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Allogeneic Hematopoietic Cell Transplantation in the Outpatient Setting

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A B S T R A C T

Conditioning with fludarabine and low-dose total-body irradiation before allogeneic hematopoietic cell transplantation (HCT) enabled treating older or medically infirm patients with advanced hematologic malignancies in the outpatient setting. Between December 1997 and June 2017, 1037 patients with hematologic malignancies received peripheral blood stem cell (PBSC) grafts from HLA-matched or 1 HLA antigen/allele-mismatched related or unrelated donors. Median age was 58 (range, 18 to 80) years. Serious comorbidities with Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) scores ≥3 were present in 52% of patients. We found that 47% of patients were either never hospitalized or only had an overnight hospital stay for infusion of late-arriving PBSCs while 53% were admitted for a median of 6 days. Main reasons for admission were infection, fever, graft-versus-host disease, and regimen-related toxicity. Two thirds of admissions occurred within 3 weeks of HCT. The 5-year risk of nonrelapse mortality (NRM) was 26% among hospitalized patients and 13% among nonhospitalized patients. Significant risk factors for hospitalization included unrelated transplants, 1 HLA antigen-mismatched transplant, high HCT-CI scores, and diagnosis of nonmyeloma malignancies. Significant risk factors for NRM were hospitalization, older age, unrelated transplants, and high HCT-CI scores. Ambulatory allogeneic HCT is feasible and safe.

INTRODUCTION

Nonmyeloablative (NMA) conditioning for allogeneic hematopoietic cell transplantation (HCT) using fludarabine and low-dose total-body irradiation (TBI) was developed at our center to treat patients with advanced hematologic malignancies who were unable to tolerate high-intensity conditioning regimens because of age or serious comorbidities [1,2]. NMA conditioning relies almost entirely on potent graft-versus-tumor effects to eradicate underlying malignancies. Toxicities from the NMA conditioning regimen are relatively low, thereby enabling the HCT to be conducted in the outpatient setting. As a result, patients can live either at home or, if from out of town, in Seattle Cancer Care Alliance (SCCA)-managed apartments or in nearby hotels. However, given that nearly half of the patients undergoing transplantation are older than 60 years, half (52%) have serious comorbidities (Hematopoietic Cell Transplantation-Specific Comorbidity Index [HCT-CI] score 3 or greater), and others arrive at the transplant service with pancytopenia and are on antibiotics or antifungal agents, complications can be expected to arise after HCT that may lead to at least 1 hospital admission.

Here we report a retrospective analysis of data from 1037 patients with various advanced hematologic malignancies who were between 18 and 80 years of age and were treated by HCT from related or unrelated donors. The analysis was aimed at determining how many patients remained outpatients throughout the transplant course, how many experienced at least 1 hospitalization and for what reasons, and whether events leading to hospitalization affected the HCT outcome.

METHODS

Patients

Retrospective data were obtained from the Fred Hutchinson Cancer Research Center (Fred Hutch) transplant database. Informed consent was obtained from all patients before HCT, and the analysis was approved by the institutional review board of the Fred Hutch. All patients were treated at Fred Hutch/SCCA. An extensive manual review of each patient's records provided the data for the current analysis. Patients referred for conditioning with fludarabine and low-dose TBI underwent transplantation without exception in the outpatient setting.

We identified 1037 consecutive patients with hematologic malignancies who underwent NMA conditioning, followed by allogeneic peripheral blood

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stem cell (PBSC) transplantation, as an outpatient procedure between December 1997 and June 2017. Of these patients, 957 were enrolled in prospective research protocols, which were registered at clinicaltrials.gov, and 80 were enrolled in treatment plans. Protocol eligibility criteria were consistent throughout the study period and included patients older than 50 years and those 50 years or younger who, through preexisting medical conditions or prior therapy, are considered at high risk for regimen-related toxicity associated with a conventional high-dose transplant. Median follow-up of patients was 12 (range, 0.3 to 19.9) years.

The initial data collection identified 1230 patients who received NMA HCT from 1997 to 2017. To ensure a relatively homogeneous study population, we excluded 193 patients for the following conditions: 1 HLA antigen-mismatched transplant before triple postgrafting immunosuppression was routinely introduced (n = 47), follow-up too short (n = 43), multiple preceding allogeneic HCT (n = 40), conditioning with more than 3 Gy TBI (n = 27), reinduction chemotherapy or other additional salvage treatment for relapse during the first 100 days after HCT (n = 22), under 18 years of age at transplantation (n = 8), not proceeding to transplantation (n = 3), and concurrent solid tumor or nonmalignant hematologic disease (n = 3).

Patient characteristics are outlined in Table 1.

Patients included in the study received grafts from the following donors: HLA identical related (n = 455), single HLA allele mismatched related (n = 2), single HLA antigen mismatched related (n = 4), 10 of 10 HLA allele matched unrelated (n = 487), single HLA allele mismatched unrelated (n = 53), and single HLA antigen mismatched unrelated (n = 36).

HCT-CI scores were assigned as described [3]. Forty-nine percent of the related recipients and 52% of the unrelated recipients had serious comorbidities with scores of 3 and higher. Median ages were 61 years for unrelated recipients and 55 years for related recipients.

Underlying diseases varied among related and unrelated recipients. Related recipients had nonmyeloma lymphoid disease in 44%, myeloid disease in 31%, and multiple myeloma in 25% of cases. In comparison, unrelated recipients had more myeloid diseases (47%), similar nonmyeloma lymphoid diseases (42%), and less multiple myeloma (10%). Complete remissions at HCT were seen in 41% of related recipients and in 58% of unrelated recipients.

Conditioning Regimen, Immunosuppression, and Prophylaxis

Patients received 2 Gy (n = 862) or 3 Gy (n = 175) TBI on day 0, with (n = 839) or without (n = 198) preceding fludarabine 30 mg/m^2/d on days −4, −3, and −2 before HCT [1,2,4]. Thirty-four patients received 2 Gy TBI and clofarabine 30 to 50 mg/m^2/d × 5 days before HCT.

In total, 405 patients had undergone autologous HCT before the allogeneic HCT, of whom 213 had planned autologous-allogenic HCT and 192 had failed autologous HCT with subsequent relapse of the underlying malignancy. They had multiple myeloma (n = 167), non-Hodgkin lymphoma (n = 147), Hodgkin disease (n = 52), acute myeloid leukemia (n = 20), myelodysplastic syndrome (n = 14), or chronic lymphocytic leukemia (n = 5). Twenty-four patients had failed 1 preceding allogeneic HCT. Eighty-one patients with chronic lymphocytic leukemia or non-Hodgkin lymphoma received rituximab in addition to the conditioning regimen as part of a clinical trial.

Immunosuppression after HCT included mycophenolate mofetil (28 days for related recipients and at most 96 days for unrelated recipients) and a calcineurin inhibitor (96 or 150 and 180 days, respectively), either cyclosporine (n = 433) or tacrolimus (n = 164), and sirolimus (180 days; n = 132) as part of 2 randomized trials and a single-arm study [1,4-6].

All patients received prophylactic ursodiol from approximately 14 days before transplantation until at least day 180 after transplantation. Infection prophylaxis and treatment followed institutional standard practice guidelines, including acyclovir for herpes simplex and varicella zoster virus prophylaxis, fluconazole for yeast prophylaxis, trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* prophylaxis, and monitoring for cytomegalovirus reactivation.

Post-HCT monitoring included marrow aspirations to assess disease status usually on days 28, 84, 180, and 365 and then as indicated. Donor chimerism was evaluated on days 28, 84, and 365 after HCT. Acute and chronic graft-versus-host disease (GVHD) were graded as described [7-9].

Outpatient Clinic

Six allogeneic outpatient clinic teams at the SCCA attend to all newly referred HCT patients scheduled to receive either myeloablative or reduced-intensity/minimal intensity conditioning regimens. They care for patients up to days 90 to 100 after HCT, when recipients are discharged to their respective local physicians.

The 6 outpatient teams are arranged in 2 groups, with each group being led by an attending physician. Each of the 6 teams consists of an advanced primary care provider and a nurse. In addition, a dietitian, a pharmacist, and 2 schedulers are part of each group. A social worker is shared by the 2 groups.

The outpatient facilities are open daily from 8 AM to 10 PM during 365 days per year. Should something happen outside of these hours, the patients will be seen by a hospitalist who can contact the respective attending physician for help in decision making (ie, admitting the patient to the inpatient service or sending the patient home with appropriate therapy).

Hospitalizations

If patients required hospitalization, they were admitted to the University of Washington hospital. Reasons for hospitalization included acute GVHD, relapse, neutropenic fever, infection, regimen-related toxicity, or cardiovascular complications. Because the outpatient clinic was closed after 10 PM and PBSC products, especially from unrelated donors, often did not arrive until later in the day, 381 recipients experienced an overnight admission for PBSC infusion. These admissions were not considered "hospitalization" in the current study, including the occasional patient who spent a second night in the hospital.

Causes of Mortality

Relapse mortality was defined as death after relapse or progression of the patients' underlying disease, regardless of other events. The diagnosis of relapse, defined as recurrence of malignancy or of progression, was based on previously published criteria [10].

Nonrelapse mortality (NRM) was defined as death without relapse or progression and included GVHD mortality in patients with a history of GVHD who died while on immunosuppressive therapy. NRM was divided into 4 major categories: GVHD, treatment related, infection, and "other"; the latter included death from comorbidities, such as cardiovascular or cerebral vascular disease, chronic obstructive pulmonary disease, and suicide.

Statistical Analysis

Univariate comparison of risk factors for hospitalization (Table 1) was based on the Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables. Multivariate analysis of risk factors for hospitalization (Table 2) was based on logistic regression. Cumulative incidence of hospitalization, relapse-related mortality, and NRM was estimated by methods previously described [11]. Cumulative incidence of relapse-related mortality and NRM according to hospitalization status was restricted to the 945 patients who survived to day 100 because absence of hospitalization required survival to 100 days. Univariate and multivariate analyses (Table 3) of risk factors for NRM were restricted to the same population. All *P* values were 2-sided.

RESULTS

Hospitalization Characteristics

Outpatient HCT

In all 1037 patients, the conditioning regimen was administered in the outpatient setting. PBSCs from the majority of related donors were infused in the outpatient clinic. Fifty-nine percent of unrelated recipients had a planned, overnight admission for the PBSC infusion. This planned brief admission was not counted as "hospitalization" in the context of the current report.

Table 1 shows that 47% of the 1037 patients (61% of related and 36% of unrelated recipients) were never hospitalized. Twenty-one percent of related and 35% of unrelated recipients had a single hospital admission, and 19% of related and 29% of unrelated recipients had more than 1 hospital admission.

Figure 1A shows that 66% of all admissions occurred within 20 days of HCT.

Reasons for Hospital Admission

The main reasons for hospital admission were infections (19% of all admissions) and regimen-related toxicity (15%), with the former being significantly more frequent among unrelated recipients (Figure 2). Eleven percent (11%) of patients remained hospitalized more than 2 days after the overnight PBSC infusion, which was prompted mostly by residual regimen-related toxicities, such as nausea, anorexia, or extreme fatigue.

GVHD and neutropenic fever were more frequent causes for admission among unrelated recipients. Cardiovascular complications, including angina, hypertension, arrhythmias, myocardial infarction, and congestive heart failure, led to admission in 7% of patients, and this was similar in related and unrelated recipients. Two percent of patients were admitted to treat relapse of malignancy, and 8% were admitted for

Table 1
Patient Characteristics

Characteristic	Related (n = 461)	Unrelated (n = 576)	Not Hospitalized (n = 489)	Hospitalized (n = 548)	*P* Value*
Age, yr					
Median (range)	55 (18-79)	61 (18-80)	56 (18-79)	60 (18-80)	<**.0001**
Age, n (%), yr					
<50	144 (31)	110 (19)	144 (29)	110 (20)	**.0005**
≥50	317 (69)	466 (81)	345 (71)	438 (80)	
Sex, n (%)					
Female	197 (43)	212 (37)	191 (39)	218 (40)	.81
Male	264 (57)	364 (63)	298 (61)	330 (60)	
Race, n (%)	20 missing		20 missing		
White	410 (91)	544 (96)	450 (94)	504 (94)	.94
Other	40 (9)	23 (4)	30 (6)	33 (6)	
HCT-CI, n (%)	28 missing		28 missing		
0-1	142 (32)	144 (25)	169 (36)	117 (22)	
2-3	186 (42)	248 (44)	205 (43)	229 (43)	<**.0001**
4+	115 (26)	174 (31)	102 (21)	187 (35)	
Diagnosis					
ALL	16 (3)	41 (7)	17 (3)	40 (7)	
AML	75 (16)	168 (29)	99 (20)	144 (26)	
CLL	51 (11)	68 (12)	50 (10)	69 (13)	
HD	34 (7)	22 (4)	33 (7)	23 (4)	<**.0001**
MDS/MPD	58 (13)	94 (16)	61 (12)	91 (17)	
MM	115 (25)	59 (10)	113 (23)	61 (11)	
NHL	98 (21)	111 (19)	95 (19)	114 (21)	
Other	14 (3)	13 (2)	21 (4)	6 (1)	
Diagnosis group, n (%)					
Myeloid	142 (31)	273 (47)	175 (36)	240 (44)	
Lymphoid	204 (44)	244 (42)	201 (41)	247 (45)	<**.0001**
MM	115 (25)	59 (10)	113 (23)	61 (11)	
Status at Tx, n (%)	52 missing		52 missing		
CR	182 (41)	313 (58)	218 (46)	277 (54)	
PR	86 (19)	54 (14)	81 (17)	59 (12)	.01
Other	178 (40)	172 (32)	175 (37)	175 (34)	
CD34 dose, n (%)	7 missing		7 missing		
>8.53	257 (56)	257 (45)	245 (51)	269 (49)	.71
≤8.53	199 (44)	317 (55)	240 (49)	276 (51)	
HLA antigen mismatch, n (%)					
No	457 (99)	540 (94)	483 (99)	514 (94)	
Yes	4 (1)	36 (6)	6 (1)	34 (6)	<**.0001**
HLA allele mismatch, n (%)	46 missing		46 missing		
No	416 (>99)	520 (91)	428 (97)	453 (93)	
Yes	2 (<1)	53 (9)	15 (3)	40 (7)	**.008**
CMV serostatus, n (%)	4 missing		1 missing		
R− and D−	109 (24)	199 (35)	155 (32)	153 (28)	
R+ or D+	352 (76)	373 (65)	332 (68)	393 (72)	.18
Hospital admissions number,† n (%)					
0	280 (61)	209 (36)	—	—	—
1	95 (21)	202 (35)	—	—	—
2	57 (12)	92 (16)	—	—	—
3	17 (4)	49 (9)	—	—	—
4	9 (2)	18 (3)	—	—	—
5	2 (<1)	4 (1)	—	—	—
6	1 (<1)	2 (<1)	—	—	—

ALL indicates acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; HD, Hodgkin disease; MDS, myelodysplastic syndrome; MPD, myeloproliferative disease; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; Tx, treatment; CR, complete remission; PR, partial remission.

* Comparison between hospitalized and non-hospitalized patients: $P < .0001$.

† Difference of hospital admissions number between related and unrelated: $P < .0001$.

Table 2
Risk Factors for Hospitalization (476 Events in 1009 Patients)

Factor	Multivariate	
	OR (95% CI)	*P* Value
HCT-CI		
0-1	1.0	
2-3	1.57 (1.1-2.1)	.005
≥4	2.38 (1.7-3.4)	<.0001
Diagnosis group		
Myeloid/lymphoid	1.0	
Multiple myeloma	0.57 (0.4-0.8)	.003
Donor		
Related	1.0	
Unrelated	2.36 (1.8-3.1)	<.0001
HLA mismatch		
No	1.0	
Yes	3.57 (1.5-8.8)	.006

OR indicates odds ratio; CI, confidence interval.

miscellaneous causes, which included invasive small procedures or diagnostic tests related to comorbidities.

Duration of Hospital Admission

Thirty-nine percent (39%) of the related and 64% of the unrelated recipients had 1 or more hospital admissions. The median length of the hospital stay for both groups of patients was 6 days. The median duration of hospitalization due to infection for the 2 groups of recipients was 6 and 5 days, respectively. The longest median stay in both groups was for relapse/progression and GVHD (10 and 9 days, respectively), and the shortest median stay (3 days) was for cardiovascular events.

Unrelated recipients had longer hospital stays when admitted for fever and regimen-related toxicity compared with the related recipients (8 versus 5 and 5 versus 4 days, respectively). In contrast, related recipients had a longer stay when admitted for infection (median, 6 versus 5 days, respectively), but admissions for infections were less frequent among related than among unrelated recipients (15% versus 23%, respectively).

Risk Factors for Admission

A multivariate analysis identified 4 patient groups to be at highly significant risk for hospital admission (Table 2). Those included patients with high comorbidity scores, malignant diseases other than myeloma, unrelated grafts, and HLA-mismatched grafts. Other factors, including patient age, sex and race, remission status, and transplanted numbers of CD34+ cells, were not significant.

NRM

Overall, 620 of the 1037 patients died within the 20-year time frame of the study, 278 from NRM and 342 from relapse.

Of the patients experiencing NRM, 116 (42%) died of complications related to GVHD; 40 (14%) died of adverse events related to treatment; 33 (12%) died of age-related causes, such as cardiovascular disease, cerebral vascular accident, chronic obstructive pulmonary disease, or a malignancy not related to the diagnosis for which the HCT was carried out; and 89 (32%) died of bacterial, fungal, or viral infections. Among the patients who died of infections, 30 had experienced acute grade 2 to 3 GVHD, 11 had chronic GVHD, 34 had experienced both, and 14 experienced neither.

Table 3
Risk Factors for NRM among Day 100 Survivors (221 Events in 916 Patients)

Factor	Multivariate Model 1		Multivariate Model 2	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, yr				
<50	1.0		1.0	
≥50	1.69 (1.2-2.4)	.005	1.75 (1.2-2.5)	.003
Donor				
Related	1.0		1.0	
Unrelated	1.47 (1.1-2.0)	.01	1.46 (1.1-2.0)	.01
CMV serostatus pretransplant				
R− and D−	1.0		1.0	
R+, D+, or R+ and D+	1.39 (1.0-1.9)	.04	1.39 (1.0-1.9)	.04
HCT-CI				
0-1	1.0		1.0	
2-3	1.42 (1.0-2.0)	.04	1.41 (1.0-2.0)	.05
≥4	1.78 (1.2-2.6)	.002	1.80 (1.3-2.6)	.002
Hospitalized				
No	1.0		—	—
Yes	1.71 (1.3-2.3)	.0003	—	—
Reason for first admission				
None	—	—	1.0	
Fever	—	—	2.42 (1.5-4.0)	.0006
Infection	—	—	1.27 (0.8-2.0)	.30
GVHD	—	—	2.77 (1.6-4.9)	.0004
Regimen-related toxicity and infusion >2 d	—	—	1.77 (1.3-2.5)	.001
Other*	—	—	1.28 (0.8-2.2)	.36

HR indicates hazard ratio; CI, confidence interval.
* Other includes cardiovascular (8%), miscellaneous causes (7%) such as invasive small procedures or diagnostic tests related to comorbidities, and relapse (2%).

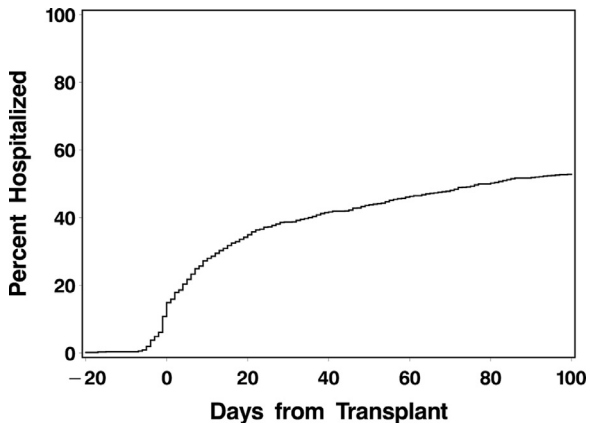

Figure 1. Cumulative incidence rate of hospital admission.

Five-year NRM among the 945 day 100 survivors was significantly higher among patients who had at least 1 hospital admission before day 100 compared with those who remained outpatients through day 100 (26% versus 13%; $P < .0001$, Figure 3B). This difference was almost entirely attributable to higher NRM among hospitalized unrelated recipients (32% versus 14%; Figure 3C), while 5-year NRM among hospitalized and nonhospitalized related recipients did not differ significantly (16% versus 13%; Figure 3D). Including deaths before day 100, overall 5-year NRM was 17% for related and 28% for unrelated recipients.

Risk factors for NRM in the multivariate analysis shown in Table 3 included age ≥50 years, unrelated PBSC donor, patient and/or donor being cytomegalovirus (CMV) positive, serious comorbidities, and having at least 1 hospital admission. When reasons for first hospital admission were added to the analysis, while deleting hospitalization as a cofactor, fever, GVHD, and regimen-related toxicities were highly significant additional risk factors for NRM.

Of note, 5-year relapse-related mortality during the 20-year time span was comparable for hospitalized and nonhospitalized patients (27% versus 28%; Figure 3A).

DISCUSSION

The HCT regimen described here was designed to extend the use of allogeneic HCT to include older and also medically infirm patients [1,2,4]. To that end, it was designed to be relatively nontoxic while enabling nearly uniform sustained hematopoietic engraftment. The downside of the regimen was its limited ability to reduce the burden of malignant cells before HCT, and tumor control depended largely on allogenic graft versus tumor effects. As a result, disease relapse or progression has remained the major problem, with a 5-year cumulative mortality of around 27%, which was comparable among related and unrelated HCT recipients. In this context, based on extensive preclinical studies in a canine model [12], a current dose-escalation trial that adds targeted radioimmunotherapy with an α-emitting radionuclide, astatine-211, coupled to an anti-CD45 monoclonal antibody to the conditioning regimen promises to reduce the problems of relapse and progression. Importantly, absent serious organ toxicities, the minimal-intensity conditioning regimen used in these patients allowed it to be performed as an outpatient procedure, thereby enabling patients to move around freely while observing commonsense infection precautions.

How well did this work in the current 1037 patients, of whom almost half were between 60 and 80 years of age, whereas those who were younger all had serious comorbidities? We found that nearly half of the patients (47%) remained outpatients, whereas the remainder had at least 1 hospital admission. One reason for hospitalization, involving 15% of all admissions, included toxicities from the regimen that largely consisted of fatigue, severe nausea, and anorexia. Other reasons included infections, fever, and GVHD. Unrelated recipients had a far higher rate of admissions than related recipients, mainly prompted by higher rates of fever, infections, GVHD, and extended hospital stay after overnight PBSC infusion. Given that most unrelated recipients were matched with their HCT donors for 10 HLA alleles, their more frequent admissions for GVHD (and perhaps also for fever) compared with HLA-identical related recipients likely reflected donor immune reactions against an inherently greater number of minor non-HLA antigen disparities. As for the observed higher rate of admission for infection among unrelated recipients, we described previously that they experienced more profound neutrophil nadirs after HCT than related recipients [13], which was likely caused by more profound donor immune reactions against host hematopoietic tissues. A lower neutrophil nadir, in turn, might increase the risk of infections.

Unsurprisingly, higher comorbidity scores and having 1 HLA antigen-mismatched donor also increased the rate of hospital admission, whereas patients with multiple myeloma experienced less admissions than patients with other malignancies, possibly related to their history of less intense chemotherapy exposure.

The events leading to hospitalization had a remarkably adverse effect on HCT outcome. Although relapse mortality

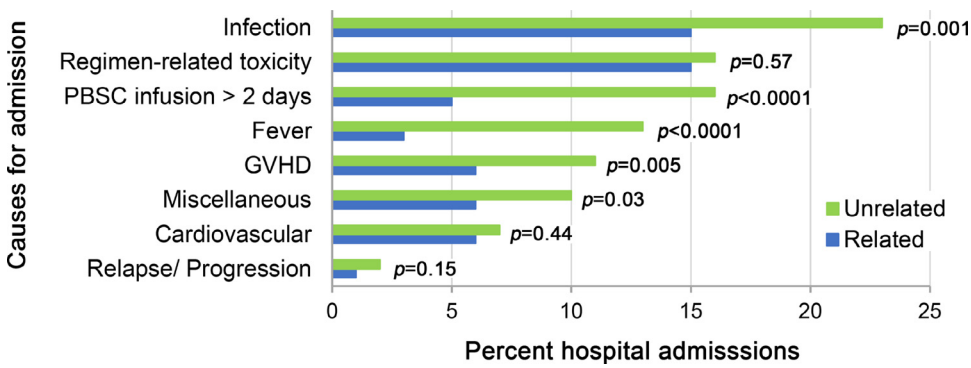

Figure 2. Reasons for hospital admissions in the first 100 days after HCT.

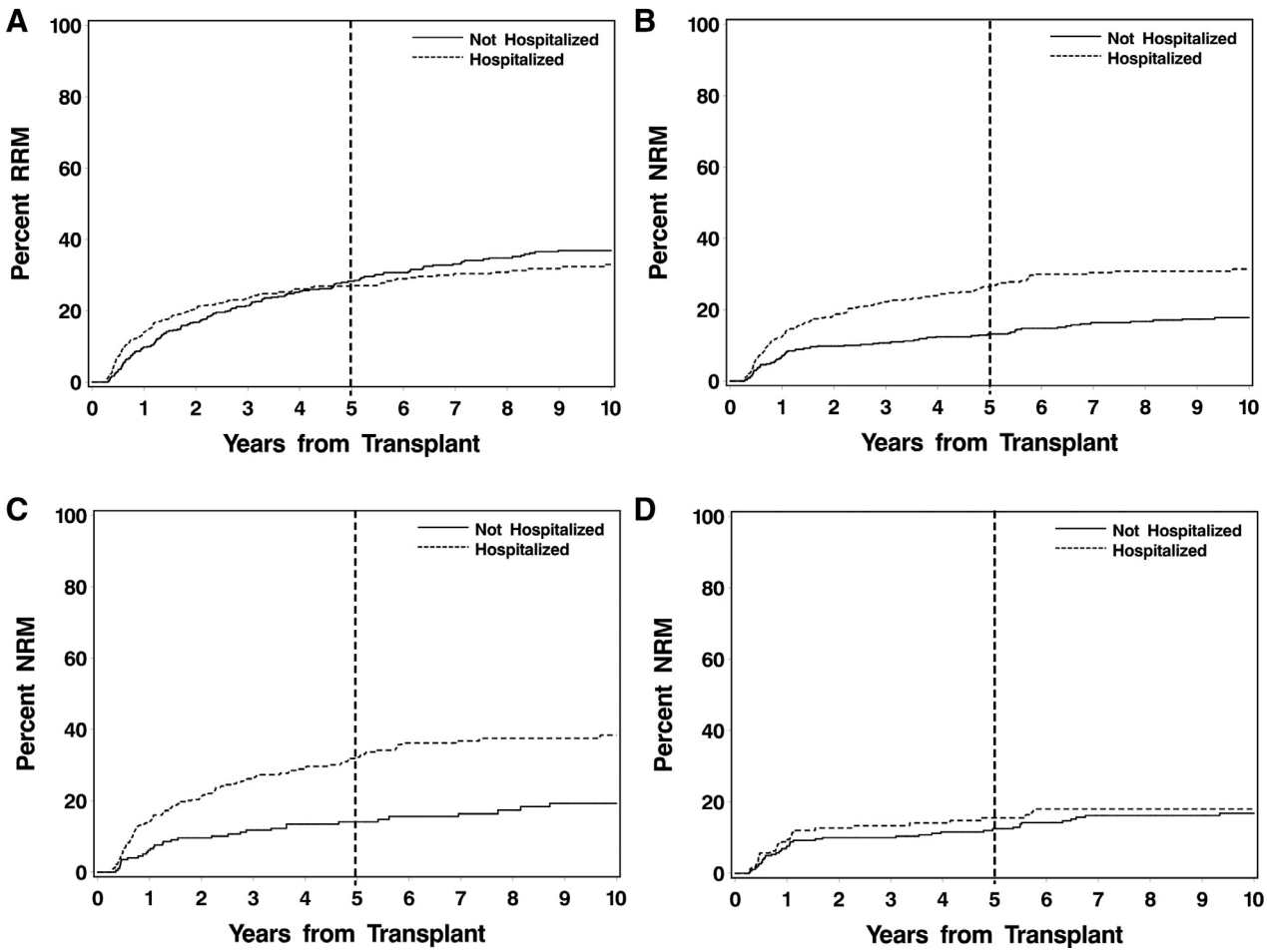

Figure 3. Cumulative incidence rates. (A) Relapse-related mortality. NRM among hospitalized and nonhospitalized patients for (B) all, (C) unrelated, and (D) related patients.

was unaffected, 5-year NRM among hospitalized patients was 26% compared with 13% among nonhospitalized patients. This increase in NRM was seen nearly exclusively among hospitalized unrelated recipients, whereas related hospitalized and nonhospitalized recipients had comparable 5-year NRM. As already discussed, a major underlying cause for both increased hospital admission and NRM among unrelated recipients was likely their greater minor histocompatibility antigen disparities with their donors compared with HLA-identical sibling donor-recipient pairs.

Other factors contributing to overall NRM included older age, high comorbidity scores, being CMV positive, or having a CMV-positive donor. Identifying age and comorbidities as causes of NRM was not surprising. For example, 1 patient, a 78-year-old man with myelodysplastic syndrome/acute myeloid leukemia (AML) and a history of myocardial infarction with stent placements before and aortic valve replacement after unrelated HCT, died at age 88 years of cardiac complications without evidence of GVHD and while in remission of his malignancy. All in all, 12% of current patients died of comorbidity-related causes, consistent with findings in previous publications [14,15]. CMV reactivation has remained an adverse risk factor as documented in a recent, large, retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) analysis, in part due to CMV disease and in part through indirect immunosuppressive effects triggered by viremia [16-18].

Three other factors predicting NRM among hospitalized patients were regimen-related toxicities, fever and GVHD as reasons for admissions, and extended hospital stay after overnight PBSC infusion. Extended hospital stay was mostly due to residual nausea, anorexia, and fatigue from the regimen. These 4 NRM causes might be interconnected by a common denominator, regimen-related cytokine release. Cytokine release has been incriminated in triggering graft-versus-host reactions such as engraftment syndrome [19] and GVHD [20].

Few centers have reported on performing allogenic HCT in the outpatient setting after our initial report from 2001 on a small number of HLA-identical sibling recipients who received minimal-intensity conditioning at Fred Hutch [1]. A small Australian retrospective study focused on tandem autologous-allogenic HCT for patients with multiple myeloma using Fred Hutch's fludarabine/TBI conditioning and GVHD prophylaxis regimens [21]. They described limited toxicity with a low 5-year NRM of 6%. This result confirmed previous experiences with that regimen in patients with multiple myeloma [22].

A recent single-center retrospective study compared complications and survivals among 116 inpatients and 35 outpatients treated with reduced-intensity conditioning (RIC) conditioning before allogeneic HCT [23]. Short-term outcomes were comparable among both cohorts, with inpatients experiencing 1-year NRM of 10.8% compared with 3.2% among outpatients. However, incidence rates of neutropenic fever and mucositis were higher in the inpatient cohort. Of note, the outpatient cohort had a higher proportion of patients with multiple myeloma (37.1% versus 15.5%), who tended to have lower NRM compared with patients with other malignancies

in other reports, whereas there were no significant differences in median patient age, HCT-CI scores, or donor type among the 2 cohorts.

One study published in 2002 described a small cohort of 36 patients given myeloablative conditioning who were treated as outpatients [24]. Outcomes were superior to those among 2 groups of patients who underwent transplantation in the hospital (3-year NRM 8% versus 49% and 35%, respectively). However, it was not clear how the patients were selected to be treated one way or the other. The authors reported a 62% admission rate among the patients whose HCT was carried out in the outpatient setting.

Several publications reported on readmissions among patients whose conditioning, HCT and early post-transplant treatment were administered in the inpatient setting.

A 2015 study at the Dana-Farber Cancer Institute compared readmission profiles after allogeneic HSCT among 503 patients receiving myeloablative HCT and 638 patients given RIC, with readmission rates of 31.1% for the RIC patients and 42.8% for the myeloablative patients by day 100 [25]. The most frequent cause for readmission during the first 100 days after HCT was infection (19%).

A recent study at the Cleveland Clinic, which examined identifying prognostic factors for survival within the first 100 days after transplantation, reported a 44% first readmission rate and 2-year NRM of 16%. Patel et al. [26] found acute GVHD or more hospitalization days within the first 100 days prognostic for increased NRM. We confirmed some of these prognostic factors, although in their retrospective study, the majority of the 413 patients underwent myeloablative allogeneic HCT with marrow as graft source.

How did the 5-year overall rates of NRM of 17% for related and 28% for unrelated recipients observed in the current study (hospitalized versus nonhospitalized related and unrelated recipients of 16% versus 13% and 32% versus 14%, respectively) compare with data on RIC/NMA conditioning published by others?

Most published studies had a shorter follow-up. A National Marrow Donor Program study showed 3-year NRM of approximately 34% for 160 unrelated recipients treated with RIC or NMA regimens [27]. Three-year NRM was higher after myeloablative conditioning (43%). Another study by this group reported 5-year NRM of 38.6% (32.9% to 44.3%) among 285 unrelated recipients treated with RIC regimens [28].

Ho and colleagues [29] reported a low 2-year NRM incidence for 433 related (8%) and unrelated (6%) recipients given RIC. Of note, NRM for both cohorts significantly improved with year of transplantation (16% and 14%, respectively, for transplants performed before 2004, compared with 6% and 3% after 2004).

The German Data Cooperative Transplant Study Group focused on results among 368 elderly patients with AML treated with RIC HCT [30]. They reported a 2-year NRM of 35% among HLA-matched sibling recipients versus 42% for unrelated recipients. A second publication by this group reported lower 2-year NRM among 122 patients with AML treated with NMA conditioning (10% for related recipients versus 22% for unrelated recipients) [31].

A recent CIBMTR study compared outcomes of patients with chronic myelogenous leukemia treated with RIC or myeloablative conditioning, with comparable 5-year NRM rates among both cohorts (29% and 32%, respectively) [32]. Another large CIBMTR study compared outcome with myeloablative, RIC, and NMA conditioning among patients with AML and myelodysplastic syndrome [33]. NRM at 3 years ranged from 33.5% to 38%, with no statistically significant difference in NRM between the treatment groups.

In conclusion, we demonstrated the feasibility and safety of carrying out allogeneic HCT after minimal-intensity conditioning in the outpatient setting. Five-year NRM compared favorably with results reported in the literature. Living at home or in a private apartment and being able to move around freely using only commonsense infection precautions were valued by the patients. Close to half of the current patients completed their transplant course entirely as outpatients, whereas the other half had at least 1 hospital admission lasting a median of 6 days. Events resulting in hospital admission did not significantly affect NRM among related recipients but led to a significant increase in NRM among unrelated recipients. The latter finding was likely caused by more intense and protracted graft-versus-host reactions among unrelated recipients. To address this issue, we conducted a phase III prospective, randomized trial that demonstrated that a triple-drug GVHD prophylaxis regimen consisting of mycophenolate mofetil, cyclosporine, and sirolimus [34] significantly reduced the rate of acute grade 2 to 4 GVHD among unrelated recipients from 53% to 25% and the rate of grade 3 to 4 acute GVHD to 2%. This encouraging result and the concomitant significant improvement in survival of triple drug-treated patients promises improved outcomes for future unrelated HCT recipients.

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