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Nonmyeloablative Unrelated Donor Hematopoietic Cell Transplantation to Treat Patients with Poor-Risk, Relapsed, or Refractory Multiple Myeloma

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ABSTRACT

The purpose of this study was to determine long-term outcome of unrelated donor nonmyeloablative hematopoietic cell transplantation (HCT) in patients with poor-risk multiple myeloma. A total of 24 patients were enrolled; 17 patients (71%) had chemotherapy-refractory disease, and 14 (58%) experienced disease relapse or progression after previous autologous transplantation. Thirteen patients underwent planned autologous transplantation followed 43–135 days later with unrelated transplantation, whereas 11 proceeded directly to unrelated transplantation. All 24 patients were treated with fludarabine (90 mg/m^2) and 2 Gy of total body irradiation before HLA-matched unrelated peripheral blood stem cell transplantation. Postgrafting immunosuppression consisted of cyclosporine and mycophenolate mofetil. The median follow-up was 3 years after allografting. One patient experienced nonfatal graft rejection. The incidences of acute grades II and III and chronic graft-versus-host disease were 54%, 13%, and 75%, respectively. The 3-year nonrelapse mortality (NRM) was 21%. Complete responses were observed in 10 patients (42%); partial responses, in 4 (17%). At 3 years, overall survival (OS) and progression-free survival (PFS) rates were 61% and 33%, respectively. Patients receiving tandem autologous-unrelated transplantation had superior OS and PFS (77% and 51%) compared with patients proceeding directly to unrelated donor transplantation (44% and 11%) (PFS *P* value = .03). In summary, for patients with poor-risk, relapsed, or refractory multiple myeloma, cytoreductive autologous HCT followed by nonmyeloablative conditioning and unrelated HCT is an effective treatment approach, with low NRM, high complete remission rates, and prolonged disease-free survival.

KEY WORDS

Multiple myeloma • Nonmyeloablative conditioning • Allogeneic hematopoietic cell transplantation • Unrelated donor • Graft-versus-tumor effect • Chronic graft-versus-host disease • Peripheral blood stem cell transplantation

INTRODUCTION

High-dose conditioning and autologous hematopoietic cell transplantation (HCT) is effective in prolonging survival for patients with multiple myeloma; nonetheless, nearly all patients eventually relapse [1-6]. Long-term remissions and possibly cures have been described with allogeneic HCT after conventional high-dose conditioning regimens [7-9]. However, high-dose conditioning regimens for allogeneic HCT are associated with a 40%–50% risk of early nonrelapse mortality (NRM) [7-10]. Nonmyeloablative conditioning regimens for allogeneic HCT have dramatically reduced early transplantation-related mortality (TRM) and sparked interest in applying this treatment to multiple myeloma [11-21]. One particularly promising treatment has been to combine the cytoreductive benefit of high-dose melphalan and autologous "rescue," followed by the graft-versus-tumor (GVT) effects of nonmyeloablative allografts, initially from HLA-matched siblings [22,23]. For patients who lack HLA-matched siblings, unrelated donor HCT is an important alternative [12]. Several reports have described reduced-intensity conditioning with unrelated donor HCT; however, the number of patients with multiple myeloma studied and the duration of follow-up have been limited to date [12,20,23-31].

In an earlier study [12], we showed that a nonmyeloablative conditioning regimen consisting of fludarabine 30 mg/m^2/day given on 3 consecutive days and 2 Gy of total body irradiation (TBI) combined with postgrafting immunosuppression with cyclosporine (CSP) and mycophenolate mofetil (MMF) allowed stable engraftment of unrelated hematopoietic cells in patients with various hematologic malignancies. In the present article, we describe the clinical outcomes of 24 patients with advanced multiple myeloma who received grafts from HLA-matched unrelated donors with a median follow-up of 3 years. Thirteen of the 24 patients had planned autologous HCT followed by unrelated HCT, whereas 11 proceeded directly to unrelated HCT.

PATIENTS AND METHODS

Eligibility Criteria

A total of 24 patients with multiple myeloma were enrolled in 3 sequential phase I/II multi-institutional Fred Hutchinson Cancer Research Centers for unrelated HCT protocols for hematologic malignancies between May 16, 2000, and November 23, 2004 [32]. The patients were treated at 9 centers. Each patient signed a consent form approved by the local institutional review board. Inclusion criteria were the diagnosis of multiple myeloma, high risk for NRM from failure of previous treatment with high-dose autologous HCT or preexisting comorbidities, and failure of 1 or more front-line therapies [12].

HLA Typing and Matching

A total of 23 patient–donor pairs had HLA-allele level typing performed for 10 HLA alleles (HLA-A, -B, -C, -DRB1, and -DQB1) [33]. Patient 5 did not have high-resolution typing for all 10 HLA alleles. Twenty patients were matched with their donors for 10 of 10 HLA alleles, and 3 patients (patients 4, 9, and 14) had single HLA-C allele-level mismatches.

Peripheral Blood Stem Cell Mobilization/ High-Dose Melphalan/Autologous HCT

Thirteen patients underwent planned high-dose autologous HCT before unrelated donor HCT. Unless previously cryopreserved, peripheral blood stem cells (PBSCs) were collected and cryopreserved after cyclophosphamide (4 g/m^2) and Mensa (4 gtm^2) given on day 1, etopside (200 mgtm^2/day), on days 1–3; dexamethasone 40 mg/day on days 1–4, and granulocyte colony-stimulating factor (G-CSF; 10 μg/kg/day) were given from day 4 until collection [34]. Melphalan (200 mg/m^2) was given $>$ 30 days after mobilization chemotherapy. Autologous PBSCs were infused 48 hours after melphalan [22]. The median CD34$^+$ cell number was 6.1 $\times$ 10^6/kg (range, 3.5–8.8 $\times$ 10^6/kg). Patients proceeded to allografting after recovery from autologous HCT.

Eleven patients proceeded directly to unrelated donor HCT because of lack of availability of cryopreserved PBSCs, physician preference, or inability to obtain medical insurance coverage for a planned tandem autologous unrelated HCT.

Nonmyeloablative Conditioning Regimen and Posttransplantation Immunosuppression

Conditioning included 3 doses of fludarabine 30 mg/m^2/day on days −4 to −2, followed by 2-Gy TBI at rates of 0.07–0.10 Gy/min from linear accelerators on day 0. Postgrafting immunosuppression included CSP and MMF, as described previously [12,32]. Patients 1–7 received MMF 15 mg/kg every 12 hours, and patients 8–24 received MMF 15 mg/kg every 8 hours. Grading and treatment of graft-versus-host disease (GVHD) was done as described previously [12,35].

Collection of Unrelated PBSCs and Supportive Care

All patients received fresh G-CSF–mobilized PBSCs from unrelated donors coordinated through unrelated donor registry protocols [12]. National Marrow Donor Program donors received G-CSF 10 μg/kg/day on days −5 through −1. The median number of CD34$^+$ cells infused was 8.87 $\times$ 10^6/kg (range,

2.1–23.1 $\times$ 10^6/kg). Antimicrobial and cytomegalovirus prophylaxis and blood product support were given as described previously [12].

Analyses of Risk Factors, Disease Responses, and Toxicities

Cytogenetic abnormalities were assessed at time of diagnosis in 14 patients using conventional karyotype G-banding (Table 1). Donor engraftment was confirmed by chimerism analyses [36]. Patients were evaluated for disease during the 2-week interval before autologous and/or unrelated HCT to estimate the baseline levels of disease activity. Disease responses were assessed using the American Bone Marrow Transplant Registry criteria [37]. Patients were considered refractory to chemotherapy if they had less than a partial response (PR) to the last regimen administered before study entry. Restaging studies were performed at 28, 56, and 84 days and 6 months after unrelated HCT, and at 6-month intervals thereafter.

Medical comorbidities were evaluated using a modified Charleson comorbidity index (CCI) [15]. Pretransplantation comorbid diseases included myocardial infarction, congestive heart failure, peripheral vascular or cerebrovascular disease, hepatic disease, diabetes (with end-organ damage), pulmonary disease (moderate–severe dyspnea on exertion), and serum creatinine level $>$ 2.0 mg/dL [15].

The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3 grading system (available at http://ctep.cancer.gov/reporting/ctc.html) was used to evaluate toxicity during the first 100 days after allografting. All toxicities were graded and reported.

Statistical Methods

OS and PFS were estimated by the Kaplan-Meier method. Cumulative incidence estimates were calculated for acute and chronic GVHD, relapse, relapse-related mortality, and NRM. Deaths were treated as competing events in analyses of graft rejection, GVHD, and disease progression. Disease progression and NRM were the components of PFS and were treated as competing events. Fisher's exact test was used to compare 2 groups. All *P* values were derived from likelihood ratio statistics and were 2-sided. Comparisons of survival and PFS were based on log-rank tests. Follow-up was as of April 1, 2006.

RESULTS

Patient Characteristics

Table 1 summarizes the clinical features of the 24 patients enrolled in the study. All patients had advanced disease at time of study enrollment. The median time from disease diagnosis to unrelated donor HCT was 25 months (range, 8–130 months). All patients had received therapy for myeloma. Twenty-three (96%) were beyond first complete remission (CR1) or never achieved CR1 despite multiple distinct chemotherapy regimens (median, 4.5 regimens; range, 2–10). Twenty-three (96%) had received vincristine, adriamycin, and dexamethasone for a median of 5 cycles (range, 1–11) [38], and 14 (58%) had received thalidomide-dexamethasone [39]. One patient had received bortezomib, with disease progression before study entry. Fourteen (58%) had relapsed/progressed after previous high-dose autologous HCT at a median of 10 months before study enrollment (range, 3–40 months). Seventeen (71%) had disease that was refractory to their most recent chemotherapy regimen, 5 (21%) had PR, and 2 (8%) had CR.

Planned Autologous HCT

Thirteen patients received planned autologous HCT for cytoreduction a median of 75 days before unrelated HCT (range, 43–135 days). After melphalan treatment, all 13 patients recovered hematopoiesis; the median duration with neutrophils $<$ 500/μL was 9.5 days (range, 7–14 days), and the median duration with platelets $<$ 20,000/μL was 2.5 days (range, 0–9 days).

Five patients had relapsed after previous autologous HCT. The disease responses after planned autologous HCT were CR in 1 patient, PR in 7 patients, and stable disease in 5 patients.

Unrelated Donor Engraftment Kinetics and Chimerism

During the first 100 days after unrelated HCT, the patients had a median duration of neutropenia of 5 days (range, 0–80) days. Transient severe thrombocytopenia ($<$ 20 $\times$ 10^3 platelets/μL) occurred in 6 patients (25%). Transfusion requirements were a median of 7 units of red blood cells (range, 0–34 units) and 0 units of platelets (range, 0–45 units).

Median levels of peripheral blood CD3, CD33, and whole marrow donor chimerism at day 28 were 94%, 99%, and 98%, respectively. One patient (4%) experienced nonfatal graft rejection by day +56, with recovery of autologous hematopoiesis. All surviving patients with engraftment eventually achieved 100% donor chimerism.

Toxicity

The regimen of fludarabine and 2-Gy TBI was well tolerated. No patient experienced mucositis, severe diarrhea, or veno-occlusive disease of the liver attributable to the conditioning regimen. For the first 100 days posttransplantation, the median number of inpatient hospital days was 13.5 (range, 0–57). Grade 4 hematologic toxicity occurred in 75% of patients,

Table 1. *Pretransplantation Patient Characteristics*

Transplant	Patient (PIN)	Age (Years)/ Sex	Known Cytogentic Abnormality	Number of Regimens Before Auto/Allo or URD HCT	Prior Local Radiotherapy	Months From Diagnosis to URD HCT	Failure of Prior Auto HCT*	Disease Stage/Type at HCT	β2 Micro-globulin at HCT	CCI Score	Response to Last Preceding Chemotherapy Line
Planned tandem auto/ unrelated HCT	3	44/F	NE	4	No	8	No	IIA IgGκ	1.7	0	Refractory
	4	49/M	NE	5	No	14	No	IIIA IgGκ	2.0	0	Refractory
	7	53/M	Δ 13, complex	2	No	10	No	IIIB κ	15.3	2	Refractory
	14	49/M	NE	2	No	14	No	IIIA IgGκ	1.5	0	Refractory
	19	59/M	Complex	2	No	11	No	IIIA IgGκ	2.4	1	Refractory
	20	51/M	Δ 13, complex	2	No	15	No	IIIA IgAκ	1.5	0	PR
	21	35/F	Δ 13, complex	6	No	28	No	IIIA IgAλ	1.7	0	Refractory
	24	51/F	None	2	Yes	8	No	IIIA IgGκ	1.3	0	PR
	6	31/M	NE	6	Yes	77	Yes	IIIA IgAλ	3.3	0	PR
	15	53/M	Complex	6	Yes	57	Yes	IIIA IgGκ	2.6	1	Refractory
	16	61/M	Δ 13, complex	10	Yes	44	Yes	IIIB IgGλ	2.1	6	Refractory
	17	29/M	Δ 13, complex	4	Yes	13	Yes	IIIB IgAλ	2.7	1	Refractory
	23	64/M	None	7	No	43	Yes	IIIB κ	4.5	3	Refractory
Proceeded directly to unrelated HCT	1	41/M	t 11;14	5	No	30	No	IIIA IgGλ	4.1	0	Refractory
	18	39/M	NE	3	No	17	No*	IIIA κ	2.2	0	CR
	2	61/M	None	5	Yes	21	Yes	IIIA IgGκ	1.6	0	Refractory
	5	54/M	t 1;4	4	No	22	Yes	IIA IgGκ	3.2	0	Refractory
	8	53/F	NE	8	Yes	130	Yes	IIIA IgGκ	1.3	0	Refractory
	9	57/M	Complex	6	No	55	Yes	IIIA IgGκ	3.9	1	Refractory
	10	66/M	NE	6	Yes	108	Yes	IIIA igGκ	3.5	0	Refractory
	11	38/M	NE	4	No	54	Yes	IIA IgGκ	2.5	0	PR
	12	61/M	Δ 13, complex	4	No	29	Yes	IIIA igAκ	1.3	0	CR
	13	53/M	NE	4	No	12	Yes	IIIA IgGλ	5.1	0	Refractory
	22	52/F	NE	8	No	80	Yes	IIA IgGκ	1.7	0	PR

Patients in shaded regions had a history of disease relapse/progression after previous autologous hematopoietic cell transplantation (HCT). Dx, diagnosis; CCI, modified Charleson comorbidity index [15].

PR indicates partial response; CR, complete response; refractory, no CR or PR to last preceding chemotherapy line; PIN, patient identification number; PINs 1–24 assigned in chronological order by day of URD HCT.

*Patient 18 received an autologous HCT 11 months before proceeding to unrelated HCT.

primarily because of transient neutropenia before donor engraftment.

Table 2 summarizes the significant nonhematologic toxicity for days 0–100. The day 100 NRM was 4%. One patient with preexisting congestive heart failure died of multiorgan failure. One patient (4%) developed grade 4 pulmonary toxicity, and 16 patients (67%) developed at least 1 grade 3 toxicity.

GVHD

Acute GVHD developed in 16 patients (67%) at a median of 33 days (range, 7–119 days) (Table 2, Figure 1A). Thirteen patients (54%) had grade II acute GVHD (aGVHD), involving primarily the skin (n = 12) and the gut (n = 6). All 13 patients responded promptly to treatment with prednisone 1–2 mg/kg/day. Three patients with grade III acute GVHD subsequently died, at 57, 153, and 215 days. There were no cases of grade IV GVHD. The cumulative incidence of chronic extensive GVHD (cGVHD) was 75% (Table 2, Figure 1B). The median day of onset of cGVHD was 132 days (range, 85–455 days).

NRM

NRM was 21% at 3 years (Figure 1C). A total of 6 patients died from nonrelapse causes at a median of 6 months (range, 2–37 months), 4 with stable disease and 2 in CR. Four patients died from complications associated with GVHD and opportunistic infections, resulting from disseminated *Aspergillus*, parainfluenza-3 virus, *Klebsiella* sp, and methicillin-resistant *Staphylococcus Aureus* bacteremia. One patient died of congestive heart failure (see Toxicity), and 1 patient died of necrotizing pancreatitis.

Disease Responses

Table 2 summarizes the disease responses for each patient. Ten patients (42%) achieved or remained in CR and 4 (17%) achieved PR, for an overall response rate of 58%. The best disease responses were observed in the 13 patients who underwent tandem autologous-unrelated HCT ($P = .01$). In this group, 7 had CR and 3 had PR, for an overall response rate of 77%. In contrast, only 2 patients (18%) who proceeded directly to unrelated HCT had measurable disease response.

No significant temporal association was found between onset of extensive cGVHD and subsequent disease responses ($P = .39$). No patient received donor lymphocyte infusion.

OS and PFS

The median follow-up of surviving patients from the time of allografting was 3 years (range, 1.2–5.5 years). For all 24 patients, the 3-year estimated OS was 61%, and the PFS was 33% (Figure 2A).

The patients who underwent tandem autologous-unrelated HCT had significantly better PFS compared with those who proceeded directly to unrelated donor HCT ($P = .03$). The difference in OS between the 2 groups was not statistically significant ($P = .30$). In the 13 patients who underwent tandem autologous-unrelated HCT, the estimated 3-year OS was 77%, and the PFS was 51% (Figure 2B). In the 11 patients who proceeded directly to unrelated donor HCT, the estimated 3-year OS was 44% and the PFS was 11% (Figure 2C).

Risk Factors for Survival

Risk factors associated with poorer OS included significant medical comorbidities before HCT, chemotherapy-refractory disease, and relapse/progression after previous autologous HCT. Survival was worse in the 7 patients with modified CCI scores ≥ 1 compared with those with scores of 0 ($P = .03$) (Figure 3A). All 3 patients with CCI scores ≥ 2 died from nonrelapse causes. In the 13 patients who underwent tandem autologous-unrelated HCT, CCI scores ≥ 1 were also associated with worse OS ($P = .01$).

All of the 7 patients who were in PR or CR at the time of study enrollment were alive with follow-up to 4 years. In contrast, survival at 3 years for the 17 patients with refractory disease was 45% ($P = .02$) (Figure 3B).

The 14 patients who experienced relapse or disease progression after a previous autologous HCT (referred to as "failure of previous autologous HCT") had worse OS and PFS than those who did not have previous HCT or failure of previous autologous HCT ($P = .10$ and .05, respectively; Figure 3C). The patients who experienced failure of previous autologous HCT had an OS of 42% and a PFS of 17% 3 years after unrelated HCT. In these 14 patients, there was no difference in OS or PFS between proceeding directly to unrelated HCT or to tandem autologous-unrelated HCT ($P = .58$ and .98, respectively).

The presence of deletion chromosome 13 had no apparent effect on outcome, but there were few evaluable patients. Other factors, such as duration of disease and β2 microglobulin, also did not influence survival.

DISCUSSION

The present multicenter study of patients with advanced, poor-risk multiple myeloma demonstrates that a nonmyeloablative conditioning regimen comprising fludarabine and 2-Gy TBI followed by unrelated donor PBSC transplantation is effective treatment. Tandem autologous-unrelated HCT provided an OS of 77% and a PFS of 51% 3 years after allografting. These results are superior to those achieved in patients who proceeded directly to unre-

Table 2. *Outcomes After Transplantation*

Transplant	Prior Auto HCT	Patient (PIN)	% Donor $CD3^+$ Cells, Day 28	Acute GVHD		Chronic GVHD		Recent IST	Toxicity Grade, Maximum, Day 0–100	Disease Response to Planned Auto HCT	Survival After URD HCT (Days) [Cause of Death]	Disease Outcome after URD HCT [Month of CR/PR/PD/Relapse]
				Grade, Organ	Day of Onset	Extensive	Day of Onset					
Planned tandem auto/unrelated HCT	No	3	85–90	II S	7	Yes	85	Taper	3	PR	>2030	CR [42]
	No	4	100	0	—	Yes	190	No	2	PR	>1829	CR [12]→ Rel [27]
	No	7	95	II S	59	Yes	89	—	2	PR	1105† [NRM, GVHD/OI]	CR [19]
	No	14	93	II S,G	9	Yes	175	Taper	3	SD	>1323	SD
	No	19	85	0	—	Yes	420	Yes	3	CR	>765	CCR
	No	20	77	II S	75	No	—	No	3	PR	>546	PR [6]
	No	21	70	0	—	No	—	No	2	SD	>615	PR [12]
	No	24	95	II S	47	Yes	127	Taper	2	PR	>428	PR [6]
	Failure of prior auto HCT	6	100	0	—	Yes	455	Taper	3	PR	>1498	CR [12]
		15	100	II S,G	14	Yes	93	Taper	3	PR	>1200	CR [3]→Rel [35]
		16	95	III G	44	No	—	—	5	SD	57† [NRM, MOF/OI]	SD
		17	85–90	II G	21	No	—	—	3	SD	106† [PD]	PD [2]
		23	100	III S,G	119	Yes	190	—	3	PR	215† [NRM, GVHD/OI]	CR [6]
Proceeded directly to unrelated HCT	No	1	80–90	II S	32	No	—	—	3	—	89† [PD]	PD [2]
	Yes	18	95	0	—	Yes	235	Taper	2	—	>1080	CCR →Rel [22]
	Failure of prior auto HCT	2	95–99	II S	29	Yes	100	—	4	—	271† [PD]	PD [4]
		5	100	II S	48	No	—	—	3	—	1030† [PD]	PD [25]
		8	93	II S,G	28	Yes	92	—	3	—	166† [NRM, MOF/OI]	SD
		9	100	III S,G,L	10	Yes	132	—	3	—	153† [NRM, GVHD/OI]	SD
		10	90–95	II S,G	37	Yes	123	—	3	—	290† [NRM, GVHD/OI]	SD
		11	5	0	—	No	—	N/A	3	—	>1124*	SD*
		12	95–99	II S,G	34	Yes	84	No	3	—	>1356	CCR →Rel [6]
		13	92	0	—	Yes	418	Taper	3	—	>1398	PR [12]
		22	69	0	—	No	—	No	2	—	>541	CR [6] →Rel [17]

Patients in the shaded region had a history of relapse/progression after previous autologous HCT.

S indicates skin; G, gut; L, liver; URD, unrelated donor; NRM, nonrelapse mortality; OI, opportunistic infection; MOF, multiorgan failure; CR, complete response; CCR, continuous CR; PR, partial response; PD, progressive disease; Rel, relapse; SD, stable disease; N/A, not applicable; Recent IST, immune suppressive therapy within 4 months of last contact date for surviving patients. PIN, patient identification number, assigned chronologically by day of URD HCT.

*Patient 11 rejected the unrelated donor graft and proceeded to second nonmyeloablative unrelated HCT at 11.5 months. He engrafted and achieved CR at 24 months.

Summary of day 0–100 toxicity: Patient 16 died of multiorgan failure on day 57. Patient 2 developed grade 4 pneumonitis requiring brief intubation and mechanical ventilation. Sixteen patients (67%) developed at least one grade 3 toxicity including bacteremia or fever of unknown origin treated with antibiotics (n = 11), pulmonary infiltrates/pneumonitis (n = 6), transient hyperbilirubinemia (n = 5), gastrointestinal nausea/vomiting (n = 4), cardiac arrhythmia or hypertension (n = 2), hemorrhage (n = 2), musculoskeletal pain (n = 1), and renal/metabolic toxicity (n = 1).

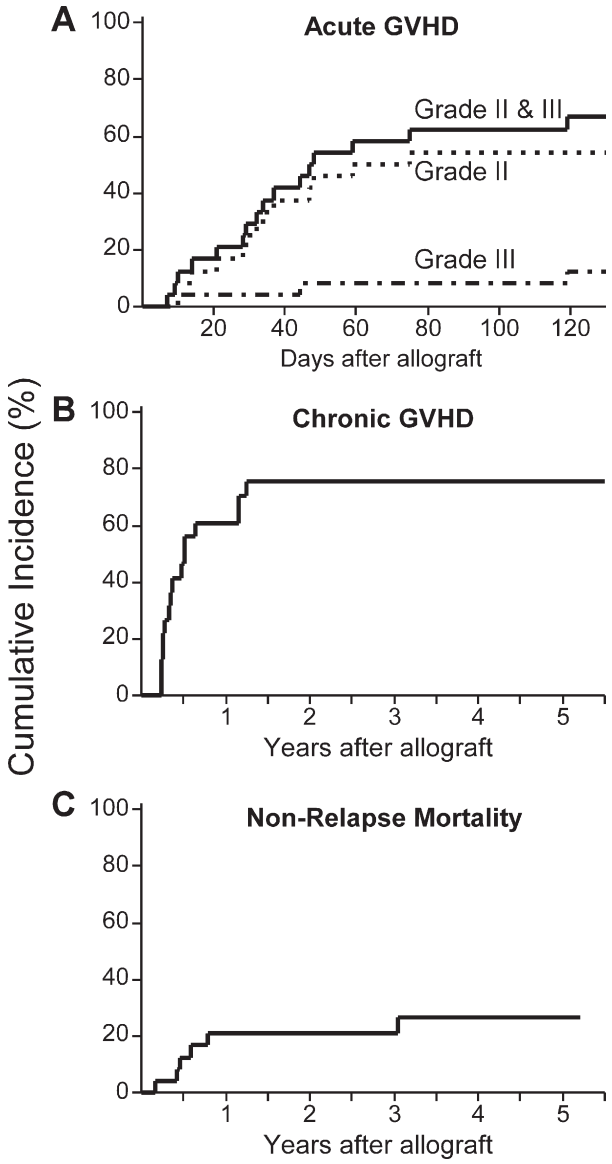

Figure 1. Cumulative incidence of GVHD after unrelated HCT (n = 24). (A) Acute GVHD: 67% all grades of GVHD, 54% grade II, and 13% grade III GVHD by day 120. (B) Chronic extensive GVHD, 75% incidence at 3 years. (C) NRM, 21% at 3 years.

lated HCT (ie, 3-year OS of 44% and PFS of 11%). Although the difference in results was likely related to patient selection, the data do suggest that tandem autologous-unrelated HCT is the optimal treatment approach. However, the relatively small number of patients evaluated limits the strength of this conclusion.

Despite having poor-risk disease and advanced age, the patients exhibited good tolerance of nonmyeloablative conditioning with fludarabine 90 mg/m^2 and 2-Gy TBI. Grade IV–V nonhematologic toxicities within the first 100 days were infrequent compared with those associated with intensive conditioning regimens in younger patients [7-10]. Consistent with recent reports, patients with significant pretransplantation medical comorbidities were at increased risk for NRM [15]; however, NRM was low in patients with CCI scores < 2.

Other prognostic risk factors for worse OS included myeloma progression/relapse after previous autologous HCT and chemotherapy-refractory disease. Kröger et al. [30] reported that patients who experienced progression/relapse after previous autologous HCT were at high risk for TRM and disease relapse after fludarabine/melphalan conditioning, with a 2-year PFS $< 10\%$. In the current study, patients with disease progression/relapse after a previous autologous HCT had a 2-year PFS of 34%.

Despite the advanced stage of multiple myeloma and the high proportions of patients with chemother-

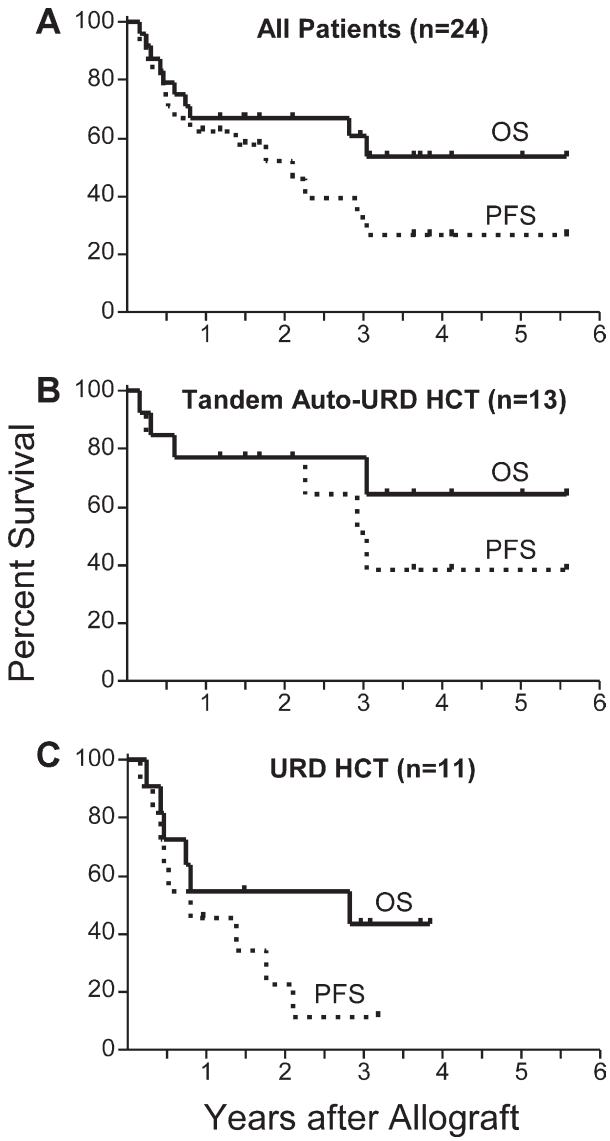

Figure 2. OS (solid line) and PFS (dotted line) after nonmyeloablative conditioning and unrelated HCT for (A) all patients studied (n = 24), (B) recipients of tandem autologous-unrelated HCT (n = 13), and (C) patients proceeding directly to unrelated HCT (n = 11).

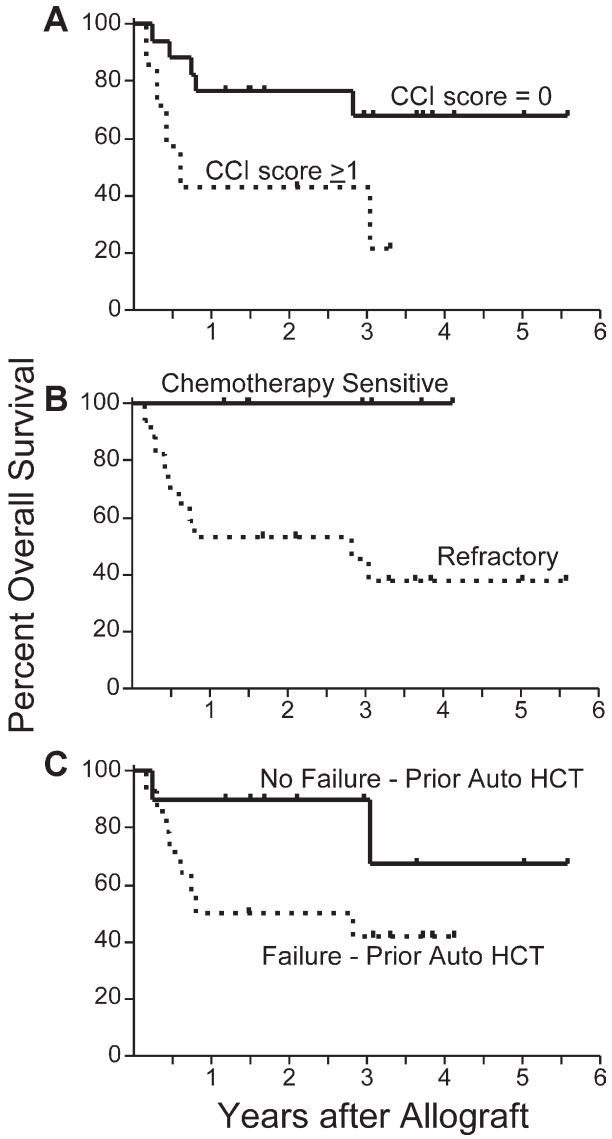

Figure 3. Risk factors for OS after nonmyeloablative conditioning and unrelated HCT for all 24 patients. (A) CCI score [15] of 0 (solid line, n = 17), or ≥ 1 (dashed line, n = 7) (P = .03). (B) Disease-sensitive (solid line, n = 7) or refractory (dashed line, n = 17) to the most recent chemotherapy regimen (P = .02). (C) Failure of previous autologous HCT (dashed line, n = 14) or no previous/no failure of previous autologous HCT (solid line, n = 10) (P = .10).

apy-refractory disease and comorbidities, our current results compare favorably with those reported previously by others [24-26,29]. Moreover, the 3-year median follow-up in our study allows for better assessment of the long-term efficacy of unrelated donor HCT compared with earlier reports. An EBMT registry analysis of 229 patients with multiple myeloma treated with various reduced-intensity conditioning regimens reported that 32 patients received HLA-matched unrelated grafts [31]; the 1-year TRM was 40%, and the 3-year OS was 17%. The authors concluded that those patients who were heavily pretreated or who had chemotherapy-resistant disease did not benefit from allogeneic HCT. Our results do not support their conclusion. Our patients with chemotherapy-refractory disease who underwent a tandem autologous-unrelated HCT had a 3–year OS of 70%, and those who experienced progression/relapse after previous autologous HCT had a 3-year OS of 40%.

Although we used high-resolution methods to identify HLA-matched unrelated donors, the cumulative incidence of cGVHD was 75% at 3 years. Most of the patients with cGVHD tolerated a tapered immunosuppressive therapy; however, some required prolonged therapy. Perhaps owing to the small number of patients studied, the cytoreduction provided by the autologous HCT, and the relatively high incidence of cGVHD, we found no significant association between cGVHD and disease response. However, in a larger cohort of patients with various hematologic malignancies who underwent nonmyeloablative allogeneic HCT, those with cGVHD exhibited improved OS and PFS [40]. The sustained PFS seen in our study is likely related to the graft-versus-myeloma benefit of cGVHD. Longer follow-up is needed to determine whether durable remission of myeloma can be achieved.

For those patients who experienced relapse/progression after previous autologous HCT, our study found no benefit of tandem autologous-unrelated HCT as opposed to proceeding directly to unrelated HCT. However, because a second autologous HCT can provide effective cytoreduction with low NRM [8,41], selected patients who experience failure of previous autologous HCT possibly could benefit from tandem autologous-unrelated HCT.

The recent development of the drugs bortezomib and lenalidomide offers patients with multiple myeloma the possibility of more effective cytoreduction before transplantation [42-44]. Despite the introduction of novel agents for myeloma, the problem of disease relapse after chemotherapy persists. Allogeneic HCT, with the immune-mediated GVT effect, offers the possibility of definitive curative therapy. However, cGVHD remains a cause of significant morbidity, and future progress will require limiting the graft-versus-host reaction to myeloma-specific antigens. Because of the relatively limited toxicity of bortezomib and lenalidomide, patients who experience disease relapse after unrelated HCT may benefit from therapy with these agents to augment the GVT effect of the allograft [45].

In conclusion, our findings support the broader application of tandem autologous-unrelated HCT for patients with multiple myeloma. The low NRM observed in patients with low CCI scores and chemotherapy-sensitive disease suggests that these patients would benefit from referral for nonmyeloablative unrelated HCT at an earlier disease stage. Patients with poor-risk but chemotherapy-sensitive disease, includ-

ing those with elevated β2 microglobulin, low serum albumin, deletion of chromosome 13, or hypodiploidy, may benefit the most from this treatment approach [46-50]. Proceeding to tandem autologous-unrelated HCT also may be beneficial for patients with multiple myeloma who have not responded well to conventional therapy. Moreover, our findings suggest that for patients with chemotherapy-refractory disease or disease progression/relapse after autologous HCT, tandem autologous-unrelated HCT may offer a substantial disease-free survival benefit. Additional follow-up and treatment of increased numbers of patients in a prospective clinical trial are needed to determine whether long-term cures of multiple myeloma can be achieved with this treatment approach.

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