BLOOD RESEARCH
VOLUME 48 · NUMBER 3
September 2013
ORIGINAL ARTICLE

Allogeneic hematopoietic cell transplantation in adult patients with myelodysplastic/myeloproliferative neoplasms

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p-ISSN 2287-979X / e-ISSN 2288-0011
http://dx.doi.org/10.5045/br.2013.48.3.178
Blood Res 2013;48:178-84.

Received on January 9, 2013
Revised on May 19, 2013
Accepted on July 1, 2013

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Background
In adults, the 2 main types of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) are chronic myelomonocytic leukemia (CMML) and atypical chronic myeloid leukemia (aCML). Both are associated with a poor prognosis. Allogeneic hematopoietic cell transplantation (HCT) is the only known curative treatment modality for these diseases, but data on outcomes following such treatment are limited. We analyzed the outcomes of patients with MDS/MPN after allogeneic HCT.

Methods
This retrospective study included 10 patients with MDS/MPN who received allogeneic HCT at Asan Medical Center from 2002 to 2010. Of these 10 patients, 7 had CMML, 2 had aCML, and 1 had unclassifiable MDS/MPN. Five patients received a myeloablative conditioning (MAC) regimen (busulfan-cyclophosphamide), and 5 received reduced-intensity conditioning (RIC) regimen.

Results
Neutrophil engraftment was achieved in all patients. After a median follow-up of 47.5 months among surviving patients, 4 had relapsed and 5 had died. There was only 1 treatment-related death. The 5-year rates of overall, relapse-free, and event-free survival were 42.2%, 51.9%, and 46.7%, respectively. Relapse was the leading cause of treatment failure, and all relapses were observed in patients who had received RIC and who did not develop chronic graft-versus-host disease.

Conclusion
Allogeneic HCT can induce durable remission in patients with MDS/MPN, but RIC cannot replace MAC in patients eligible for myeloablative treatments.

Key Words MDS/MPN, Allogeneic HCT, Reduced-intensity, Relapse

INTRODUCTION

Although myelodysplastic syndrome (MDS) and myeloproliferative disorder (MPD) appear to have entirely different pathophysiological mechanisms, the existence of conditions with overlapping features is well established [1, 2]. The World Health Organization (WHO) classification of myeloid neoplasms clearly defines a MDS/MPD group, which includes chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), *BCR-ABL*-negative atypical chronic myeloid leukemia (aCML), and unclassifiable MDS/MPD (MDS/MPD-U) [3]. In the recently updated WHO classification system, the term MPD has been replaced by myeloproliferative neoplasm (MPN) [4]. Patients with MDS/MPN have various combinations of cytopenias and cytoses, with dysplasia of at least one lineage. Their bone marrow is characteristically hypercellular and shows dysplastic and proliferative features, as predicted from peripheral blood. By definition, the percentage of blasts in blood and bone marrow must be less than 20%.

In adults, the 2 main types of MDS/MPN are CMML and aCML, both of which are associated with poor prognosis. CMML is a progressive disease that often leads to death

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within months [5, 6]. Various chemotherapy regimens, including hydroxyurea, etoposide, low-dose cytarabine, topotecan, intensive chemotherapy, and hypomethylating agents, have generally been inadequate in patients with CMML owing to low response rates and short response durations [7, 8]. In approximately 25% to 40% of patients with aCML, the disease evolves into acute leukemia, while the remaining patients die of marrow failure; the median survival in patients treated with conventional chemotherapy is less than 20 months [9-11]. The only currently available therapy that is potentially curative for patients with MDS/MPN is allogeneic hematopoietic cell transplantation (HCT), but little is known about the impact of allogeneic HCT on the natural history of MDS/MPN [12-16]. We analyzed the outcomes of patients with MDS/MPN after allogeneic HCT.

MATERIALS AND METHODS

Patients

Between October 2002 and July 2010, 10 patients (9 men) with MDS/MPN underwent allogeneic HCT at the Asan

Table 1. Patient characteristics at the time of hematopoietic cell transplantation.

UPN	Gender	Age (yr)	Dx	Dx to HCT (months)	Prior Tx	KPS (%)	HCT-CI score	MDAPS	Disease status	BM cellularity (%)	BM blasts (%)	Comments
265	M	34	CMML	6.8	None	60	1	High	Persistent	100	14.0	Normal karyotype
267	M	48	aCML	2.2	None	90	0		Persistent	100	9.8	Normal karyotype
281	M	28	aCML	3.8	None	90	0		Persistent	100	.8	Normal karyotype
370	M	32	MDS /MPN-U	4.0	None	80	0		Persistent	50	3.0	Normal karyotype
408	M	28	CMML	19.6	FLAG-D	80	0	INT-1	Persistent	85	8.4	Normal karyotype
521	M	48	CMML	2.5	None	90	0	INT-2	Persistent	70	15.4	Chromosome 6 abnormalities
628	F	35	CMML	2.1	Azacitidine#1	80	0	INT-2	Persistent	95	6.4	Complex karyotype Prior chemo-radiotherapy for NHL
709	M	53	CMML	5.3	Decitabine#4	90	0	INT-2	Persistent	65	13.4	Normal karyotype
740	M	53	CMML	4.2	Decitabine#4	90	0	Low	Marrow CR	100	.6	Trisomy 8
897	M	47	CMML	8.0	Decitabine#1	80	4	INT-1	Persistent	90	1.2	Normal karyotype

Abbreviations: UPN, unique patient number; M, male; F, female; Dx, diagnosis; CMML, chronic myelomonocytic leukemia; aCML, atypical chronic myeloid leukemia; MDS/MPN-U, myelodysplastic syndrome/myeloproliferative neoplasm-unclassifiable; HCT, hematopoietic cell transplantation; Tx, treatment; FLAG-D, fludarabine, cytarabine, granulocyte colony-stimulating factor plus daunorubicin; KPS, Karnofsky performance score; HCT-CI, hematopoietic cell transplantation-comorbidity index; MDAPS, M.D. Anderson Prognostic Score; INT, intermediate; CR, complete remission; BM, bone marrow; NHL, non-Hodgkin lymphoma.

Table 2. Transplantation data.

UPN	Donor gender	Donor age (year)	Donor type	No. HLA mismatch[a]	ABO type		GVHD Prophylaxis	Conditioning regimen	Graft source	Stem cell dose	
					Patient	Donor				MNC (10^8/kg)	CD34 cells (10^6/kg)
265	M	25	Unrelated	0	B+	O+	CSA+MTX	BuCy	BM	0.12	0.45
267	M	47	Sibling	0	A+	A+	CSA	BuCy	BM	0.52	4.77
281	M	26	Sibling	0	O+	O+	CSA	BuCy	BM	0.95	3.28
370	M	29	Unrelated	0	A+	O+	CSA+MTX	BuFluATG	BM	3.01	1.80
408	F	28	Unrelated	0	A+	B+	CSA+MTX	BuFluCampath	PB	8.12	25.40
521	M	48	Sibling	0	A+	A+	CSA+MTX	BuCy	BM	0.39	1.20
628	F	36	Sibling	0	A+	A+	CSA+MTX	MelFlu	PB	5.77	4.67
709	M	26	Unrelated	1	O+	O+	CSA+MTX	BuFluATG	PB	5.75	5.28
740	M	25	Son	3	B+	B+	CSA+MTX	BuFluATG	PB	6.11	0.48
897	M	37	Sibling	0	B+	A+	CSA+MTX	BuCy	PB	5.76	9.49

[a]Number of incompatibilities among 8 ABDR loci between donor and recipient.
Abbreviations: UPN, unique patient number; HLA, human leukocyte antigen; GVHD, graft-vs-host disease; CSA, cyclosporin; MTX, methotrexate; BuCy, busulfan+cytoxan; BuFluATG, busulfan+fludarabine+thymoglobulin; BuFluCampath, busulfan+fludarabine+alemtuzumab; MelFlu, melphalan-fludarabine; BM, bone marrow; PB, peripheral blood stem cell; MNC, mononuclear cell.

Medical Center, Seoul, Korea (Table 1). Median age at the time of HCT was 43 years (range, 28 to 53 years). Seven patients had CMML, 2 had aCML, and 1 had MDS/MPN-U. MDS/MPN was diagnosed and classified using WHO criteria [3, 4]. The median interval from diagnosis to HCT was 4.1 months (range, 2.1 to 19.6 months). Five patients had not received any specific treatment for MDS/MPN, whereas the other 5 were treated with intensive chemotherapy (N=1) or hypomethylating agents (N=4) before HCT. Among the 5 previously treated patients, only 1 had responded to treatment. Eight patients had HCT-comorbidity index (HCT-CI) scores [17] of 0, with 1 each having scores of 1 and 4. Of the 7 patients with CMML, 1 had a low-risk MD Anderson Prognostic score (MDAPS) [6], 2 had intermediate-1 scores, 3 had intermediate-2 scores, and 1 had a high risk score. At the time of HCT, 7 patients had > 5% bone marrow blasts and 3 had cytogenetic abnormalities. One patient had received chemotherapy and radiotherapy for non-Hodgkin's lymphoma (NHL).

Transplantation procedures

The 10 donors consisted of 8 men and 2 women, of median age 28.5 years (range, 25 to 48 years) (Table 2). Five donors were HLA-matched siblings, 4 were unrelated volunteers (3 HLA matched and 1 mismatched in the HLA-B-allele), and 1 was an HLA-haplo-identical familial donor. ABO incompatibilities were observed in 4 donor-recipient pairs: 2 minor and 2 major and minor incompatibilities. Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine plus short-course methotrexate in 8 patients and cyclosporine alone in 2. Five patients received a myeloablative conditioning (MAC) regimen, consisting of intravenous busulfan (3.2 mg/kg) for 4 days and cyclophosphamide (60 mg/kg) for 2 days (BuCy). The other 5 received reduced-intensity conditioning (RIC) regimens, including 3 who received intravenous busulfan (3.2 mg/kg) for 2 days plus fludarabine (30 mg/m^2) for 6 days plus anti-thymocyte globulin (Thymoglobulin; 3 mg/kg) for 3 days (BuFluATG), 1 who received intravenous busulfan (3.2 mg/kg) for 2 days plus fludarabine (30 mg/m^2) for 6 days plus alemtuzumab (20 mg) for 1 day (BuFluCampath), and 1 who received melphalan (100 mg/m^2) for 1 day plus fludarabine (30 mg/m^2) for 5 days (MelFlu). The administration of an RIC regimen was at the discretion of the attending physician. One patient (UPN 408) received alemtuzumab owing to a shortage of anti-thymocyte globulin in Korea at that time, and 1 patient (UPN 628) received MelFlu due to the concurrent presence of active lymphoma and CMML at the time of HCT. The hematopoietic cell graft was bone marrow in 5 patients and granulocyte colony-stimulating factor (G-CSF)-mobilized peripheral blood mononuclear cells in 5.

Day 0 was defined as the first day of infusion of hematopoietic cell graft. Time to neutrophil engraftment was the time from day 0 until the first of 3 consecutive days at which absolute neutrophil count was $\geq 0.5\times10^9$/L, and time to platelet engraftment was the time from day 0 until the first of 7 consecutive days at which platelet count was $\geq 20\times10^9$/L without transfusion support. Hematopoietic chimerism was evaluated in bone marrow or peripheral blood cells by PCR analysis of short tandem repeats [18]. Relapse was defined according to standard morphologic criteria and/or conventional cytogenetic analysis.

Acute and chronic GVHD were diagnosed on the basis

Table 3. Post-transplant outcomes.

UPN	Time to engraftment (post-transplant day)			Chimerism (days)	GVHD		Hepatic SOS	CMV		F/U duration (months)	Outcomes
	ANC	PLT	Reti		Acute	Chronic		Infection	Disease		
265	16	-	22	CC (2)	None	NE	Moderate	Yes	IP	2.7	Died of CMV IP
267	12	26	21	CC (2)	None	Extensive	None	Yes	None	98.8	Alive in NED
281	12	25	40	CC (2)	Gr II	Extensive	None	Yes	None	96.3	Alive in NED
370	20	30	33	CC (2)	None	None	None	Yes	None	36.2	Relapse → 2nd HCT → died of 2nd graft failure
408	24	19	19	MC	None	None	None	No	None	25.6	Relapse → 2nd HCT → DLI for MC → died of GVHD
521	21	33	33	CC (28)	None	Extensive	None	Yes	None	47.5	Alive in NED
628	17	17	17	CC (2)	None	Extensive	None	Yes	None	31.2	Alive in NED
709	16	20	36	CC (2)	None	None	None	Yes	None	8.7	Died of relapse
740	11	13	33	CC (8)	Gr II	None	None	Yes	None	10.1	Died of AML transformation
897	12	81	-	CC (12)	None	None	Moderate	Yes	None	4.6	Alive in NED

Abbreviations: UPN, unique patient number; ANC, absolute neutrophil counts $\geq 0.5\times10^9$/L; PLT, platelet counts $\geq 20\times10^9$/L; Reti, absolute reticulocyte counts ≥1.0%; CC, complete chimerism; MC, mixed chimerism; GVHD, graft-versus-host disease; Gr, grade; NE, not evaluable; SOS, sinusoidal obstruction syndrome; CMV, cytomegalovirus; IP, interstitial pneumonitis; F/U, follow-up; NED, no evidence of disease; HCT, hematopoietic cell transplantation; DLI, donor lymphocyte infusion; AML, acute myeloid leukemia.

of clinical symptoms, laboratory tests, and, when possible, histopathologic assessment of the skin, oral mucosa, and gastrointestinal tract. Acute GVHD was classified according to clinical criteria [19], and chronic GVHD was graded as limited (localized to the skin or a single organ) or extensive (generalized skin or multiple organ involvement) [20].

Hepatic sinusoidal obstruction syndrome (SOS) diagnosis [21] and severity [22] was made according to previously established criteria.

Statistical analysis

Analyses were performed using the SPSS statistical package (version 18.0, IBM Corp., Armonk, NY, USA). Overall survival (OS), relapse-free survival (RFS), and event-free survival (EFS) were defined as the time from the date of HCT to the date of death, relapse, and relapse or death, respectively. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Differences were considered statistically significant if the 2-tailed P value was <0.05.

RESULTS

Engraftment and chimerism

All patients achieved neutrophil engraftment (absolute neutrophil count $\geq 0.5\times10^9$/L) at a median of 16 days (range, 12 to 24 days), and 9 patients achieved transfusion- independent platelet engraftment ($\geq 20\times10^9$/L) at a median of 25 days (range, 13 to 81 days). One patient died of cytomegalovirus (CMV) interstitial pneumonitis before platelet engraftment (Table 3). Nine patients attained complete chimerism, 2 to 28 weeks after HCT, but 1 showed persistent mixed chimerism and relapsed 7.8 months after HCT.

Post-transplant complications

Acute GVHD occurred in 2 patients (20.0%); both were of grade II. Chronic GVHD occurred in 4 (44.4%) of 9 assessable patients, with all 4 being extensive. All patients experienced CMV infection, as shown by the pp65 CMV antigenemia assay, but only 1 developed CMV disease (interstitial pneumonitis) (Table 3). Two patients developed hepatic SOS

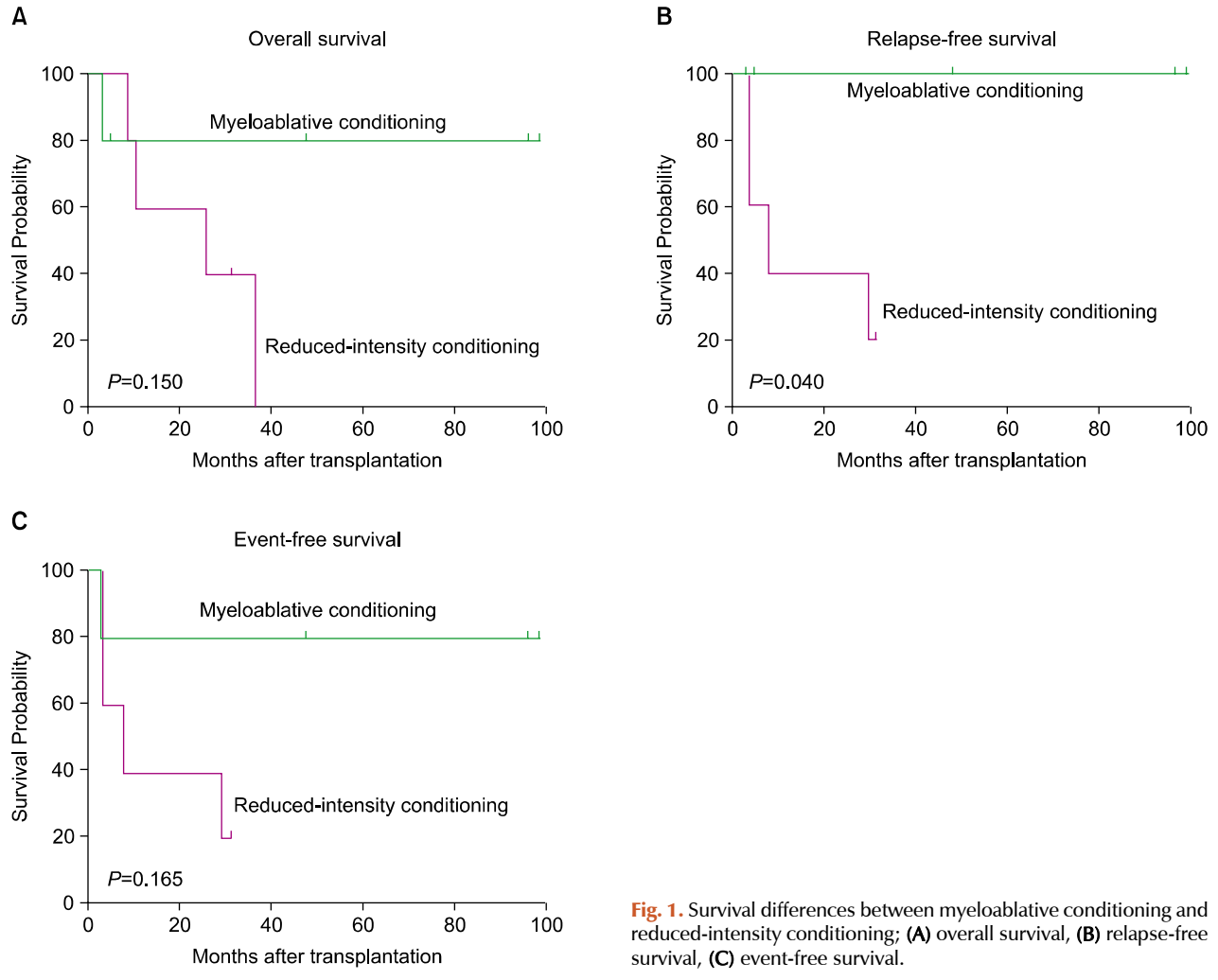

Fig. 1. Survival differences between myeloablative conditioning and reduced-intensity conditioning; **(A)** overall survival, **(B)** relapse-free survival, **(C)** event-free survival.

of moderate severity.

Post-transplant outcomes

After a median follow-up of 47.5 months (range, 4.6 to 98.8 months) in the surviving patients, 5 patients had died. Four of these deaths were related to disease relapse, but 1 was due to CMV interstitial pneumonitis (Table 3). Four patients relapsed after allogeneic HCT. Two relapsed patients underwent a second allogeneic HCT from different donors, but both died, one of secondary engraftment failure and the other of GVHD after donor lymphocyte infusion for mixed chimerism. At the time of writing this manuscript, 5 of the 10 patients remain alive without disease relapse. The 5-year OS, RFS, and EFS rates were 42.2%, 51.9%, and 46.7%, respectively. Survival was not correlated with pre-transplant HCT-CI score or MDAPS. Four of 5 patients without chronic GVHD relapsed, compared with 0 of 4 with chronic GVHD.

Post-transplant outcomes were compared between patients who received MAC and those who received RIC conditioning regimens. Of the 5 patients who received MAC regimens, 4 were alive without relapse and 1 had died of a non-relapse related cause. In contrast, 4 of 5 patients who received RIC regimens relapsed and died, with only 1 remaining alive without relapse. Fig. 1 shows that patients who received MAC regimens had superior OS (P=0.150), RFS (P=0.040), and EFS (P=0.165) compared with patients who received RIC regimens.

DISCUSSION

Although allogeneic HCT has curative potential for patients with MDS/MPN, its role has not been established, primarily owing to limited data. Retrospective studies of allogeneic HCT for CMML in 12 to 50 patients have shown

Table 4. Published data for post-transplant outcomes in MDS/MPN (except juvenile myelomonocytic leukemia).

Author	Year	Disease	Donor type	Graft source	Conditioning regimen	Post-transplant outcomes
Kroger *et al*. [28]	2002	CMML (N=50)	MRD (N=39) MMRD (N=5) MUD (N=6)	BM (N=40) PB (N=9) BM+PB (N=1)	TBI-based (N=26) Chemotherapy only (N=24)	TRM (N=26; 35% at day 100 and 55% at 1 year) Relapse (N=14) OS 21% (5 years), DFS 18% (5 years)
Kerbauy *et al*. [13]	2005	CMML (N=43)	MRD (N=18) MMRD (N=3) MUD (N=17) MMUD (N=5)	BM (N=23) PB (N=20)	Various MAC (N=41) RIC (N=2)	TRM (N=15) Relapse (N=10; 23% at 4 years) OS 41% (at 4 years), RFS 41% (at 4 years)
Elliott *et al*. [12]	2006	CMML (N=17)	MRD (N=14) MUD (N=2) MMUD (N=1)	BM (N=8) PB (N=7) BM+PB (N=2)	Cytoxan+TBI (N=16) RIC (N=1)	TRM (N=7) Relapse (N=7) OS 18% (at 3 years), DFS 18% (at 3 years)
Ocheni *et al*. [16]	2009	CMML (N=12)	MRD (N=2) MUD (N=5) MMUD (N=5)	PB (N=12)	MAC (N=7): BuCy ± etoposide ± ATG RIC (N=5): FLAMSA	TRM (N=3) Relapse (N=2) OS 75% (at 3 years), DFS 50% (at 3 years)
Mittal *et al*. [15]	2004	CMML (N=8) aCML (N=7) MF (N=5)	MRD (N=13) MMRD (N=2) MUD (N=5)	BM (N=11) PB (N=9)	BuCy (N=6), BuFlu (N=1), Cytoxan+TBI based (N=5) MelFlu based (N=6) FAI (N=2)	TRM (N=7) Relapse (N=6; aCML 1, CMML 5) OS 35% (at 4 years), DFS 31% (at 4 years) Alive (N=8; aCML 2, CMML 3, MF 3)
Koldehoff *et al*. [14]	2004	aCML (N=9)	MRD (N=4) MUD (N=4) Twin (N=1)	BM (N=3) PB (N=6)	BuCy (N=2) Cytoxan+TBI based (N=3) BuFluATG (N=1)	TRM (N=1) Relapse (N=1; twin donor; retransplantation) Alive (N=8)
Current study		CMML (N=7) aCML (N=2) MDS/MPN-U (N=1)	MRD (N=5) MMRD (N=1) MUD (N=3) MMUD (N=1)	BM (N=5) PB (N=5)	BuCy (N=5) BuFluATG (N=3) BuFluCampath (N=1) MelFlu (N=1)	TRM (N=1) Relapse (N=4) OS 42.4% (at 5 years), RFS 51.9% (at 5 years), EFS 46.7% (at 5 years)

Abbreviations: MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm; MDS/MPN-U, MDS/MPN-unclassified; CMML, chronic myelomonocytic leukemia; aCML, atypical chronic myeloid leukemia; MF, myelofibrosis; MRD, matched related donor; MMRD, mismatched related donor; MUD, matched unrelated donor; MMUD, mismatched unrelated donor; BM, bone marrow; PB, peripheral blood; TBI, total body irradiation; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; BuCy, busulfan+cytoxan; ATG, antithymocyte globulin; FLAMSA, fludarabine+amsacrine+cytarabine; BuFlu, busulfan+fludarabine; MelFlu, melphalan+fludarabine; FAI, fludarabine+cytarabine+idarubicin; BuFluATG, busulfan+fludarabine+ATG; BuFluCampath, busulfan+fludarabine+alemtuzumab; TRM, treatment- related mortality; OS, overall survival; RFS, relapse-free survival; DFS, disease-free survival; EFS, event-free survival.

survival rates of 18% to 75% and day 100 treatment-related mortality (TRM) rates of 25% to 41% (Table 4) [12, 13, 16]. According to the available literature, allogeneic HCT has been performed in a total of 17 patients with aCML, with 11 remaining alive at the time of the report [14, 15, 23]. Our findings (in 7 patients with CMML, 2 with aCML, and one with MDS/MPN-U) were similar. There were 4 relapses and 1 treatment-related death. The 5-year rates of OS, RFS, and EFS were 42.2%, 51.9%, and 46.7%, respectively. At a median follow-up of 47.5 months, 4 of 7 patients with CMML, 0 of 2 with aCML, and 1 of 1 with MDS/MPN-U had died. The discrepancies in survival rates after allogeneic HCT in the literature suggest the need for guidelines related to indications and conditioning strategies. When 43 CMML patients were classified according to MDAPS and HCT-CI scores, those at higher risk, as determined by MDAPS, tended to have a higher relapse rate than those at lower risk, and those with higher comorbidity scores had reduced OS than those with lower scores [13]. The results suggest that early disease stage and low comorbidity score may be optimal indications for allogeneic HCT in patients with MDS/MPN. Our previous study of patients with MDS showed that pre-transplant comorbidity and prognostic scores were important for post-transplant outcomes [24]. Owing to the small number of patients in this study, however, we could not correlate MDAPS or HCT-CI scores with post-transplant outcomes in patients with MDS/MPN.

One important issue related to allogeneic HCT for MDS/MPN is the choice of optimal conditioning regimen. Various intensities and combinations of chemotherapeutic agents or irradiation have been used [12-16], making it difficult to determine optimal conditioning regimens prior to allogeneic HCT for MDS/MPN. Several retrospective studies in patients with MDS showed that RIC regimens resulted in lower TRM than standard MAC regimens, but this benefit was offset by higher relapse rates [25, 26]. Of our 10 patients, 5 had received MAC and 5 had received RIC. Relapses were observed only in patients who had received RIC, and survival parameters were inferior for RIC compared with MAC. Our results suggest that RIC cannot replace MAC in patients who are eligible for myeloablative treatments.

Many patients with MDS/MPNs are elderly and frequently have comorbidities, making them ineligible for MAC regimens. RIC may enable allogeneic HCT in these patients. A study of 148 patients ineligible for conventional HCT, including 65 with MDS, 49 with acute myeloid leukemia after MDS/MPN, 27 with MPN, and 7 with CMML, assessed outcomes of allogeneic HCT following RIC (low-dose total body irradiation with or without fludarabine) [27]. In that study, the 3-year TRM for patients with CMML was 32%, and the 3-year OS and RFS rates were 43% each. Relapse was the leading cause of treatment failure. Strategies are needed to reduce relapse after HCT in patients who receive RIC. One possible strategy may be to augment alloimmunity after HCT. In a study assessing the post-transplant outcomes of 50 patients with CMML, relapse probability was found to be lower in patients with acute GVHD and higher in those with T cell-depleted grafts [28]. In addition, of 5 CMML patients who received donor lymphocyte infusions (DLIs) for relapse or mixed chimerism, 2 achieved durable remission [12]. We found an association between chronic GVHD and lower relapse rate, suggesting that graft-versus-leukemia effects, which have been well documented in various diseases [29, 30], may also occur in patients with MDS/MPN. Prophylactic DLI or early withdrawal of immunosuppressive agents following RIC HCT seems to be worth evaluating in future studies.

In summary, allogeneic HCT following MAC conditioning can induce durable remission in patients with MDS/MPN. Relapse was the leading cause of treatment failure; relapse was observed only in patients who had received RIC and who had not developed chronic GVHD. Our results suggest that RIC cannot replace MAC in patients eligible for myeloablative treatments. Future studies aiming to reduce relapse rates after RIC HCT are warranted for elderly patients and those with comorbidities, who account for most patients with MDS/MPN.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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