ASBMT American Society for Blood and Marrow Transplantation

Nonmyeloablative Second Transplants are Associated with Lower Nonrelapse Mortality and Superior Survival Than Myeloablative Second Transplants

Brian T. Hill,[1] Brian J. Bolwell,[1] Lisa Rybicki,[2] Robert Dean,[1] Matt Kalaycio,[1] Brad Pohlman,[1] Shawnda Tench,[2] Ronald Sobecks,[1] Steven Andresen,[1] Edward Copelan[1]

Allogeneic hematopoietic stem cell transplantation (SCT) for patients who have previously undergone allogeneic or autologous SCT is potentially curative, but dangerous. To identify patient, disease, and treatment characteristics associated with outcome, we analyzed prognostic factors in 98 consecutive patients who underwent second transplants using allogeneic donors at the Cleveland Clinic between May 1987 and October 2008. Inclusion criteria included age ≥18 years, first SCT either autologous or allogeneic, and second SCT allogeneic. Patients whose second transplant was myeloablative (MA) had shorter survival (median 3.2 versus 14.7 months, $P < .001$) than patients whose second transplant was nonmyeloablative (NMA). In multivariable analysis, MA second transplant was associated with a higher risk of NRM (hazard ratio [HR] 2.01, $P = 0.022$) and death (HR 2.13, $P = 0.002$). Improved survival after NMA second transplant occurred primarily in patients without acute leukemia and when the first transplant was autologous. Among 17 patients transplanted within 3 months of first transplant, mortality was 100% and median survival was 2.3 months. MA transplantation within 3 months of prior SCT carries an unacceptably high rate of NRM. NMA second transplants were associated with substantially less NRM and despite a higher incidence of relapse, significantly improved survival compared to MA second transplants.

Biol Blood Marrow Transplant 16: 1738-1746 (2010) © *2010 American Society for Blood and Marrow Transplantation*

KEY WORDS: Myeloablative, Nonmyeloablative, Allogeneic, Autologous, Stem cell Transplant, Bone marrow Transplant

INTRODUCTION

Despite recent advances, following hematopoietic stem cell transplantation (SCT), many patients will develop disease relapse, graft failure, or treatment-related myelodysplastic sydrome [1]. Performing a second allogeneic SCT represents the only curative treatment in these circumstances, but it is dangerous for patients who have previously undergone either allogeneic or autologous SCT.

A number of retrospective series have examined outcomes of second transplant for patients with hematologic malignancies [2-5]. The best outcomes occur when the second transplant is performed for graft failure, with estimated survival rates of 30%-37% after 3 years [6-11]. For patients who exhibit graft failure after umbilical cord SCT, results appear less favorable with a reported 2-year survival of 24% [3].

The largest published series of patients with relapsed acute leukemia after autologous SCT showed superior 2-year survival for patients who underwent second transplant compared to those treated with chemotherapy alone [12]. Younger age and longer interval between transplants were associated with better survival in multivariate analysis. Radich et al. [5] reported the outcomes of 59 adult and pediatric patients with relapsed hematologic malignancy after autologous transplantation. Univariate analysis demonstrated that superior disease-free survival (DFS) was associated with age <17 years at the time of the second transplantation, remission before the second transplantation, total body irradiation (TBI)-based preparative regimen for the second transplant, and a diagnosis of acute myelogenous leukemia (AML). The probabilities of nonrelapse mortality (NRM),

From the [1]Hematologic Oncology and Blood Disorders, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio; and [2]Quantitative Health Sciences, Cleveland Clinic Lerner Research Institute, Cleveland, Ohio.

Financial disclosure: See Acknowledgments on page 1745.

Correspondence and reprint requests: Brian T. Hill, MD, PhD, Cleveland Clinic Taussig Cancer Institute, Hematologic Oncology and Blood Disorders, Cleveland, OH 44195 (e-mail: hillb2@ccf.org).

Received February 10, 2010; accepted June 6, 2010

1083-8791/$36.00
doi:10.1016/j.bbmt.2010.06.009

relapse, and DFS, 2 years after second transplant, were 51%, 26%, and 23%, respectively.

Performing a repeat myeloablative (MA) allogeneic transplant clearly carries high risk of NRM. For patients with relapsed leukemia after initial allogeneic transplant, performing a second allogeneic transplant is associated with NRM between 42% and 46% at 5 years [2,13]. In studies from the European Cooperative Group for Bone Marrow Transplant and the International Bone Marrow Registry, young age, longer duration of remission after first transplant, and complete remission (CR) at the time of second transplant were associated with improved survival.

Because of the high NRM rates of second MA transplants, nonmyeloablative (NMA) conditioning regimens have been utilized to improve outcomes. Shaw et al. report NRM of 27% at 2 years for 71 patients who underwent reduced-intensity conditioning (RIC) for relapsed hematologic malignancy after an initial allogeneic transplant [4].

We retrospectively analyzed results of second transplants using allogeneic donors to determine whether NRM, relapse, and overall survival (OS) differed significantly between MA and NMA groups. We define NMA transplantation as those utilizing preparative regimens that have been demonstrated to not directly result in complete loss of recipient hematopoiesis. We used univariate and multivariate analyses to determine prognostic factors.

METHODS AND MATERIALS

Patient Population

Ninety-eight adult patients (≥18 years old) who underwent a second SCT from May 1987 to October 2008, after prior allogeneic or autologous SCT, were identified from the Unified Transplant Database of the Cleveland Clinic Taussig Cancer Institute. All patients were treated on protocols approved by the institutional review board of the Cleveland Clinic and gave written informed consent.

Second Transplant Regimens

Second transplant regimens are detailed in Table 1. All hospitalized patients stayed in a dedicated inpatient unit in laminar airflow rooms with standard infection control procedures. Graft-versus-host disease (GVHD) prophylaxis consisted of a combination of mycophenolate mofetil and cyclosporine or tacrolimus and methotrexate, with or without corticosteroids.

Classification of Acute Leukemia

We classified acute leukemia as AML, acute lymphoblastic leukemia (ALL), and chronic myelogenous leukemia (CML) in blast crisis.

Statistical Analysis

The primary study variables were compared between MA and NMA second transplants using Fisher's exact test (categoric variables) or the Wilcoxon rank sum test (continuous variables). Outcomes were calculated relative to the date of second transplant, until the event of interest, or until the date of last follow-up. Relapse and NRM were estimated using the cumulative incidence method and compared between MA and NMA transplants using the Pepe-Mori test. Survival was estimated using the Kaplan-Meier test and compared between MA and NMA transplants using the log-rank test. Cox proportional hazard analysis was used to identify univariate and multivariate risk factors for relapse, NRM, and mortality. For the multivariate analysis, stepwise analysis was used with

Table 1. Second Transplant Preparative Regimens

Regimen	Bu (mg/kg)	TBI (cGy)	Flu (mg/m^2)	Cy (mg/kg)	VP (mg/kg)	ATG (mg/kg)
MA (59)						
Bu-Cy (10)	12.8 i.v. or 16 p.o.	—	—	120	—	—
Bu-Cy-VP (14)	11.2 i.v. or 14 p.o.	—	—	120	50	—
VP-TBI (8)	—	1320	—	—	50	—
Cy-TBI (13)	—	1200	—	120	—	—
Cy-ATG (8)	—	—	—	200	—	150
Other MA* (6)						
NMA (39)						
Flu-TBI 100 (1)	—	100	90	—	—	—
Flu-TBI 200 (11)	—	200	90	—	—	—
Flu-TBI 300 (1)	—	300	90	—	—	—
Flu-TBI 400 (16)	—	400	90	—	—	
ATG (5)						150
Other NMA† (5)						

Bu indicates busulfan; TBI, total-body irradiation; Flu, fludarabine; Cy, cyclophosphamide; VP, etoposide (VP-16); ATG, antithymocyte globulin; i.v., intravenously; p.o., orally; MEDI507, experimental anti-CD2 monoclonal antibody.

*Other MA include 2 patients who received preparative regimen of Cy alone and 1 patient who received the following preparative regimens: Bu-Cy-thiotepa, Bu-Cy-thioptepa, Bu-ATG, TBI-VP-ATG.

†Other NMA includes 1 patient each who received the following preparative regimens: Flu/alemtuzumab, alemtuzumab alone, Flu-Cy, Cy-TBI-MEDI507, and TBI-MEDI507 alone.

Table 2. Characteristics of Patients Who Received MA and NMA Second Transplant

Characteristic	MA (n = 59) Number (%)		NMA (n = 39) Number (%)		P
Age at second transplant, years, median (range)		34 (18-56)		45 (21-63)	<.001
Male	32 (54.2)		24 (61.5)		0.54
KPS ≤80 (n = 55 for MA, 26 for NMA)	12 (23.5)		9 (30.0)		0.60
First transplant type					<.001
Autologous	23 (39.0)		25 (64.1)		
Allogeneic	36 (61.0)		14 (35.9)		
Preparative regimen for first transplant					.12
Busulfan-based	52 (88.1)		30 (76.9)		
TBI-based	4 (6.8)		6 (15.4)		
Other	3 (5.1)		3 (7.7)		
Time between first and second transplant					
Median time in months (range)		10.6 (0.9-129)		16.2 (0.9- 193)	.027
<3 months	11 (18.6)		6 (15.4)		
>3 months	48 (81.4)		33 (84.6)		0.79
Diagnosis for second transplant					<.001
Acute leukemia					
AML	22 (37.3)			6 (15.4)	
ALL	12 (20.3)			1 (2.6)	
CML in blast crisis	2 (3.4)			1 (2.6)	
Other					
CML, chronic phase or remission	9 (10.2)			5 (12.8)	
NHL	6 (10.2)			9 (23.1)	
MDS	6 (10.2)			4 (10.2)	
HL	4 (6.8)			5 (12.8)	
Myeloma	0			7 (18.0)	
Myeloproliferative neoplasm	0			1 (2.6)	
CLL	1 (1.7)			0	
Aplastic anemia	1 (1.7)			0	
Same diagnosis for first and second transplant	51 (86.4)		34 (87.2)		1.0
Disease status at second transplant					1.0
CR	14 (23.7)		9 (23.1)		
<CR	45 (76.3)		30 (76.9)		
Donor relationship for second transplant					0.68
Related	32 (54.2)		23 (59.0)		
Unrelated	27 (45.8)		16 (41.0)		
Preparative regimen for second transplant					<.001
Busulfan-based	24 (40.6)		0		
TBI-based	22 (37.3)		31 (79.5)		
Other	13 (22.0)		3 (20.5)		
$CD34^+$ dose, median, $\times 10^6$/kg (range), (n = 44 for MA, 33 for NMA)		2.7 (0.7-15.0)		5.6 (0.4-11.9)	<.001
Length of hospital stay in days, median, days (range), (n = 59 for MA, 8 for NMA)		32 (8-109)		25 (11-110)	—
Time until PMN >500/μL, median, days (range), (n = 47 for MA, 20 for NMA)		15 (0-40)		10 (0-30)	0.004
Time until platelet count >20,000/μL, median, days, (range) (n = 33 for MA, 18 for NMA)		22 (11-78)		13 (6-159)	.021
Worst episode of acute GVHD					—
None	20 (33.9)		20 (51.3)		
Grade I	8 (13.6)		4 (10.3)		
Grade II	14 (23.7)		6 (15.4)		
Grade III	9 (15.3)		4 (10.3)		
Grade IV	9 (13.6)		5 (12.8)		
Worst episode of chronic GVHD					
None	41 (69.5)		25 (64.1)		—
Limited	5 (8.4)		45 (112.8)		
Extensive	13 (22.0)		9 (27.3)		
Secondary malignancy	2 (3.4)		3 (7.7)		—
Follow-up among living patients, median, months (range)		72.9 (12.9-136.4)		36.1 (7.1-83.6)	.17

KPS indicates Karnofsky performance status; TBI, total body irradiation; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin lymphoma; MDS, myelodysplastic syndrome; HL, Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CR, complete remission; PMN, polymorphonuclear cells; GVHD, graft-versus-host disease; MA, myeloablative; NMA, nonmyeloablative.

a variable entry criterion of $P < .10$ and a variable retention criterion of $P < .05$. Cox analyses are summarized as the hazard ratio (HR), 95% confidence interval (CI) for the HR, and the corresponding *P*-value. All analyses were done using SAS® software (SAS Institute Inc., Cary, NC). All statistical tests were 2-sided, and $P < .05$ was used to indicate statistical significance.

Table 3. Outcomes of MA and NMA Second Transplant

Characteristic	MA (n = 59) Number (%)	NMA (n = 8) Number (%)	P
Cumulative incidence of:			
Relapse	15 (25.4)	18 (46.2)	0.12
Nonrelapse mortality	36 (61.0)	16 (41.0)	0.16
Death	53 (90.6)	24 (61.5)	<.001
Survival, median, months	3.2	14.7	<.001
Cause of death (n = 53 for MA, n = 24 for NMA)			—
Relapse	17 (32.1)	8 (33.3)	
Acute GVHD	11 (20.8)	4 (16.7)	
Chronic GVHD	6 (11.3)	3 (12.5)	
Infection	6 (11.3)	0	
Pulmonary toxicity	3 (5.7)	3 (12.5)	
Nonpulmonary organ failure	5 (9.4)	0	
Graft failure	2 (3.8)	2 (8.3)	
Cardiac	1 (1.9)	1 (4.2)	
Secondary malignancy	1 (1.9)	1 (4.2)	
Brain herniation	1 (1.9)	0	
CNS hemorrhage	0	1 (4.2)	
Unknown	1 (1.9)	0	

MA indicates myeloablative; NMA, nonmyeloablative; GVHD, graft-versus-host disease; CNS, central nervous system.

RESULTS

Patient Characteristics

The characteristics of the 98 consecutive patients who underwent MA or NMA second transplants are summarized in Table 2. The median age of patients who underwent MA second transplant was 34 years (range: 18-56 years) compared to 45 years (range: 21-63 years) for patients who underwent NMA second transplant ($P < .001$). There were comparable distributions of males and females in both groups. Twelve of 59 (23.5%) patients who underwent MA second transplant had a Karnofsky performance status (KPS) of 80 or lower, compared to 9 of 39 (30.0%) of patients who underwent NMA second transplant ($P = .60$). Thirty-six of 59 (61%) patients who underwent MA second transplant had undergone allogeneic first transplant, compared to 14 of 39 (35.9%) patients who underwent NMA second transplant ($P < .001$). The use of busulfan (Bu) and TBI during first transplant was similar in both groups. The median time from first transplant to MA second transplant was shorter (10.6 months [range: 0.9-129 months]) than the time from first transplant to NMA second transplant (16.2 months [range: 0.9-193], $P = .027$). Thirty-six of 59 (61.0%) patients who underwent MA second transplant had a diagnosis of acute leukemia, compared to 8 of 39 (20.5%) patients who underwent NMA second transplant ($P < .001$). The indication for second transplant was the same as for first transplant in a significant majority of cases. Donor type and disease status at the time of second transplant did not differ significantly between groups.

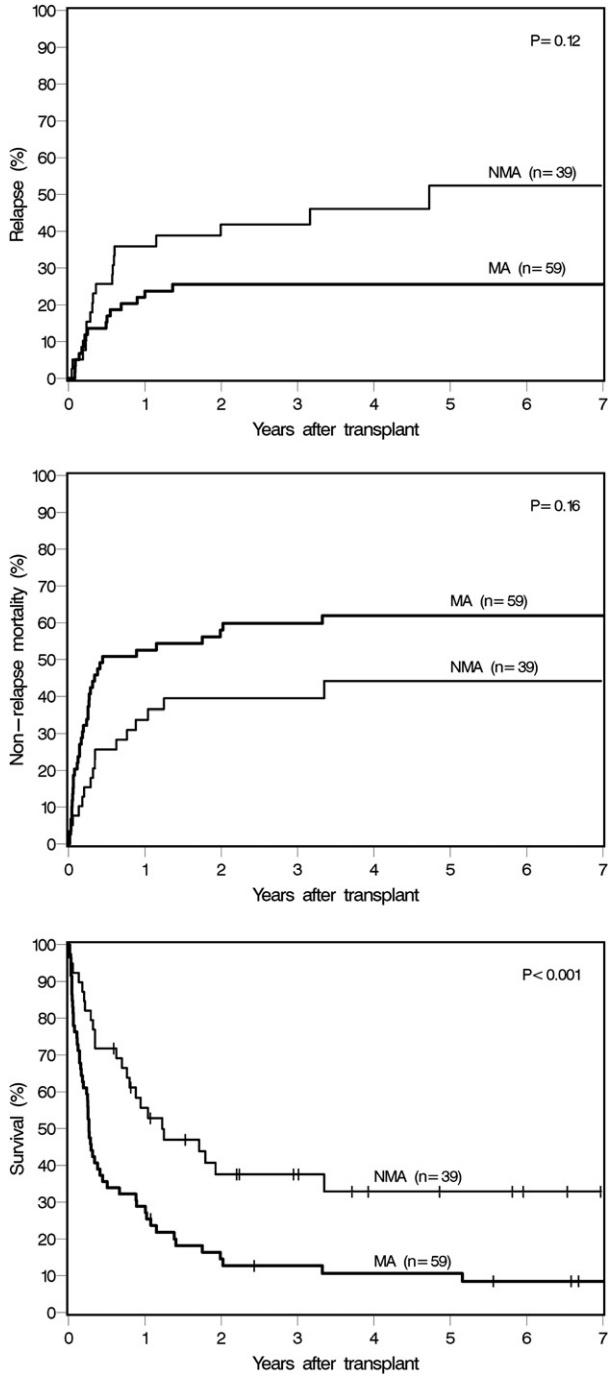

Figure 1. Kaplan-Meier estimates of relapse, NRM, and OS after MA (thick lines) and NMA (thin lines) second transplant.

Second Transplant Characteristics

Characteristics of second transplant procedures are also shown in Table 2. The median number of $CD34^+$ cells infused during MA second transplant was 2.7×10^6 cells/kg (range: 0.7-15.0) compared to 5.6×10^6 cells/kg (range: 0.4-11.9) for patients undergoing NMA SCT ($P < .001$). All patients who underwent MA second transplant required continuous hospitalization whereas only 8 of 39 (20.5%) patients

who underwent NMA second transplant were hospitalized during the transplant period. Recipients of NMA second transplant required shorter periods of hospitalization (median of 25 days [range: 11-110]) compared to patients who underwent MA second transplant (median of 32 days [range: 8-109]). Patients who underwent NMA second transplant also had a shorter time to achieve a polymorphonuclear cell count of 500 cells/μL (10 days [range: 0-30] versus 15 days [range: 8-40], $P = 0.004$) and platelet count of 20,000 cells/μL (13 days [range: 0-159] versus 22 days [range: 11-78], $P = .021$). The incidences of both acute and chronic GVHD (aGVHD, cGVHD) was comparable in both groups. The two groups also had similar incidences of secondary malignancies and comparable duration of follow-up.

Second Transplant Regimens

Twenty-four of 59 (40.6%) patients who underwent an MA second transplant received a Bu-based preparative regimen compared to none of the patients who underwent an NMA second transplant. Thirty-one of 39 (79.5%) patients who received an NMA second transplant received a TBI-based preparative regimen, compared to 22 of 59 (37.3%) patients who received an MA second transplant ($P < .001$). Preparative regimens for MA and NMA transplants are shown in Table 1. Bu was used at a cumulative dose of 11.2 or 12.8 mg/kg intravenously (i.v.) (14 or 16 mg/kg orally [p.o.]) depending on whether or not it was combined with VP16. MA TBI doses were 1200 or 1320 cGy. The NMA dose of TBI was in the range of 100-400 cGy in combination with fludarabine 90 mg/kg. It has previously been demonstrated that a regimen utilizing TBI 400 cGy combined with fludarabine 90 mg/m^2 is NMA [14].

Mortality and Disease Relapse after MA and NMA Second Transplant

The incidences of disease relapse, NRM, and mortality after second transplant are shown in Table 3. Patients who underwent MA second transplant experienced less disease relapse than those who underwent NMA second transplant (25.4% versus 46.2%, $P = 0.12$). NRM was higher for patients who underwent MA second transplant compared to patients who underwent NMA second transplant (61.0% versus 41.0%, $P = .16$). NRM and overall mortality were both higher for patients who underwent MA second transplant compared to patients who underwent NMA second transplant (61.0% vs 41.0%, $P = 0.16$ for NRM and 89.8 vs. 61.5%, $P < 0.001$ for death). The median survival of patients who underwent MA second transplant was 3.2 months, compared to 14.7 months for patient who underwent NMA second transplant ($P < .001$). Causes of death after MA and NMA second transplant are shown. Estimates of relapse, NRM, and OS after second transplant are shown in Figure 1.

Outcomes Stratified by Initial Diagnosis and Type of Second Transplant

We analyzed patient outcomes by diagnosis at the time of first transplant as well as by type of second transplant. Patients who underwent NMA second transplant for a diagnosis of acute leukemia experienced higher relapse rates, but also a trend toward superior OS relative to patients with acute leukemia who underwent MA second transplant (Figure 2) ($P < 0.001$). This trend for superior overall survival is similar for patients with acute leukemia ($P = 0.38$).

Outcomes Stratified by Type of First Transplant and Type of Second Transplant

For patients who underwent autologous first transplant, NMA second transplant was associated with an improvement in OS relative to MA second transplant

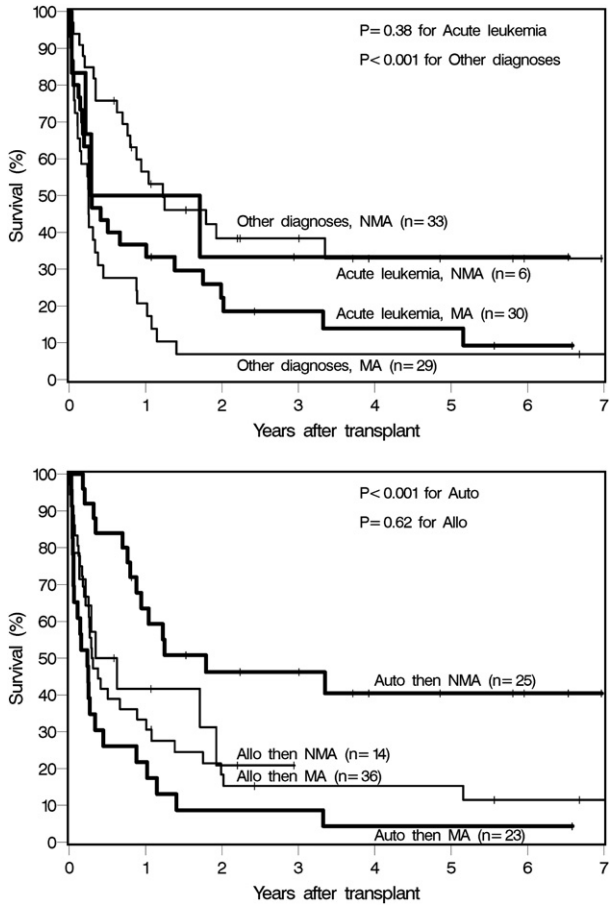

Figure 2. Top panel: Kaplan-Meier estimates of OS after myeloablative (MA) and nonmyeloablative (NMA) second transplant for patients with acute leukemia (thick lines) and diagnoses other than acute leukemia (thin lines). Bottom panel. Kaplan-Meier estimates of OS MA and NMA second transplant for patients who underwent prior autologous (thick lines) or allogeneic (thin lines) transplant.

Table 4. Univariate Risk Factors for Relapse, NRM, and Mortality

	Relapse		NRM		Mortality	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age at transplant (years)						
per 10 year increase	1.20 (0.92-1.58)	.17	0.93 (0.75-1.16)	.53	0.97 (0.81-1.16)	.73
Sex						
Male/female	1.15 (0.58-2.29)	.68	1.12 (0.65-1.94)	.68	1.19 (0.76-1.88)	.44
KPS (n = 82)						
30-70/100	3.81 (0.66-21.9)	.13	2.60 (0.93-7.24)	.07	3.03 (1.23-7.48)	.016
80/100	1.40 (0.35-5.64)	.63	1.03 (0.39-2.70)	.96	1.35 (0.59-3.06)	.48
90/100	2.45 (0.81-7.41)	.11	1.46 (0.69-3.07)	.32	1.96 (1.02-3.78)	.044
Preparative regimen for first transplant						
TBI/busulfan	1.24 (0.43-3.59)	.69	0.49 (0.15-1.58)	.23	0.81 (0.37-1.76)	.59
Other/busulfan	2.06 (0.62-6.86)	.24	0.96 (0.30-3.10)	.95	0.92 (0.34-2.54)	.88
First transplant type						
Auto/MA	2.21 (0.98-4.98)	.06	0.67 (0.38-1.16)	.15	0.71 (0.45-1.12)	.14
Donor relationship for second transplant						
Unrelated/related	1.01 (0.50-2.06)	.98	1.50 (0.87-2.59)	.14	1.31 (0.83-2.06)	.24
Second transplant type						
MA/NMA	0.75 (0.42-1.65)	0.60	2.24 (1.73-6.63)	0.008	2.30 (1.42-3.74)	<.001
Time between transplants						
≤3 months/>3 months	—	—	4.10 (2.22-7.60)	<.001	2.97 (1.69-5.22)	<.001
Disease status at second transplant						
<CR/CR	3.22 (1.12-9.27)	.031	1.18 (0.62-2.25)	.62	1.22 (0.72-2.08)	.46
Preparative regimen for second transplant						
TBI/busulfan	0.63 (0.29-1.34)	.23	0.69 (0.35-1.35)	.28	0.51 (0.30-0.85)	.011
Other/busulfan	0.52 (0.14-1.91)	.33	1.65 (0.76-3.56)	.21	1.14 (0.60-2.15)	.69

CI indicates confidence interval; NRM, nonrelapse mortality; TBI, total body irradiation; KPS, Karnofsky performance status; Auto, autologous stem cell transplant; MA, myeloablative; NMA, nonmyeloablative; CR, complete remission; HR, hazard ratio.

(Figure 2) ($P < 0.001$). This difference in outcome was not statistically significant for those patients who underwent allogeneic first transplant ($P = 0.62$).

Prognostic Variables

Univariate risk factors for relapse, NRM, and overall mortality are shown in Table 4. Factors not associated with any of these outcomes included patient age, sex, preparative regimen for first transplant, first transplant type, and donor relationship for second transplant. In univariate Cox analysis, the only prognostic factor identified for relapse was disease status; patients not in CR at the time of second transplant were at increased risk of relapse relative to patients in CR at the time of second transplant (HR of 3.22, $P = .031$). Disease status was not associated with NRM or death. Relative to NMA second transplant, MA second transplant was associated with increased risk of NRM (HR 2.24, $P = 0.008$) and death (HR 2.30, $P < .001$). Likewise, an interval between transplants of <3 months was also associated with an increased risk of NRM (HR 4.10, $P < .001$) and death (HR 2.97, $P < .001$). Additionally, in univariate analysis, patients who received a TBI-based second transplant regimen had lower risk of mortality than those who received a Bu-based regimen (HR 0.51, $P = .011$).

Multivariate risk factors for relapse, NRM, and mortality are shown in Table 5. MA second transplant conferred less risk of relapse (HR 0.42, $P = .10$), but an increased risk of NRM (HR 2.01, $P = 0.022$) and death (HR 2.13, $P = .002$) when compared to NMA second

Table 5. Multivariable Risk Factors for Relapse, NRM, and Mortality

	Relapse		NRM		Mortality	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Second transplant type						
MA/NMA	0.42 (0.15-1.18)	0.10	2.01 (1.10-3.65)	0.022	2.13 (1.30-3.47)	0.002
Time between transplants						
≤3 months/>3 months	—	—	3.71 (2.00-6.89)	<.001	2.61 (1.49-4.59)	<0.001
Disease status at second transplant						
<CR/CR	4.87 (1.58-15.04)	.006	—	—	—	—
Preparative regimen for second transplant						
TBI/busulfan	0.20 (0.05-0.59)	.008				
Other/busulfan	0.36 (0.09-1.42)	.14	—	—	—	—

Auto indicates autologous stem cell transplant; MA, myeloablative; NMA, nonmyeloablative; NRM, nonrelapse mortality; TBI, total body irradiation; CR, complete remission; CI, confidence interval; HR, hazard ratio.

transplant. Patients not in CR at the time of second transplant had increased risk of relapse (HR 4.87, $P = .006$). Patients who underwent second transplant within 3 months of first transplant were at an increased risk of NRM (HR 3.71, $P < .001$) and death (HR 2.61, $P < .001$) relative to patients whose interval between transplants was longer than 3 months.

Second Transplants Performed within 3 Months of First Transplant

Characteristics of outcomes for patients who underwent second transplant within 3 months of first transplant are shown in Table 6 and compared to the outcomes of patients who underwent second transplant more than 3 months after first transplant. Eleven of 17 (64.7%) patients whose interval between transplants was <3 months received an MA second transplant. Forty-eight of 81 (59.3%) patients whose interval between transplants exceeded 3 months received MA second transplants. The remainder of patients received an NMA second transplant. For patients whose interval between transplants was <3 months, the incidence of NRM and mortality were 94.1% and 100%, respectively. Median survival was 2.3 months. For patients whose interval between transplants was >3 months the cumulative rates of relapse, NRM, and mortality were 40.7%, 44.4%, and 74.1%, respectively. Kaplan-Meier estimates of OS for patients whose interval between transplants was <3 months are shown in Figure 3 (top left panel).

We also assessed the outcomes of patients who were transplanted >3 months after first transplant based on whether the second transplant was MA or NMA. As shown in Figure 3, patients who underwent an NMA conditioning regimen more than 3 months after first transplant had higher relapse rates but lower NRM resulting in superior OS. Five-year survival estimates were 23.4% among patients who transplanted >3 months after first transplant, 13.1% among patients who underwent MA second transplant >3 months after first transplant, and 38.9% among patients who underwent NMA >3 months after the first transplant ($P < .001$).

Table 6. Characteristics of Patients Who Underwent Second Transplant within 3 Months and after 3 Months of First Transplant

	<3 months (n = 17)	>3 months (n = 81)	
	Number (percent)	Number (percent)	*P*
Type of transplant			
Myeloablative	11 (64.7)	48 (59.3)	—
Incidence of			<.001
Relapse	0	33 (40.7)	
NRM	16 (94.1)	36 (44.4)	
Death	17 (100)	60 (74.1)	
Median survival, months	2.3	10.6	<.001

NRM indicates nonrelapse mortality.

DISCUSSION

Allogeneic transplantation represents the only potentially curative therapy for most patients who have failed prior allogeneic or autologous transplant, but it is performed infrequently because of its substantial morbidity and mortality. To avoid this excessive toxicity, NMA second transplantation has been utilized. We describe here the largest series of patients in whom a direct comparison can be made between the outcomes of NMA second transplants and traditional MA second transplants. There is limited evidence demonstrating any setting in which NMA is superior to MA transplant [15,16].

Our results confirm that MA second transplant is associated with a remarkably high rate of NRM. The incidence of NRM of 64.1% observed in this analysis is similar to that observed by others [2,5,13]. The lower incidence of NRM following NMA second transplant more than offsets high relapse rates resulting in improved OS.

Is it possible that the improved outcomes of patients who underwent NMA second transplant are because of inherent differences in the 2 groups of patients? Patients who underwent MA second transplant were more likely to have undergone prior allogeneic transplant. Importantly, the OS of patients who underwent autologous first transplant was superior for those whose second transplant was NMA. This difference favoring NMA second transplant was not clearly observed for patients whose first transplant was allogeneic, possibly due to the small numbers of patients in these subgroups.

Patients in this study who underwent an MA second transplant were more likely to have a diagnosis of acute leukemia than those who underwent an NMA second transplant. There was a statistically significant improvement in overall survival of patients without acute leukemia treated with an NMA second transplant and a trend towards improved survival of patients with acute leukemia. This difference was statistically significant in favor of NMA second transplants for patients with a diagnosis other than acute leukemia.

Which patients are good candidates for NMA second transplant? Several studies have identified young age, long duration between transplants, and CR at the time of second transplant as good-risk prognostic factors for outcomes after second transplant [2,3,5,12,13]. Our data identify duration between transplants and disease status as predictors of relapse, NRM, and death. Consistent with the Seattle experience, a TBI-based second transplant regimen was also favorable in univariate analysis [5]. Patient age was not identified as a prognostic factor. These

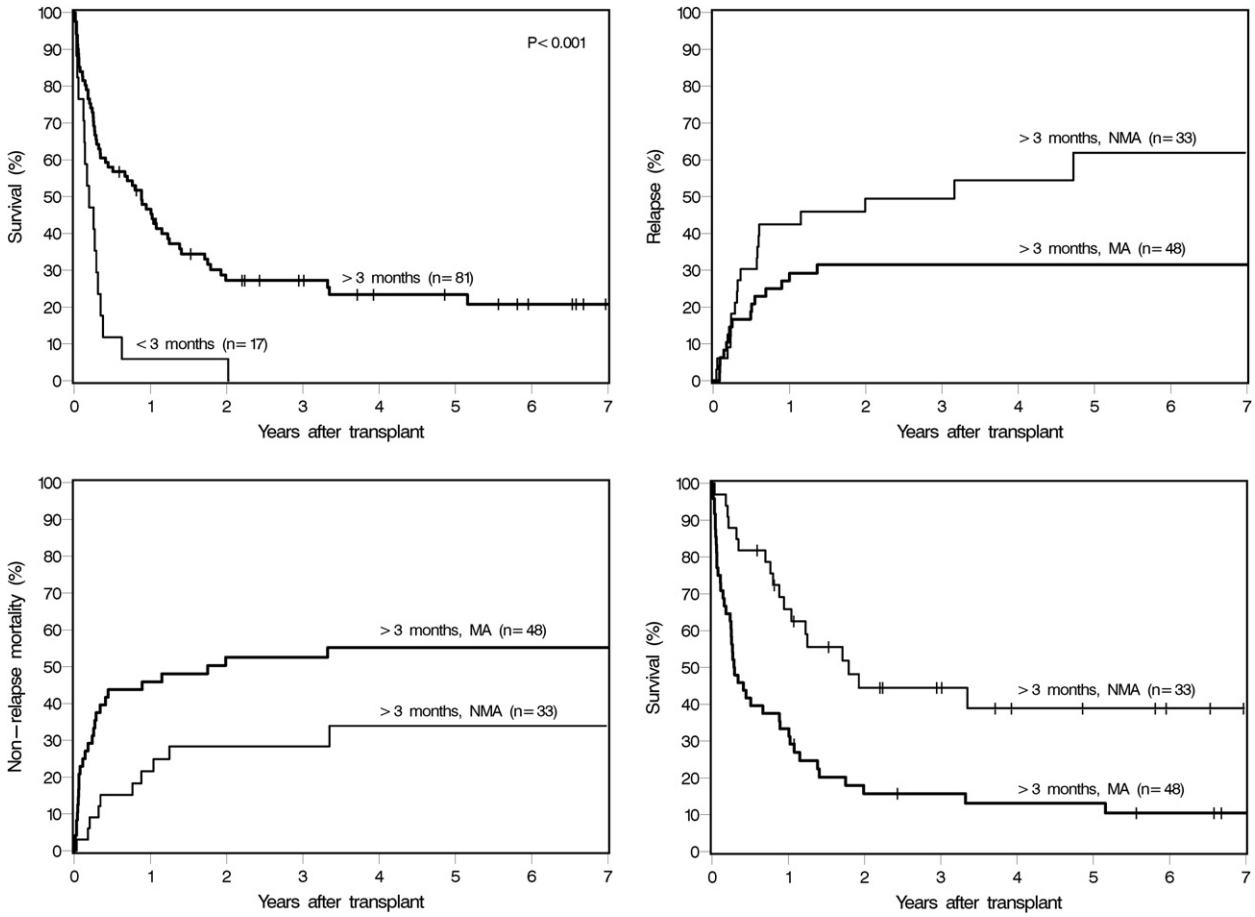

Figure 3. Upper left panel: Kaplan-Meier estimates of OS after all patients undergoing second transplant more than 3 months after first transplant (thick line) and fewer than 3 months after first transplant (thin line). Other panels: Kaplan-Meier estimates of relapse, NRM, and OS for patients undergoing MA (thick lines) and NMA (thin lines) second transplant more than 3 months after first transplant.

factors should clearly be considered when evaluating any individual patient for second transplant.

Special note should be made about short intervals between transplants. Patients who undergo second transplant within 3 months of failed first transplant have a median survival of 2.3 months and almost 100% mortality at 1 year. It is our recommendation that this group of patients should not receive an MA second transplant. Extrapolating from the finding of improved OS and decreased NRM after an NMA second transplant, this approach should be considered first-line therapy for all patients, particularly those requiring treatment soon after original transplant.

ACKNOWLEDGMENTS

Financial disclosure: The authors have nothing to disclose.

REFERENCES

1. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;27(354):1813-1826.
2. Bosi A, Laszlo D, Labopin M, et al. Second allogeneic bone marrow transplantation in acute leukemia: results of a survey by the european cooperative group for blood and marrow transplantation. *J Clin Oncol*. 2001;19:3675-3684.
3. Arfons LM, Tomblyn M, Rocha V, Lazarus HM. Second hematopoietic stem cell transplantation in myeloid malignancies. *Curr Opin Hematol*. 2009;16:112-123.
4. Shaw BE, Mufti GJ, Mackinnon S, et al. Outcome of second allogeneic transplants using reduced-intensity conditioning following relapse of haematological malignancy after an initial allogeneic transplant. *Bone Marrow Transplant*. 2008;42:783-789.
5. Radich JP, Gooley T, Sanders JE, Anasetti C, Chauncey T, Appelbaum FR. Second allogeneic transplantation after failure of first autologous transplantation. *Biol Blood Marrow Transplant*. 2000;6:272-279.
6. Platzbecker U, Binder M, Schmid C, Rutt C, Ehninger G, Bornhauser M. Second donation of hematopoietic stem cells from unrelated donors for patients with relapse or graft failure after allogeneic transplantation. *Haematologica*. 2008;93:1276-1278.
7. Guardiola P, Kuentz M, Garban F, et al. Second early allogeneic stem cell transplantations for graft failure in acute leukaemia, chronic myeloid leukaemia and aplastic anaemia. french society of bone marrow transplantation. *Br J Haematol*. 2000;111:292-302.
8. Byrne BJ, Horwitz M, Long GD, et al. Outcomes of a second non-myeloablative allogeneic stem cell transplantation following graft rejection. *Bone Marrow Transplant*. 2008;41:39-43.
9. Chewning JH, Castro-Malaspina H, Jakubowski A, et al. Fludarabine-based conditioning secures engraftment of second hematopoietic stem cell allografts (HSCT) in the treatment of initial graft failure. *Biol Blood Marrow Transplant*. 2007;13:1313-1323.

10. Fernandes J, Rocha V, Robin M, et al. Second transplant with two unrelated cord blood units for early graft failure after haematopoietic stem cell transplantation. *Br J Haematol*. 2007;137:248-251.
11. Narimatsu H, Kami M, Miyakoshi S, et al. Graft failure following reduced-intensity cord blood transplantation for adult patients. *Br J Haematol*. 2006;132:36-41.
12. Ringden O, Labopin M, Gorin NC, et al. The dismal outcome in patients with acute leukaemia who relapse after an autograft is improved if a second autograft or a matched allograft is performed. acute leukaemia working party of the european group for blood and marrow transplantation (EBMT). *Bone Marrow Transplant*. 2000;25:1053-1058.
13. Eapen M, Giralt SA, Horowitz MM, et al. Second transplant for acute and chronic leukemia relapsing after first HLA-identical sibling transplant. *Bone Marrow Transplant*. 2004;34:721-727.
14. Sobecks RM, Dean R, Rybicki LA, et al. 400 cGy TBI with fludarabine for reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2008;42:715-722.
15. Blaise D, Vey N, Faucher C, Mohty M. Current status of reduced-intensity-conditioning allogeneic stem cell transplantation for acute myeloid leukemia. *Haematologica*. 2007;92:533-541.
16. Kim DH, Sohn SK, Baek JH, et al. Retrospective multicenter study of allogeneic peripheral blood stem cell transplantation followed by reduced-intensity conditioning or conventional myeloablative regimen. *Acta Haematol*. 2005;113:220-227.