possible, the overall 3 year EFS of the UCBT group in our cohort was 17%. Case reports and small series have suggested that a graft-versus-malignancy effect may exist, but investigators are unable to quantify the survival advantage, if any, that is seen with this modality[9-11, 25]. There is indirect evidence that neuroblastoma may respond to a graft-versus-tumor effect after allo-HCT or other immunomodulatory therapies. This observation is supported by the use of such therapies to treat this disorder using dendritic cells, natural killer cells, and anti-GD2 antibodies[26, 27]. The DFS rates reported in this study are inferior for the entire group when compared to the baseline of 45-55% reported for auto-HCT. However, a direct comparison is not possible given the potential differences in disease responsiveness and relapse risk between Group 1, Group 2, and large reported cohorts of neuroblastoma patients who underwent auto-HCT after induction chemotherapy. When examining the patients in Group 1, the DFS rates compare favorably given the degree of HLA mismatch between donors and recipients, the percentage of recipients with poor performance scores, and the extensive prior therapy of this patient population. The use of novel agents such as immunomodulatory agents and radioactive treatments may further increase survival [28].

These outcomes, however, remain poor. Although 37% of subjects were alive in remission at one year after HCT, only 20% were alive and free of disease progression at five years post HCT. For recipients who had not received a prior auto-HCT, 48% and 27% were alive and in remission at one and five years post-allogeneic HCT, respectively. It is quite likely that this group was at higher risk for relapse than a group of patients undergoing auto-HCT for consolidation after induction therapy. Only 23% of this group had chemosensitive disease (judged by their treating physician) although many of them were in CR, VGPR, or PR. Thus, it is difficult to discern a positive impact of allo-HCT in this group of patients without clearer data regarding disease risk. Patients who had undergone an auto-HCT at any point prior to allo-HCT had extremely poor outcomes, with 19% and 6% alive and in remission at 1 and 5 years post-allo-HCT. In addition to the fact that the patients in Group 2 likely had higher-risk disease than those in Group 1, potential reasons for the differences in Group 1 and Group 2 include: i) that there was a fraction of patients undergoing allo-HCT without a prior autograft who would have been cured using a conventional auto-HCT, ii) less treatment prior to the allograft, or ii) the possibility that the use of allo-HCT earlier prevented the development of tumor resistance.

It is noteworthy that even patients with chemotherapy-resistant disease were curable in our series, suggesting that in some cases an immunologic graft-versus-tumor effect may be operational, although in this series there was no relationship between outcome and acute or chronic GVHD, similar to other reports [9-11, 26]. It is possible that another immunologic mechanism distinct from GVHD may be mediating the antitumor effects [4]. Our study

supports the observation that chemotherapy-resistant disease is a marker for poor outcome, although it may not be an absolute contraindication to allo-HCT. It is unclear which portions of the donor immune system, if any, mediate this effect. It is postulated that T-cell alloreactivity of NK cell mediated cell destruction may be operational [29, 30], but has not been clearly demonstrated.

The study is limited by its retrospective nature and the lack of data regarding the underlying reasons behind the clinical decisions to utilize allo-HCT. A significant number of the recipients in this trial had low performance scores and chemorefractory disease (Table 1). These characteristics suggest that the treating clinicians were considering an allo-HCT to reduce relapse rates in this high-risk group. This analysis does not attempt to compare outcomes of subjects with neuroblastoma based on donor-recipient relationship or HLA mismatch. Our results suggest that allo-HCT can result in long-term DFS in some patients with neuroblastoma. However, it is unclear which patients may benefit from this modality. Future investigation of allogeneic approaches in this disease should focus on dissecting immunological parameters that define an increased likelihood of a graft-vs.-neuroblastoma effect, hopefully leading to decreases in post-transplant disease recurrence and improved survival in patients with resistant disease[30].

ACKNOWLEDGMENTS

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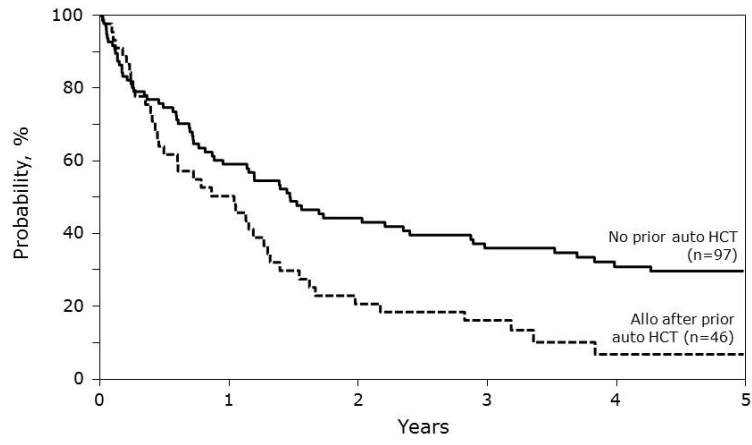
Figure 1.
Overall survival following allogeneic HCT for neuroblastoma.

Table 1

Characteristics of patients receiving allogeneic transplantation for neuroblastoma between 1990-2007 and registered to the CIBMTR

Characteristics of patients	Did not receive prior auto, N (%)	Received prior auto, N (%)
Number of patients	97	46
Number of centers	48	24
Age at transplant, median (range), years	5 (<1- 55)	7 (2-32)
0 – 5	51 (53)	9 (20)
6 -10	27 (28)	31 (67)
11 – 20	13 (13)	5 (11)
> 20	6 (6)	1 (2)
Male sex	58 (60)	23 (50)
Karnofsky score prior to TX		
< 90%	13 (13)	11 (24)
90%	39 (40)	28 (61)
Unknown	45 (46)	7 (15)
Time from diagnosis to allogeneic transplant		
Median (range), months	9 (<1-97)	27 (8 - 76)
6	12 (12)	0
7 12	50 (52)	3 (7)
13 – 24	19 (20)	10 (22)
25 – 36	6 (6)	18 (39)
> 36	9 (9)	15 (33)
Missing	1 (1)	0
Had prior autologous transplant		46 (100)
Time from autologous transplant to allogeneic transplant		
Median (range), months	NA	20 (1- 68)
0 - 12		10 (22)
13 – 24		19 (41)
24 – 36		17 (37)
Disease status prior to transplant		
CR	30 (31)	8 (17)
Very good partial response	8 (8)	4 (9)
Partial response	17 (18)	8 (17)
Minimal response	1 (1)	1 (2)
No response	17 (18)	2 (4)
Progressive disease	6 (6)	11 (24)
Unknown	18 (19)	12 (26)
Conditioning regimen		
TBI + other	59 (61)	15 (33)
Bu + CY ± Other	4 (4)	1 (2)

Characteristics of patients	Did not receive prior auto, N (%)	Received prior auto, N (%)
CY + other	6 (6)	7 (15)
Bu + Fludara ± Other	3 (3)	6 (13)
Bu + Other	1 (1)	3 (7)
Melphalan + Fludara ± other	3 (3)	9 (20)
Melphalan ± Other	11 (11)	0
Other[a]	2 (2)	0
Unknown	8 (8)	5 (11)
Donor type		
HLA-identical sibling	56 (58)	18 (39)
Other related donor	25 (26)	4 (9)
Unrelated	16 (16)	24 (52)
Graft source		
BM	69 (71)	16 (35)
PBSC	10 (10)	13 (28)
Cord Blood	16 (16)	17 (37)
Unknown	2 (2)	0
Year of transplant		
1990 – 1994	38 (39)	1 (2)
1995 – 1999	26 (27)	10 (22)
2000 – 2004	24 (25)	18 (39)
2005 – 2007	9 (9)	17 (37)
GVHD prophylaxis		
T-cell depletion	5 (5)	1 (2)
MTX + CSA ± other	21 (22)	9 (20)
MTX ± other	19 (20)	3 (7)
CSA ± Other	30 (31)	23 (50)
Other	1 (1)	3 (7)
Unknown[b]	21 (22)	7 (15)
Median (range) follow-up [c], months	84 (<1- 191)	45 (<1- 58)

Abbreviations: TBI = total body irradiation; CY = cyclophosphamide; CsA = cyclosporine; MTX = methotrexate; CMV = cytomegalovirus; GVHD = graft-versus-host disease; FK506 = tacrolimus.

Table 2

Characteristics of patients receiving allogeneic transplantation for neuroblastoma between 1990-2007 and reported to the CIBMTR

Characteristics of patients	Did not receive prior auto, N (%)	Received prior auto, N (%)
Number of patients[a]	35	31
Number of centers	24	19
Age at transplant, median (range), years	5 (2-39)	7 (1-32)
0 – 5	18 (51)	7 (23)
6 -10	9 (26)	20 (65)
11 – 20	5 (14)	3 (10)
> 20	3 (9)	1 (3)
Male sex	17 (49)	12 (39)
Karnofsky score prior to TX		
< 90%	13 (37)	9 (29)
90%	21 (60)	20 (65)
Unknown	1 (3)	2 (6)
Time from diagnosis to allogeneic transplant		
Median (range), months	11 (5-97)	27 (9-76)
0 – 6	3 (9)	0
7 12	17 (49)	3 (10)
13 – 24	7 (20)	5 (16)
25 – 36	2 (6)	13 (42)
> 36	6 (17)	10 (32)
Had prior autologous transplant Time from autologous transplant to allogeneic transplant		
Median (range), months		19 (1-68)
0 - 12	NA	8 (26)
13 - 24		12 (39)
24 – 36		11 (35)
Disease status prior to transplant		
CR	9 (26)	5 (16)
Very good partial response	3 (9)	4 (13)
Partial response	9 (26)	7 (23)
Minimal response	1 (3)	1 (3)
No response	4 (11)	1 (3)
Progressive disease	3 (9)	5 (16)
Unknown	6 (17)	8 (26)
Conditioning regimen		
TBI + other	18 (51)	10 (32)
Bu + CY ± other	3 (9)	1 (3)
CY + other	4 (11)	6 (19)

Characteristics of patients	Did not receive prior auto, N (%)	Received prior auto, N (%)
Bu + Fludara ± other	2 (6)	6 (19)
Bu + other	1 (3)	2 (6)
Fludara + Melphalan	1 (3)	6 (19)
Melphlan + other	5 (14)	0
Etopside + Carboplatin	1 (3)	0
Donor recipient HLA match		
HLA-identical sibling	18 (51)	10 (32)
Other related donor	3 (9)	2 (6)
Matched unrelated donor	0	5 (16)
Mismatched unrelated donor	14 (40)	13 (42)
Matching unknown, unrelated donor	0	1 (3)
Graft source		
BM	16 (46)	11 (35)
PBSC	4 (11)	8 (26)
Cord Blood	15 (43)	12 (39)
Year of transplant		
1990 – 1994	14 (40)	1 (3)
1995 – 1999	5 (14)	8 (26)
2000 – 2004	12 (34)	9 (29)
2005 – 2007	4 (11)	13 (42)
GVHD prophylaxis		
T-cell depletion	3 (9)	1 (3)
MTX + CSA ± other	8 (23)	7 (23)
MTX ± other	4 (11)	2 (6)
CSA ± Other	17 (49)	17 (55)
Fk506 ± Other	0	2 (6)
Unknown[b]	3 (9)	2 (6)
Previous bone marrow involvement		
No	4 (11)	6 (19)
Yes	10 (29)	14 (45)
Unknown	21 (60)	11 (35)
Previous CNS involvement		
No	12 (34)	19 (61)
Yes	2 (6)	1 (3)
Unknown	21 (60)	11 (35)
Metastases present at diagnosis		
No	1 (3)	2 (6)
Yes	14 (40)	16 (52)
Missing	20 (57)	13 (42)
disease INSS stage at diagnosis		
Stage 1	1 (3)	0

Characteristics of patients	Did not receive prior auto, N (%)	Received prior auto, N (%)
Stage 3	4 (11)	3 (10)
Stage 4	10 (29)	14 (45)
Missing	20 (57)	14 (45)
Number of sites of disease at allogeneic transplant		
1	1 (3)	3 (10)
2	3 (9)	3 (10)
3	2 (6)	2 (6)
4	1 (3)	2 (6)
Missing	16 (46)	12 (39)
NA (disease status was CR, VGPR)	12 (34)	9 (29)
Chemo sensitive to last line of therapy		
No	2 (6)	1 (3)
Yes	8 (23)	12 (39)
did not receive chemotherapy as last line of therapy	2 (6)	0
Missing	23 (66)	18 (58)
Radiotherapy given as part of initial treatment		
No	12 (34)	12 (39)
Yes (primary tumor bed after resection as sit of radiotherapy)	1 (3)	2 (6)
Unknown	22 (63)	17 (55)
Donor-recipient sex match		
M – M	9 (26)	4 (13)
M – F	9 (26)	7 (23)
F – M	8 (23)	6 (19)
F – F	8 (23)	10 (32)
Unknown	1 (3)	4 (13)
Donor-recipient CMV status		
–/–	17 (49)	11 (35)
+/–	3 (9)	3 (10)
–/+	10 (29)	9 (29)
+/+	3 (9)	4 (13)
Unknown	2 (6)	4 (13)
Median (range) follow-up [c], months	72 (3-150)	45 (3-58)

Abbreviations: TBI = total body irradiation; CY = cyclophosphamide; CsA = cyclosporine; MTX = methotrexate; CMV = cytomegalovirus; GVHD = graft-versus-host disease; FK506 = tacrolimus.

Table 3a

Univariate probabilities of outcomes of all patients

Outcome event	All patients with available outcome data	
	N eval.	Prob (95% CI)[a]
ANC $> 0.5 \times 10^9$/L	111	
@ 28 days		83 (74-89)
@100 days		92 (85-96)
Platelets $> 20 \times 10^9$ /L	95	
@ 60 days		57 (46-67)
@100 days		60 (49-70)
Acute GVHD, Grades 2-4	103	
@100 days		28 (20-37)
@ 180 days		29 (21-38)
Chronic GVHD	112	
@ 1 year		14 (8-21)
@ 3 years		15 (9-22)
@5 years		15 (9-22)
Transplant-related mortality	115	
@ 100days		18 (12-26)
@ 1 year		25 (17-33)
@ 3 years		25 (18-34)
@ 5 years		25 (18-34)
Relapse	115	
@ 1 year		38 (29-47)
@ 3 years		52 (42-61)
@ 5 years		55 (45-64)
Disease-free survival	115	
@ 1 year		37 (28-46)
@ 3 years		23 (15-31)
@ 5 years		20 (13-27)
Overall survival	143	
@ 1 year		56 (47-64)
@ 3 years		29 (22-37)
@ 5 years		22 (15-30)

Table 3b

Univariate probabilities of outcomes by whether received prior autologous transplant

Outcome event	Did not receive prior auto		Received prior auto		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	
ANC > 0.5 × 10⁹/L	69		42		
@ 28 days		78 (66-86)		90 (76-96)	0.0806
@ 100 days		88 (78-94)		98 (84-100)	0.0433
Platelets > 20 × 10⁹ /L	54		41		
@ 60 days		65 (50-76)		47 (28-64)	0.1309
@ 100 days		69 (54-79)		50 (30-67)	0.1115
Acute GVHD, Grades 2-4	65		38		
@ 100 days		23 (14-34)		37 (22-52)	0.1466
@ 180 days		25 (15-36)		37 (22-52)	0.202
Chronic GVHD	68		44		
@ 1 year		10 (5-19)		19 (9-32)	0.2359
@ 3 years		12 (6-21)		19 (9-32)	0.3395
@ 5 years		12 (6-21)		19 (9-32)	0.3395
Transplant-related mortality	73		42		
@ 100days		19 (11-29)		17 (7-29)	0.7332
@ 1 year		25 (16-35)		24 (12-37)	0.8916
@ 3 years		26 (17-37)		24 (12-37)	0.7572
@ 5 years		26 (17-37)		24 (12-37)	0.7572
Relapse	73		42		
@ 1 year		27 (17-38)		57 (41-70)	0.0012
@ 3 years		43 (31-55)		67 (50-79)	0.0131
@ 5 years		46 (34-58)		70 (53-82)	0.0123
Disease-free survival	73		42		
@ 1 year		48 (36-59)		19 (9-32)	0.0006
@ 3 years		30 (20-41)		10 (3-21)	0.0037
@ 5 years		27 (17-38)		6 (1-17)	0.0018
Overall survival	97		46		

Outcome event	Did not receive prior auto		Received prior auto		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	
@ 1 year		59 (48-68)		50 (35-64)	0.3439
@ 3 years		36 (26-46)		16 (7-28)	0.0086
@ 5 years		29 (20-39)		7 (1-18)	0.0005

Table 3c

Univariate probabilities of outcomes by donor type

Outcome event	HLA-identical sibling		Other related		Unrelated		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	
ANC > 0.5 × 10⁹/L	50		23		38		
@ 28 days		86 (72-93)		87 (64-96)		76 (59-87)	0.4703
@ 100 days		92 (80-97)		87 (64-96)		95 (81-99)	0.6149
Platelets > 20 × 10⁹ /L	39		19		37		
@ 60 days		65 (48-78)		63 (38-80)		45 (27-61)	0.199
@ 100 days		68 (50-81)		63 (38-80)		51 (32-66)	0.3311
Acute GVHD, Grades 2-4	51		19		33		
@ 100 days		25 (15-38)		21 (7-41)		36 (20-52)	0.4306
@ 180 days		25 (15-38)		21 (7-41)		40 (23-56)	0.2802
Chronic GVHD	53		21		38		
@ 1 year		12 (5-22)		19 (6-38)		14 (5-27)	0.7333
@ 3 years		12 (5-22)		24 (9-43)		14 (5-27)	0.489
@5 years		12 (5-22)		24 (9-43)		14 (5-27)	0.489
Transplant-related mortality	55		21		39		
@ 100days		18 (9-29)		19 (6-38)		18 (8-31)	0.9944
@ 1 year		24 (14-36)		34 (15-54)		21 (10-34)	0.5397
@ 3 years		26 (15-38)		34 (15-54)		21 (10-34)	0.5397
@ 5 years		26 (15-38)		34 (15-54)		21 (10-34)	0.5436
Relapse	55		21		39		
@ 1 year		30 (18-42)		15 (4-33)		63 (46-76)	<.0001
@ 3 years		52 (38-64)		25 (9-45)		66 (49-79)	0.0043
@ 5 years		56 (41-68)		31 (13-51)		66 (49-79)	0.0263
Disease-free survival	55		21		39		
@ 1 year		47 (33-59)		51 (28-70)		16 (7-29)	0.0007
@ 3 years		22 (12-34)		41 (20-61)		13 (5-26)	0.079
@ 5 years		19 (10-30)		35 (15-55)		13 (5-26)	0.2133

Outcome event	HLA-identical sibling		Other related		Unrelated		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	
Overall survival	74		29		40		
@ 1 year		63 (51–73)		60 (39–75)		40 (25–55)	0.0529
@ 3 years		30 (19–41)		48 (28–65)		16 (7–29)	0.0175
@ 5 years		22 (13–33)		33 (16–52)		16 (7–29)	0.3101

Table 3d

Univariate probabilities of outcomes by disease status prior to transplant

Outcome event	CR, VGPR		PR		MR, NR, Progressive		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	
ANC > 0.5 × 10^9/L	41		20		28		
@ 28 days		85 (69-93)		80 (55-92)		89 (68-97)	0.6971
@ 100 days		93 (78-98)		100		89 (68-97)	
Platelets > 20 × 10^9/L	34		19		25		
@ 60 days		69 (50-82)		57 (30-76)		48 (27-66)	0.2639
@ 100 days		72 (53-85)		62 (35-81)		52 (31-70)	0.2919
Acute GVHD, Grades 2-4	36		19		25		
@ 100 days		19 (9-34)		32 (13-52)		36 (18-55)	0.3178
@ 180 days		19 (9-34)		32 (13-52)		40 (21-58)	0.2031
Chronic GVHD	41		20		28		
@ 1 year		5 (1-15)		10 (2-28)		25 (11-42)	0.0755
@ 3 years		7 (2-18)		10 (2-28)		25 (11-42)	0.1634
@ 5 years		7 (2-18)		10 (2-28)		25 (11-42)	0.1634
Transplant-related mortality	41		19		33		
@ 100days		15 (6-27)		21 (7-41)		24 (11-40)	0.5641
@ 1 year		15 (6-27)		21 (7-41)		36 (21-52)	0.0973
@ 3 years		15 (6-27)		21 (7-41)		36 (21-52)	0.0973
@ 5 years		15 (6-27)		21 (7-41)		36 (21-52)	0.0973
Relapse	41		19		33		
@ 1 year		18 (8-31)		67 (41-84)		48 (31-64)	<.0001
@ 3 years		44 (28-59)		67 (41-84)		55 (36-70)	0.223
@ 5 years		47 (30-61)		67 (41-84)		61 (42-75)	0.2627
Disease-free survival	41		19		33		
@ 1 year		67 (50-80)		12 (2-31)		16 (6-29)	<.0001
@ 3 years		41 (26-56)		12 (2-31)		9 (2-22)	0.0019
@ 5 years		39 (24-54)		12 (2-31)		3 (0-13)	0.0001

Outcome event	CR, VGPR		PR		MR, NR, Progressive		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	
Overall survival	50		25		38		
@ 1 year		79 (65-88)		43 (22-62)		39 (24-55)	<.0001
@ 3 years		52 (37-65)		14 (4-32)		11 (4-24)	<.0001
@ 5 years		47 (32-61)		9 (2-26)		6 (1-16)	<.0001

Abbreviations: VGPR- Very good partial response; PR- Partial response; MR- Minimal response; NR- No response

[a]Probabilities of ANC>0.5 × 10^9/L, Platelets > 20 × 10^9/L, acute GVHD, chronic GVHD, treatment related mortality and relapse were calculated using the cumulative incidence estimate. Probabilities of overall survival and disease free survival were calculated using the Kaplan-Meier product limit estimate

Table 4

Outcomes of patients by disease status prior to transplant for patients without prior auto transplants

Outcome event	In CR, VGPR, PR		In MR, NR, progressive		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)[a]	
Transplant-related mortality	41		19		
@ 100days		15 (6-27)		32 (13-52)	0.1582
@ 1 year		15 (6-27)		42 (20-62)	0.0292
@ 3 years		15 (6-27)		42 (20-62)	0.0292
@ 5 years		15 (6-27)		42 (20-62)	0.0292
Relapse	41		19		
@ 1 year		26 (13-40)		37 (17-57)	0.4068
@ 3 years		45 (29-60)		47 (24-67)	0.8577
@ 5 years		48 (31-62)		53 (29-72)	0.7178
Disease-free survival	41		19		$P_{overall}$<0.0001
@ 1 year		59 (42-73)		21 (7-41)	0.0017
@ 3 years		41 (25-55)		11 (2-28)	0.0048
@ 5 years		38 (23-53)		5 (0-21)	0.0005
Overall survival	55		24		$P_{overall}$<0.0001
@ 1 year		67 (52-78)		44 (24-63)	0.0644
@ 3 years		45 (31-59)		13 (3-30)	0.0015
@ 5 years		41 (27-54)		9 (2-24)	0.0006

Table 5

Cause of death

	Did not receive prior auto, N (%)	Received prior auto, N (%)	All patients, N (%)
Number of patients	97	46	143
Number of death	66	40	106
Primary disease	42 (64)	30 (75)	72 (68)
Infection	7 (11)	2 (5)	9 (8)
ARDS	3 (5)	1 (3)	4 (3)
Organ failure	4 (6)	4 (10)	8 (8)
Graft failure	1 (2)	0 (.)	1 (1)
Hemorrhage	1 (2)	1 (3)	2 (2)
GVHD	4 (5)	0 (.)	4 (4)
Vascular	0 (.)	1 (2)	1 (1)
Unknown	4 (5)	1 (2)	5 (5)

Table 6

Outcomes of patients who had cord blood transplants

Outcome event		
	N eval.	**Prob (95% CI)**
Transplant-related mortality		
@ 100days	31	19 (8-35)
@ 1 year		23 (10-39)
@ 3 years		23 (10-39)
@ 5 years		23 (10-39)
Relapse	31	
@ 1 year		57 (37-72)
@ 3 years		60 (41-75)
@ 5 years		60 (41-75)
Disease-free survival	31	
@ 1 year		20 (8-36)
@ 3 years		17 (6-32)
@ 5 years		17 (6-32)
Overall survival	33	
@ 1 year		39 (22-56)
@ 3 years		20 (8-35)
@ 5 years		20 (8-35)

Abbreviations: CI: confidence interval.

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Table 7

Outcomes by conditioning regimen subtype

Outcome event	Non-myeloablative/RIC		Myeloablative		P-value
	N eval.	Prob (95% CI)[a]	N eval.	Prob (95% CI)	
Transplant-related mortality	33		73		
@ 100days		9 (2-22)		23 (14-33)	0.0437
@ 1 year		15 (6-30)		30 (20-41)	0.0742
@ 3 years		19 (8-34)		30 (20-41)	0.1803
@ 5 years		19 (8-34)		30 (20-41)	0.1803
Relapse					
@ 1 year		65 (46-79)		27 (17-37)	0.0001
@ 3 years		69 (49-82)		43 (31-54)	0.011
@ 5 years		69 (49-82)		47 (35-58)	0.036
Disease-free survival	33		73		P_overall=0.167
@ 1 year		19 (8-34)		43 (31-54)	0.0097
@ 3 years		13 (4-27)		27 (17-38)	0.0776
@ 5 years		13 (4-27)		22 (13-33)	0.2175
Overall survival	35		96		P_overall=0.128
@ 1 year		51 (33-67)		56 (45-65)	0.6248
@ 3 years		16 (6-30)		34 (25-44)	0.026
@ 5 years		16 (6-30)		25 (17-35)	0.2348

Abreviations: CI: confidence interval, RIC: reduced intensity conditioning