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Supportive Care

Clinical effects of granulocyte colony-stimulating factor administration and the timing of its initiation on allogeneic hematopoietic cell transplantation outcomes for myelodysplastic syndrome

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A B S T R A C T

Granulocyte colony-stimulating factor (G-CSF) accelerates neutrophil recovery after allogeneic hematopoietic cell transplantation (HCT). However, the optimal use of G-CSF and the timing of its initiation after allogeneic HCT for myelodysplastic syndrome (MDS) according to graft type have not been determined. This retrospective study aimed to investigate the effects of using G-CSF administration and the timing of its initiation on transplant outcomes in adult patients with MDS undergoing allogeneic HCT. Using Japanese registry data, we retrospectively investigated the effects of G-CSF administration and the timing of its initiation on transplant outcomes among 4140 adults with MDS after bone marrow transplantation (BMT), peripheral blood stem cell transplantation (PBSCT), or single-unit cord blood transplantation (CBT) between 2013 and 2022. Multivariate analysis showed that early (days 0 to 4) and late (days 5 to 10) G-CSF administration significantly accelerated neutrophil recovery compared with no G-CSF administration following BMT, PBSCT, and CBT, but there was no benefit of early G-CSF initiation for early neutrophilic recovery regardless of graft type. Late G-CSF initiation was significantly associated with a higher risk of overall chronic GVHD following PBSCT (hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.18 to 2.24; $P = .002$) and CBT (HR, 2.09; 95% CI, 1.21 to 3.60; $P = .007$) compared with no G-CSF administration. Late G-CSF initiation significantly improved OS compared with no G-CSF administration only following PBSCT (HR, 0.74; 95% CI, 0.58 to 0.94; $P = .015$). However, G-CSF administration and the timing of its initiation did not affect acute GVHD, relapse, or non-relapse mortality, irrespective of graft type. These results suggest that G-CSF administration significantly accelerated neutrophil recovery after BMT, PBSCT, and CBT, but increased risk of overall chronic GVHD after PBSCT and CBT. However, the effect of early and late G-CSF initiation on transplant outcomes needs further study in adult patients with MDS.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment for myelodysplastic syndrome (MDS). Granulocyte colony-stimulating factor (G-CSF) accelerates neutrophil recovery after allogeneic HCT and reduces complications associated with neutropenia. However, administering G-CSF after allogeneic HCT can increase the risk of acute and chronic graft-versus-host disease (GVHD) [1–5]. Although the early initiation (day 0 to 4) of G-CSF may accelate neutrophil recovery after allogeneic HCT, previous prospective studies failed to improve neutrophil recovery following allogeneic bone marrow transplantation (BMT), or peripheral blood stem cell transplantation (PBSCT) [6–9], but the optimal timing of G-CSF initiation following cord blood transplantation (CBT) remains unexplored. Furthermore, G-CSF can induce blast cell proliferation in patients with MDS [10], raising the risk of leukemic transformation or relapse, especially with G-CSF administration early after allogeneic HCT. Concerningly, there is no consensus on the optimal use of G-CSF and the timing of its initiation after allogeneic HCT for MDS. Using a nationwide Japanese database, we performed a retrospective analysis of a large cohort of adult patients with MDS who were treated with allogeneic BMT, PBSCT, or single-unit CBT to evaluate the effect of G-CSF administration and the timing of its initiation on posttransplant outcomes.

METHODS

Data Collection

The Adult MDS Working Group of the Japanese Society for Transplantation and Cellular Therapy (JSTCT) performed this retrospective study. Clinical information was taken from the Transplant Registry Unified Management Program sponsored by the Japanese Data Center for Hematopoietic Cell Transplantation (JDCHCT) and the JSTCT [11,12]. Patients with MDS aged 16 years and over who had their first allogeneic HCT in Japan between 2013 and 2022 were identified for potential inclusion in this study. Patient eligibility criteria for this trial included those who did not receive G-CSF or who received it following graft infusion, provided that the initial G-CSF administration occurred between days 0 to 10, that G-CSF

started prior to neutrophil engraftment, and that G-CSF administration continued over a minimum of three days. There were 4,140 patients who fulfilled these requirements and were enrolled in the study. The JSTCT's Adult MDS Working Group and Institutional Review Board at the Institute of Medical Science, the University of Tokyo (2024-44-1015), where the study was carried out, approved this study.

Study Objectives

The primary objective of this study was to investigate the effect of G-CSF treatment on acute and chronic GVHD. Examining how G-CSF treatment affected neutrophil and platelet recovery, relapse, non-relapse mortality (NRM), overall survival (OS), and disease-free survival (DFS) were secondary objectives.

Definitions

The diagnosis and severity of GVHD were based on previously established standard criteria [13,14]. Neutrophil recovery was defined as an absolute neutrophil count exceeding 0.5×10^9/L on three consecutive days. Platelet recovery was characterized by a platelet count exceeding 20×10^9/L on seven consecutive days following the last platelet transfusion. Relapse was defined as morphologic evidence of MDS. Death during remission was defined as NRM. The inverse of overall mortality, OS, was defined as the time from HCT to death from any cause, and DFS was defined as the time from HCT to relapse or death from any cause. Surviving patients were censored at the time of their last observation. The HCT-CI [15] and intensity of the conditioning regimen [16] were classified according to published criteria. Karyotype risk at diagnosis was defined according to the International Prognostic Scoring System [17]. According to disease status at HCT, patients with refractory anemia with an excess of blasts (RAEB)-1, RAEB-2, or MDS with an excess of blasts (World Health Organization, 2008 or 2016 classification [18,19]) were classified as high-risk, and others as low-risk. The number of human leukocyte antigen (HLA) disparities between recipients and donors was defined based on low-resolution HLA-A, -B, and -DR matching in the graft-versus-host direction.

Statistical Analysis

Group comparisons were conducted using chi-squared or Fisher's exact tests for categorical variables and Kruskal–Wallis tests for continuous variables. Cumulative incidence estimates were used to calculate the unadjusted cumulative incidence of GVHD, hematopoietic recovery, relapse, and NRM, which were compared using Gray's test. The Kaplan–Meier method was used to estimate the unadjusted OS and DFS probabilities, which were compared using the log-rank test. Multivariate analyses used the Fine and Gray proportional hazards model for GVHD, hematopoietic recovery, relapse, and NRM, and the Cox proportional hazards regression model for overall mortality (1-OS) and treatment failure (1-DFS). Hazard ratios (HR) with 95% confidence intervals (CI) were estimated for G-CSF administration (no administration vs. administration), or administration and timing of G-CSF initiation (no administration vs. 0 to 4 days vs. 5 to 10 days), adjusting for covariates: age ($<$60 years vs. $\geq$60 years), recipient sex (male vs. female), HCT-CI (0 to 2 vs. $\geq$3), cytogenetic risk (other than poor vs. poor), disease status at HCT (low-risk vs. high-risk), conditioning regimen (MAC vs. RIC), GVHD prophylaxis (calcineurin inhibitors and methotrexate vs. others), use of antithymocyte globulin (ATG) (without ATG vs. with ATG), HLA disparities (match vs. mismatch), and year of HCT (2013 to 2017 vs. 2018 to 2022). For BMT and PBSCT, donor type (related vs. unrelated) was also included as a variable in the multivariate analysis. Analyses were conducted separately for each cohort based on graft type (BMT, PBSCT, and CBT).

To adjust for multiple testing for each outcome in univariate and multivariate analysis, $P < .0166$ (0.05/3) was statistically significant with the Bonferoni correction. P values between .0166 and .05 were considered to have a marginal significance.

Statistical analyses were performed using EZR version 1.68 (Saitama Medical Center, Jichi Medical University) [20], a graphical user interface for R 4.4.0 software (R Foundation for Statistical Computing).

RESULTS

Patients and Transplant Procedures

Characteristics of the patients and their transplant procedures are summarized in Table 1. Among the 4140 patients, 1781 received BMT, 1168 received PBSCT, and 1191 received CBT. The median recipient age at HCT was 57 years for BMT, 58 years for PBSCT, and 61 years for CBT ($P < .001$). The BMT recipients were less likely to have an HCT-CI $\geq$3 ($P = .045$), poor karyotype ($P = .045$), and high-risk disease status at HCT ($P = .004$). The MAC regimen ($P < .001$) and calcineurin inhibitors and methotrexate-based GVHD prophylaxis regimens ($P < .001$) were predominantly

Table 1
Characteristics of Patient, Disease, and Transplantation According to Graft Source

	BMT	PBSCT	CBT	*P*
Number of patients	1781	1168	1191	
Median recipient age, years (IQR)	57 (47-63)	58 (49-63)	61 (53-66)	<**.001**
Recipient age, number (%)				<**.001**
<60 years	1019 (57.2)	681 (58.3)	530 (44.5)	
≥60 years	762 (42.8)	487 (41.7)	661 (55.5)	
Recipient sex, number (%)				**.037**
Male	1184 (66.5)	827 (70.8)	797 (66.9)	
Female	596 (33.5)	341 (29.2)	394 (33.1)	
Missing	1	0	0	
HCT-CI, number (%)				**.045**
0-2	1425 (80.1)	910 (78.2)	907 (76.3)	
≥ 3	353 (19.9)	254 (21.8)	281 (23.7)	
Missing	3	4	3	
Karyotype, number (%)				**.045**
Good	720 (40.4)	392 (33.6)	397 (33.3)	
Intermediate	343 (19.3)	227 (19.4)	239 (20.1)	
Poor	608 (34.1)	465 (39.8)	480 (40.3)	
Unevaluable	110 (6.2)	84 (7.2)	75 (6.3)	
Disease risk at HCT, number (%)				**.004**
Low-risk	593 (37.1)	345 (32.9)	339 (31.3)	
High-risk	1004 (62.9)	703 (67.1)	743 (68.7)	
Missing	184	120	109	
Conditioning regimen, number (%)				<**.001**
MAC	1126 (63.2)	668 (57.2)	677 (56.8)	
RIC	655 (36.8)	500 (42.8)	514 (43.2)	
GVHD prophylaxis, number (%)				<**.001**
CI + MTX	1631 (91.8)	728 (62.3)	637 (53.6)	
CI + MMF	65 (3.7)	361 (30.9)	483 (40.7)	
Others	81 (4.6)	79 (6.8)	68 (5.7)	
Missing	4	0	3	
ATG, number (%)				<**.001**
No use	1513 (85.0)	930 (79.6)	1109 (93.1)	
Use of ATG	268 (15.0)	238 (20.4)	82 (6.9)	
PTCy, number (%)				<**.001**
No PTCy	1763 (99.0)	852 (72.9)	1191 (100.0)	
Use of PTCy	18 (1.0)	316 (27.1)	0	
Donor type, number (%)				<**.001**
Related	222 (13.3)	823 (73.2)	0	
Unrelated	1453 (86.7)	302 (26.8)	1191 (100.0)	
Missing	106	43	0	
HLA disparity, number (%)				<**.001**
Match	1463 (82.1)	693 (59.5)	80 (6.7)	
Mismatch	318 (17.9)	472 (40.5)	1108 (93.3)	
Missing	0	3	3	
HCT year, number (%)				<**.001**
2013-2017	946 (53.1)	399 (34.2)	492 (41.3)	
2018-2022	835 (46.9)	769 (65.8)	699 (58.7)	
G-CSF, number (%)				<**.001**
No administration	336 (18.9)	194 (16.6)	122 (10.2)	
Administration	1445 (81.1)	974 (83.4)	1069 (89.8)	

used in BMT recipients. The PBSCT recipients were more likely to receive ATG ($P < .001$) and post-transplant cyclophosphamide (PTCy) ($P < .001$). Graft types differed by donor type ($P < .001$), HLA disparities ($P < .001$), and year of HCT ($P < .001$). Administration of G-CSF was performed in 81.1% of BMT, 83.4% of PBSCT, and 89.8% of CBT recipients ($P < .001$).

According to G-CSF administration and the timing of its initiation, there were significant differences in conditioning regimen ($P = .006$) and GVHD prophylaxis ($P < .001$) in BMT (Supplementary Table 1), GVHD prophylaxis ($P < .001$), use of PTCy ($P < .001$), HLA disparities ($P = .002$), and year of HCT ($P = .005$) in PBSCT (Supplementary Table 2), and karyotype ($P = .031$), conditioning regimen ($P = .048$), GVHD prophylaxis ($P = .013$), use of ATG ($P = .005$), and HLA disparities ($P = .032$) in CBT (Supplementary Table 3).

Effects of G-CSF Administration on Transplant Outcomes

In the univariate analysis, the cumulative incidence of neutrophil recovery was significantly accelerated in patients receiving G-CSF compared to those not receiving it, irrespective of graft type ($P < .001$ for BMT, $P < .001$ for PBSCT, $P = .012$ for CBT) (Supplementary Figure 1a–c). The cumulative incidence of platelet recovery was significantly slower in patients receiving G-CSF compared to those not receiving it only following BMT ($P = .003$) (Supplementary Figure 1d–f). Administration of G-CSF did not affect the incidences of acute and chronic GVHD, relapse, NRM, OS, and DFS in univariate analysis (Supplementary Figure 2, Supplementary Figure 3), except that administration of G-CSF was significantly associated with better OS following PBSCT ($P = .001$) (Supplementary Figure 3h).

In the multivariate analysis, administration of G-CSF was significantly associated with an accelerated neutrophil recovery, irrespective of graft type (HR 1.74, 95% CI 1.57 to 1.94, $P < .001$ for BMT, HR 1.66, 95% CI 1.41 to 1.95, $P < .001$ for PBSCT, HR 1.41, 95% CI 1.15 to 1.73, $P < .001$ for CBT) (Table 2). Administration of G-CSF was significantly associated with a slower platelet recovery following BMT (HR 0.82, 95% CI 0.71 to 0.95, $P = .010$) (Table 2). Administration of G-CSF was significantly associated with a higher risk of overall chronic GVHD following PBSCT (HR 1.54, 95% CI 1.12 to 2.11, $P = .007$) and CBT (HR 2.08, 95% CI 1.22 to 3.56, $P = .006$) (Table 2). However, administration of G-CSF did not affect the incidence of relapse, NRM, OS, and DFS in multivariate analysis (Table 2).

We also evaluated the impact of G-CSF administration on neutrophil and platelet recovery, and overall chronic GVHD stratified by conditioning regimen and GVHD prophylaxis for each donor type. The accelerated effect of G-CSF administration on neutrophil recovery was significant in patients who received GVHD prophylaxis other than calcineurin inhibitors and methotrexate following CBT (p for interaction= 0.036), but not in those who received GVHD prophylaxis with calcineurin inhibitors and methotrexate (Supplementary Figure 4). Similarly, the increased effect of G-CSF administration on overall chronic GVHD was significant in patients who received MAC following PBSCT (p for interaction = .018), but not in those who received RIC (Supplementary Figure 4).

Effects of G-CSF Administration and the Timing of its Initiation on Neutrophil and Platelet Recovery

In the univariate analysis, the cumulative incidence of neutrophil recovery significantly varied with G-CSF administration and the timing of its initiation following BMT ($P < .001$) and PBSCT ($P < .001$), but not CBT ($P = .034$) (Figure 1a–c). In the multivariate analysis, early and late G-CSF initiations were significantly associated with accelerated neutrophil recovery across all graft types, but with marginal significance between no administration of G-CSF and early administration of G-CSF following CBT (Table 3).

In the univariate analysis, the cumulative incidence of platelet recovery varied with G-CSF administration and the timing of its initiation following BMT ($P = .007$), but not PBSCT ($P = .495$) or CBT ($P = .650$) (Figure 1d–f). In the multivariate analysis, late G-CSF initiation was significantly associated with a slower platelet recovery following BMT (HR 0.81, 95% CI 0.70 to 0.94, $P = .006$) compared to those not receiving G-CSF (Table 3).

Effects of G-CSF Administration and the Timing of its Initiation on Acute and Chronic GVHD

There were no significant differences in grade II to IV or grade III to IV acute GVHD among each donor type regarding G-CSF administration and the timing of its initiation in either univariate (Figure 2a-f) or multivariate analyses (Table 3).

In the univariate analysis, G-CSF administration and the timing of its initiation showed a marginal significance on overall chronic GVHD following PBSCT ($P = .023$), but not BMT ($P = .656$) or CBT ($P = .203$) (Figure 2g-i). In the multivariate analysis, early G-CSF initiation was significantly associated with a higher risk of overall chronic GVHD

Table 2
Multivariate Analysis of Transplant Outcomes of G-CSF Administration According to Graft Type

	BMT		PBSCT		CBT	
	Adjusted HR (95%CI)	P	Adjusted HR (95%CI)	P	Adjusted HR (95%CI)	P
Neutrophil recovery*	1.74 (1.57-1.94)	< **.001**	1.66 (1.41-1.95)	< **.001**	1.41 (1.15-1.73)	< **.001**
Platelet recovery†	0.82 (0.71-0.95)	**.010**	0.99 (0.80-1.23)	.970	0.92 (0.73-1.16)	.530
Grade II to IV acute GVHD‡	0.98 (0.79-1.22)	.910	1.22 (0.91-1.63)	.180	1.12 (0.79-1.58)	.510
Grade III to IV acute GVHD	0.82 (0.57-1.19)	.310	1.14 (0.70-1.86)	.580	0.87 (0.52-1.46)	.620
Overall chronic GVHD §	0.90 (0.72-1.13)	.400	1.54 (1.12-2.11)	**.007**	2.08 (1.22-3.56)	**.006**
Extensive chronic GVHD‖	1.10 (0.80-1.50)	.530	1.55 (1.00-2.41)	.049	1.57 (0.72-3.41)	.250
Relapse¶	0.94 (0.73-1.22)	.670	0.97 (0.71-1.33)	.870	0.91 (0.63-1.32)	.640
Non-relapse mortality	1.03 (0.79-1.33)	.800	0.76 (0.53-1.09)	.150	1.11 (0.73-1.67)	.620
Overall mortality (1-OS)#	1.01 (0.84-1.23)	.856	0.75 (0.59-0.95)	.018	0.96 (0.72-1.28)	.804
Treatment failure (1-DFS)8	0.97 (0.81-1.16)	.776	0.83 (0.66-1.05)	.135	0.99 (0.75-1.31)	.980

GVHD, graft-versus-host disease; OS, overall survival; DFS, disease-free survival; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation; HR, hazard ratio; CI, confidence interval.

* For neutrophil recovery, male recipients (HR, 0.84; 95% CI, 0.74 to 0.96; $P = .014$), RIC (HR, 0.80; 95% CI, 0.70 to 0.92; $P = .001$), HLA mismatch (HR, 0.63; 95% CI, 0.51 to 0.78; $P < .001$), and recent year of HCT (HR, 0.76; 95% CI, 0.66 to 0.87; $P < .001$) were significantly associated with slower neutrophil recovery, but the use of ATG (HR, 1.32; 95% CI, 1.09 to 1.60; $P = .003$) was also significantly associated with faster neutrophil recovery following PBSCT. HLA mismatch (HR, 0.74; 95% CI, 0.60 to 0.92; $P = .007$) was significantly associated with slower neutrophil recovery, but GVHD prophylaxis other than CI+MTX (HR, 1.18; 95% CI, 1.04 to 1.34; $P = .010$), and recent year of HCT (HR, 1.24; 95% CI, 1.09 to 1.41; $P = .001$) were also significantly associated with faster neutrophil recovery following CBT.

† For platelet recovery, male recipients (HR, 0.82; 95% CI, 0.73 to 0.92; $P = .001$), HCT-CI≥3 (HR, 0.83; 95% CI, 0.73 to 0.95; $P = .010$), and HLA mismatch (HR, 0.78; 95% CI, 0.67 to 0.91; $P = .016$) were also significantly associated with slower platelet recovery following BMT. The HCT-CI≥3 (HR, 0.70; 95% CI, 0.57 to 0.88; $P = .001$), RIC (HR, 0.81; 95% CI, 0.70 to 0.95; $P = .011$), and HLA mismatch (HR, 0.70; 95% CI, 0.57 to 0.88; $P = .001$) were significantly associated with slower platelet recovery following PBSCT. The recent year of HCT (HR, 1.28; 95% CI, 1.11 to 1.47; $P < .001$) was significantly associated with faster platelet recovery following CBT.

‡ For grades II to IV acute GVHD, the HLA mismatch (HR, 1.38; 95% CI, 1.09 to 1.76; $P = .007$) was significantly associated with a higher risk of grades II to IV acute GVHD following BMT.

§ For overall chronic GVHD, the recent year of HCT (HR, 0.75; 95% CI, 0.63 to 0.91; $P = .003$) was significantly associated with a lower risk of overall chronic GVHD following BMT. The poor cytogenetics (HR, 0.71; 95% CI, 0.56 to 0.90; $P = .004$), and recent year of HCT (HR, 0.71; 95% CI, 0.57 to 0.89; $P = .003$) were also significantly associated with a lower risk of overall chronic GVHD following PBSCT.

‖ For extensive chronic GVHD, the poor cytogenetics (HR, 0.65; 95% CI, 0.47 to 0.88; $P = .006$), and recent year of HCT (HR, 0.67; 95% CI, 0.49 to 0.90; $P = .009$) were significantly associated with a lower risk of extensive chronic GVHD following PBSCT.

¶ For relapse, the poor cytogenetics (HR, 2.72; 95% CI, 2.21 to 3.35; $P < .001$) and high-risk disease status (HR, 1.62; 95% CI, 1.29 to 2.04; $P < .001$) were significantly associated with higher risk of relapse following BMT. The poor cytogenetics (HR, 3.71; 95% CI, 2.83 to 4.86; $P < .001$) and high-risk disease status (HR, 1.50; 95% CI, 1.12 to 2.01; $P = .005$) were significantly associated with a higher risk of relapse following PBSCT. The poor cytogenetics (HR, 2.27; 95% CI, 1.77 to 2.91; $P < .001$) was associated with a higher risk of relapse, but GVHD prophylaxis other than CI+MTX (HR, 0.73; 95% CI, 0.56 to 0.93; $P = .014$) was associated with a lower risk of relapse following CBT.

For overall mortality, the age≥60 years (HR, 1.32; 95% CI, 1.12 to 1.54; $P < .001$), HCT-CI≥3 (HR, 1.37; 95% CI, 1.14 to 1.63; $P < .001$), poor cytogenetics (HR, 1.75; 95% CI, 1.50 to 2.03; $P < .001$), and high-risk disease status (HR, 1.31; 95% CI, 1.12 to 1.54; $P < .001$) were associated with a higher risk of overall mortality following BMT. The age≥60 years (HR, 1.59; 95% CI, 1.30 to 1.95; $P < .001$), HCT-CI≥3 (HR, 1.34; 95% CI, 1.08 to 1.66; $P = .006$), and poor cytogenetics (HR, 2.55; 95% CI, 2.10 to 3.10; $P < .001$) were associated with a higher risk of overall mortality following PBSCT. The age≥60 years (HR, 1.52; 95% CI, 1.25 to 1.84; $P < .001$), poor cytogenetics (HR, 1.80; 95% CI, 1.51 to 2.15; $P < .001$), and high-risk disease status (HR, 1.28; 95% CI, 1.05 to 1.54; $P = .011$) were associated with a higher risk of overall mortality, but the recent year of HCT (HR, 0.80; 95% CI, 0.66 to 0.95; $P = .014$) was associated with a lower risk of overall mortality following CBT.

8 For treatment failure, the age≥60 years (HR, 1.32; 95% CI, 1.13 to 1.53; $P < .001$), HCT-CI≥3 (HR, 1.29; 95% CI, 1.08 to 1.52; $P = .003$), poor cytogenetics (HR, 1.78; 95% CI, 1.54 to 2.06; $P < .001$), and high-risk disease status (HR, 1.39; 95% CI, 1.19 to 1.62; $P < .001$) were associated with a higher risk of treatment failure following BMT. The age≥60 years (HR, 1.48; 95% CI, 1.22 to 1.80; $P < .001$), poor cytogenetics (HR, 2.58; 95% CI, 2.14 to 3.11; $P < .001$), and high-risk disease status (HR, 1.29; 95% CI, 1.06 to 1.58; $P = .011$) were associated with a higher risk of treatment failure following PBSCT. The age≥60 years (HR, 1.36; 95% CI, 1.13 to 1.64; $P < .001$), poor cytogenetics (HR, 1.70; 95% CI, 1.43 to 2.01; $P < .001$), and high-risk disease status (HR, 1.27; 95% CI, 1.06 to 1.53; $P = .009$) were associated with a higher risk of treatment failure following CBT.The P-values in bold are statistically significant (<0.0166).

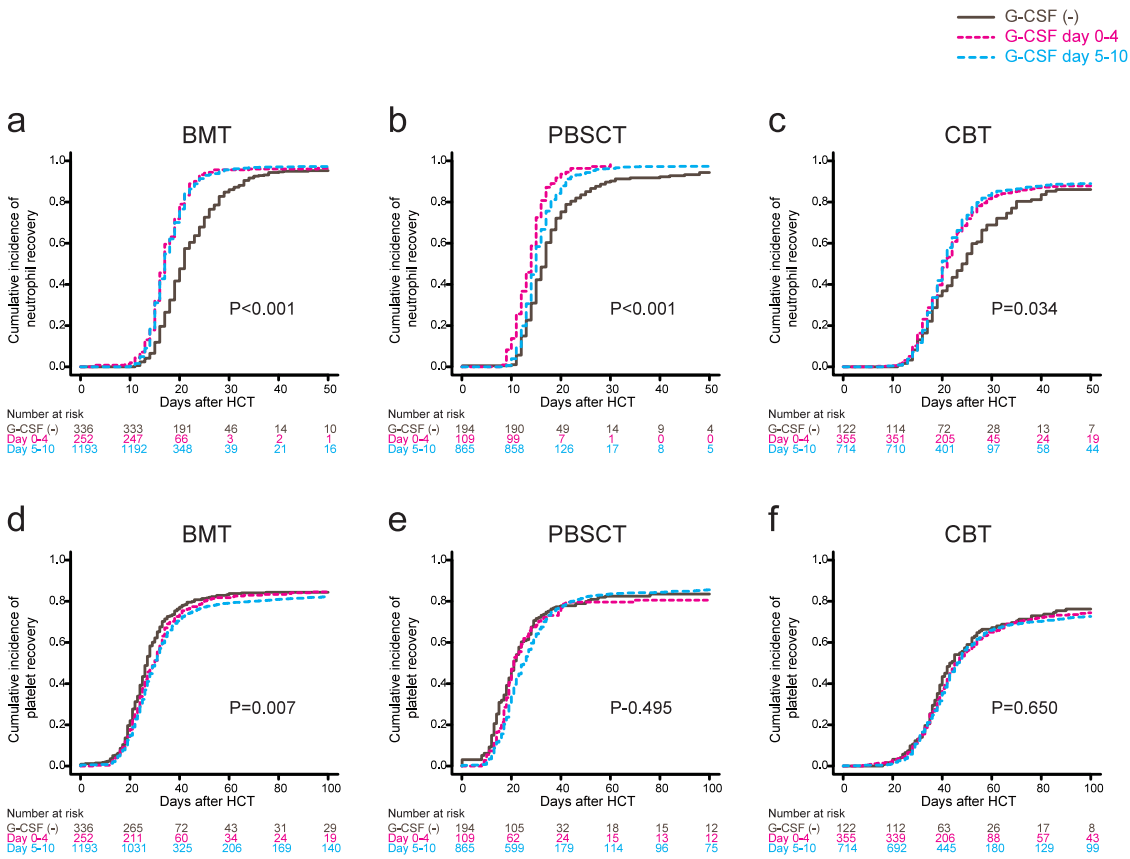

Figure 1. Effects of G-CSF administration and the timing of its initiation on neutrophil and platelet recovery according to graft type. The P-values are statistically significant (< .0166).

following CBT (HR 2.07, 95% CI 1.17 to 3.65, P = .012) compared to those not receiving G-CSF. Late G-CSF initiation was significantly associated with a higher risk of overall chronic GVHD following PBSCT (HR 1.63, 95% CI 1.18 to 2.24, P = .002) and CBT (HR 2.09, 95% CI 1.21 to 3.60, P = .007) compared to those not receiving G-CSF. Late G-CSF initiation was significantly associated with a higher risk of overall chronic GVHD following PBSCT (HR 1.80, 95% CI 1.18 to 2.73, P = .005) compared to early initiation (Table 3).

In the univariate analysis, G-CSF administration and the timing of its initiation showed a marginal significance on extensive chronic GVHD following PBSCT (P = .034) and CBT (P = .029), but not BMT (P = .835) (Figure 2j-l). In the multivariate analysis, late initiation of G-CSF significantly associated with a higher risk of extensive chronic GVHD following CBT (HR 1.88, 95% CI 1.14 to 3.10, P = .013) compared to early initiation (Table 3).

Effects of G-CSF Administration and the Timing of its Initiation on Relapse and NRM

In the univariate analysis, the cumulative incidence of relapse did not differ with G-CSF administration and the timing of its initiation for any graft type (P = .417 for BMT, P = .787 for PBSCT, P = .567 for CBT) (Figure 3a-c). In the multivariate analysis, there was no significant difference in relapse among each donor type regarding G-CSF administration and the timing of its initiation (Table 3).

In the univariate analysis, the cumulative incidence of NRM did not differ with G-CSF administration and the timing of its initiation for any graft type (P = .127 for BMT, P = .181 for PBSCT, P = .169 for CBT) (Figure 3d-f). In the multivariate analysis, there were no significant differences in NRM among each donor type regarding G-CSF administration and the timing of its initiation (Table 3).

Effects of G-CSF Administration and the Timing of its Initiation on OS and DFS

In the univariate analysis, the probability of OS significantly varied with G-CSF administration and the timing of its initiation only following PBSCT (P = .006), but with marginal significance following CBT (P = .041) (Figure 3g-i). In the multivariate analysis, late G-CSF initiation was significantly associated with better OS following PBSCT (HR 0.74, 95% CI 0.58 to 0.94, P = .015) compared with those not receiving G-CSF (Table 3).

Table 3
Multivariate Analysis of Transplant Outcomes Based on the Administration and Timing of G-CSF Initiation According to Graft Type

	BMT		PBSCT		CBT	
	Adjusted HR (95%CI)	P	Adjusted HR (95%CI)	P	Adjusted HR (95%CI)	P
Neutrophil recovery*						
Early administration of G-CSF vs. none	1.79 (1.51-2.13)	<**.001**	2.01 (1.52-2.65)	<**.001**	1.40 (1.11-1.77)	.035
Late administration of G-CSF vs. none	1.73 (1.55-1.94)	<**.001**	1.62 (1.38-1.91)	<**.001**	1.41 (1.15-1.73)	**.001**
Late vs. early administration of G-CSF	0.96 (0.82-1.13)	.690	0.80 (0.63-1.03)	.092	1.00 (0.86-1.15)	.950
Platelet recovery†						
Early administration of G-CSF vs. none	0.88 (0.72-1.08)	.230	0.95 (0.69-1.32)	.800	0.97 (0.75-1.25)	.830
Late administration of G-CSF vs. none	0.81 (0.70-0.94)	**.006**	1.00 (0.81-1.23)	.990	0.91 (0.72-1.15)	.440
Late vs. early administration of G-CSF	0.92 (0.78-1.08)	.310	1.04 (0.79-1.36)	.750	0.93 (0.80-1.09)	.400
Grade II to IV acute GVHD‡						
Early administration of G-CSF vs. none	0.97 (0.72-1.31)	.880	1.49 (0.98-2.26)	.059	1.10 (0.75-1.60)	.610
Late administration of G-CSF vs. none	0.99 (0.79-1.23)	.930	1.19 (0.88-1.60)	.250	1.13 (0.79-1.60)	.490
Late vs. early administration of G-CSF	1.01 (0.75-1.30)	.920	0.79 (0.56-1.12)	.190	1.02 (0.82-1.27)	.810
Grade III to IV acute GVHD						
Early administration of G-CSF vs. none	0.87 (0.51-1.47)	.620	1.64 (0.85-3.15)	.140	0.68 (0.37-1.25)	.220
Late administration of G-CSF vs. none	0.81 (0.55-1.18)	.290	1.08 (0.65-1.77)	.760	0.96 (0.57-1.60)	.880
Late vs. early administration of G-CSF	0.93 (0.59-1.46)	.760	0.65 (0.39-1.10)	.120	1.39 (0.93-2.06)	.100
Overall chronic GVHD§						
Early administration of G-CSF vs. none	0.80 (0.58-1.10)	.170	0.90 (0.55-1.49)	.700	2.07 (1.17-3.65)	**.012**
Late administration of G-CSF vs. none	0.93 (0.74-1.17)	.540	1.63 (1.18-2.24)	**.002**	2.09 (1.21-3.60)	**.007**
Late vs. early administration of G-CSF	1.16 (0.88-1.52)	.280	1.80 (1.18-2.73)	**.005**	1.01 (0.76-1.34)	.950
Extensive chronic GVHD‖						
Early administration of G-CSF vs. none	0.91 (0.59-1.41)	.690	0.81 (0.39-1.66)	.570	0.98 (0.41-2.33)	.980
Late administration of G-CSF vs. none	1.14 (0.83-1.57)	.400	1.66 (1.06-2.59)	.025	1.85 (0.84-4.06)	.120
Late vs. early administration of G-CSF	1.25 (0.87-1.79)	.210	2.04 (1.10-3.76)	.022	1.88 (1.14-3.10)	**.013**
Relapse¶						
Early administration of G-CSF vs. none	1.00 (0.70-1.43)	.960	0.98 (0.58-1.65)	.950	0.93 (0.62-1.41)	.760

(*continued*)

Table 3 (*Continued*)

	BMT		PBSCT		CBT	
	Adjusted HR (95%CI)	P	Adjusted HR (95%CI)	P	Adjusted HR (95%CI)	P
Late administration of G-CSF vs. none	0.93 (0.72-1.21)	.610	0.97 (0.70-1.33)	.860	0.90 (0.61-1.32)	.610
Late vs. early administration of G-CSF	0.92 (0.69-1.24)	.620	0.98 (0.62-1.56)	.960	0.96 (0.73-1.26)	.800
Non-relapse mortality						
Early administration of G-CSF vs. none	1.19 (0.85-1.67)	.300	0.79 (0.45-1.38)	.420	1.03 (0.66-1.61)	.890
Late administration of G-CSF vs. none	0.99 (0.76-1.30)	1.000	0.76 (0.53-1.09)	.140	1.14 (0.75-1.73)	.520
Late vs. early administration of G-CSF	0.83 (0.63-1.10)	.200	0.96 (0.59-1.55)	.880	1.11 (0.86-1.43)	.420
Overall mortality (1-OS)[#]						
Early administration of G-CSF vs. none	1.22 (0.95-1.58)	.115	0.81 (0.55-1.19)	.290	0.88 (0.64-1.20)	.433
Late administration of G-CSF vs. none	0.97 (0.80-1.18)	.828	0.74 (0.58-0.94)	**.015**	1.00 (0.75-1.33)	.983
Late vs. early administration of G-CSF	0.79 (0.64-0.98)	.034	0.91 (0.65-1.27)	.589	1.13 (0.93-1.38)	.200
Treatment failure (1-DFS)[8]						
Early administration of G-CSF vs. none	1.10 (0.86-1.42)	.413	0.86 (0.59-1.24)	.421	0.97 (0.72-1.32)	.883
Late administration of G-CSF vs. none	0.94 (0.78-1.14)	.577	0.83 (0.65-1.05)	.132	1.00 (0.75-1.33)	.969
Late vs. early administration of G-CSF	0.85 (0.69-1.05)	.136	0.96 (0.70-1.33)	.846	1.02 (0.85-1.23)	.765

GVHD, graft-versus-host disease; OS, overall survival; DFS, disease-free survival; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; CBT, cord blood transplantation; HR, hazard ratio; CI, confidence interval.

[*] For neutrophil recovery, the male recipients (HR, 0.85; 95% CI, 0.74 to 0.97; $P = .019$), RIC (HR, 0.80; 95% CI, 0.69 to 0.91; $P = .001$), HLA mismatch (HR, 0.63; 95% CI, 0.51 to 0.78; $P < .001$), and recent year of HCT (HR, 0.76; 95% CI, 0.66 to 0.87; $P < .001$) were significantly associated with slower neutrophil recovery, but the use of ATG (HR, 1.33; 95% CI, 1.10 to 1.61; $P = .003$) was also significantly associated with faster neutrophil recovery following PBSCT. The male recipients (HR, 0.83; 95% CI, 0.73 to 0.95; $P = .010$), and HLA mismatch (HR, 0.74; 95% CI, 0.60 to 0.92; $P = .007$) were significantly associated with slower neutrophil recovery, but GVHD prophylaxis other than CI+MTX (HR, 1.18; 95% CI, 1.03 to 1.34; $P = .011$), and recent year of HCT (HR, 1.24; 95% CI, 1.09 to 1.41; $P = .001$) was also significantly associated with faster neutrophil recovery following CBT.

[†] For platelet recovery, the male recipients (HR, 0.82; 95% CI, 0.73 to 0.92; $P = .001$), HCT-CI≥3 (HR, 0.84; 95% CI, 0.73 to 0.96; $P = .011$), and HLA mismatch (HR, 0.78; 95% CI, 0.67 to 0.91; $P = .001$) were also significantly associated with slower platelet recovery following BMT. The HCT-CI≥3 (HR, 0.79; 95% CI, 0.66 to 0.93; $P = .007$), RIC (HR, 0.82; 95% CI, 0.70 to 0.95; $P = .011$) and HLA mismatch (HR, 0.70; 95% CI, 0.57 to 0.88; $P = .001$) were significantly associated with slower platelet recovery following PBSCT. The recent year of HCT (HR, 1.28; 95% CI, 1.11 to 1.48; $P < .001$) was significantly associated with faster platelet recovery following CBT.

[‡] For grades II to IV acute GVHD, the HLA mismatch (HR, 1.38; 95% CI, 1.09 to 1.76; $P = .007$) was significantly associated with a higher risk of grades II to IV acute GVHD following BMT.

[§] For overall chronic GVHD, the recent year of HCT (HR, 0.75; 95% CI, 0.63 to 0.91; $P = .003$) was significantly associated with a lower risk of overall chronic GVHD following BMT. The poor cytogenetics (HR, 0.71; 95% CI, 0.56 to 0.90; $P = .004$), and recent year of HCT (HR, 0.70; 95% CI, 0.56 to 0.87; $P = .001$) were significantly associated with a lower risk of overall chronic GVHD following PBSCT.

[‖] For extensive chronic GVHD, the poor cytogenetics (HR, 0.65; 95% CI, 0.47 to 0.89; $P = .007$), and recent year of HCT (HR, 0.65; 95% CI, 0.48 to 0.88; $P = .005$) were significantly associated with a lower risk of extensive chronic GVHD following PBSCT.

[¶] For relapse, the poor cytogenetics (HR, 2.73; 95% CI, 2.21 to 3.36; $P < .001$) and high-risk disease status (HR, 1.62; 95% CI, 1.29 to 2.05; $P < .001$) were significantly associated with a higher risk of relapse following BMT. The poor cytogenetics (HR, 3.71; 95% CI, 2.83 to 4.86; $P < .001$), and high-risk disease status (HR, 1.50; 95% CI, 1.12 to 2.02; $P = .006$) were significantly associated with a lower risk of relapse following PBSCT. The poor cytogenetics (HR, 2.27; 95% CI, 1.78 to 2.91; $P < .001$) was significantly associated with a lower risk of relapse following CBT.

[#] For overall mortality, the age≥60 years (HR, 1.31; 95% CI, 1.12 to 1.54; $P < .001$), HCT-CI≥3 (HR, 1.38; 95% CI, 1.15 to 1.64; $P < .001$), poor cytogenetics (HR, 1.77; 95% CI, 1.52 to 2.06; $P < .001$), and high-risk disease status (HR, 1.32; 95% CI, 1.12 to 1.55; $P < .001$) were significantly associated with a higher risk of overall mortality following BMT. The age≥60 years (HR, 1.58; 95% CI, 1.29 to 1.94; $P < .001$), HCT-CI≥3 (HR, 1.34; 95% CI, 1.08 to 1.66; $P = .006$), and poor cytogenetics (HR, 2.55; 95% CI, 2.10 to

3.10; $P < .001$) were significantly associated with a higher risk of overall mortality following PBSCT. The age≥60 years (HR, 1.50; 95% CI, 1.24 to 1.83; $P < .001$), poor cytogenetics (HR, 1.80; 95% CI, 1.51 to 2.15; $P < .001$), and high-risk disease status (HR, 1.27; 95% CI, 1.05 to 1.54; $P = .012$) were significantly associated with a higher risk of overall mortality, but the recent year of HCT (HR, 0.79; 95% CI, 0.66 to 0.95; $P = .013$) was significantly associated with a lower risk of overall mortality following CBT.

[8] For treatment failure, the age≥60 years (HR, 1.31; 95% CI, 1.13 to 1.53; $P < .001$), HCT-CI≥3 (HR, 1.29; 95% CI, 1.09 to 1.53; $P = .003$), poor cytogenetics (HR, 1.79; 95% CI, 1.55 to 2.08; $P < .001$), and high-risk disease status (HR, 1.40; 95% CI, 1.20 to 1.63; $P < .001$) were significantly associated with a higher risk of treatment failure following BMT. The age≥60 years (HR, 1.48; 95% CI, 1.22 to 1.80; $P < .001$), poor cytogenetics (HR, 2.58; 95% CI, 2.14 to 3.11; $P < .001$), and high-risk disease status (HR, 1.29; 95% CI, 1.06 to 1.59; $P = .011$) were significantly associated with a higher risk of treatment failure following PBSCT. The age≥60 years (HR, 1.36; 95% CI, 1.13 to 1.64; $P < .001$), poor cytogenetics (HR, 1.70; 95% CI, 1.43 to 2.01; $P < .001$), and high-risk disease status (HR, 1.27; 95% CI, 1.06 to 1.53; $P = .009$) were significantly associated with a higher risk of treatment failure following CBT.The P-values in bold are statistically significant (<0.0166).

In the univariate analysis, the probability of DFS did not differ with G-CSF administration or the timing of its initiation for any graft type ($P = .505$ for BMT, $P = .060$ for PBSCT, $P = .338$ for CBT) (Figure 3j-l). In the multivariate analysis, there were no significant differences in DFS among each donor type regarding G-CSF administration and the timing of its initiation (Table 3).

DISCUSSION

In this study, we demonstrated that both early and late G-CSF administration enhanced neutrophil recovery, irrespective of graft type, compared with no G-CSF administration. However, early G-CSF initiation was not beneficial for neutrophil recovery, regardless of the type of graft. Late G-CSF initiation was significantly associated with a higher risk of overall chronic GVHD in PBSCT and CBT recipients compared with no G-CSF administration. Late G-CSF initiation significantly improved OS compared with those not receiving G-CSF following PBSCT.

Our data revealed that G-CSF administration, regardless of early or late initiation, accelerated neutrophil recovery after BMT, PBSCT, and CBT. In contrast, the late G-CSF initiation was significantly associated with slower platelet recovery only following BMT, which is similar to previous reports [2,3,5,21]. The effects of G-CSF on platelet recovery according to graft type have been unclear to date, but the variance might be partly a result of the different cellular compositions of megakaryocyte lineage. Bone marrow grafts contain megakaryocyte lineage but not mobilized peripheral blood stem cells or cord blood grafts. Therefore, G-CSF administration could strongly affect platelet recovery only following BMT. In addition, previous prospective studies show that early G-CSF initiation does not contribute to early neutrophil recovery following BMT or PBSCT [6–9], consistent with our results following BMT, PBSCT, and CBT for MDS. Thus, these data indicate that early G-CSF initiation offers no advantage for neutrophil recovery, irrespective of graft type.

Previous studies have demonstrated that G-CSF administration is associated with an increased risk of both acute [1–3] and chronic GVHD [2–4] following BMT and PBSCT. However, our study shows only an association between G-CSF administration and chronic GVHD, not acute GVHD, following PBSCT and CBT for adult patients with MDS. As for chronic GVHD, G-CSF administration, regardless of early or late initiation, increased the incidence of overall chronic GVHD following CBT, consistent with our previous report on adult AML [5]. However, unlike our previous report on adult AML [5], we observed increased incidences of overall chronic GVHD with late G-CSF initiation following PBSCT in the present study. This might be partly due to the higher proportions of HLA mismatch among late initiation groups in PBSCT, although confounding factors, including HLA disparities, were adjusted in multivariate analysis. The exact biological mechanism underlying the association between late G-CSF initiation and development of overall chronic GVHD after PBSCT and CBT have not been fully elucidated. It has been hypothesized, however, that late G-CSF induces Th-2 polarization [22], which could exacerbate chronic GVHD late after allogeneic PBSCT and CBT, because Th2 dominated immune responses is associated with development of chronic GVHD [23]. These results indicate that the effect of G-CSF administration and the timing of its initiation on acute and chronic GVHD varies between MDS and AML patients.

For adult AML, our previous study reported that G-CSF administration significantly improved OS only following CBT [5]. Although almost all previous studies did not demonstrate a beneficial effect of G-CSF administration on survival after allogeneic HCT [1,3,4,24,25], our data showed that late G-CSF initiation significantly improved OS compared with no G-CSF administration only

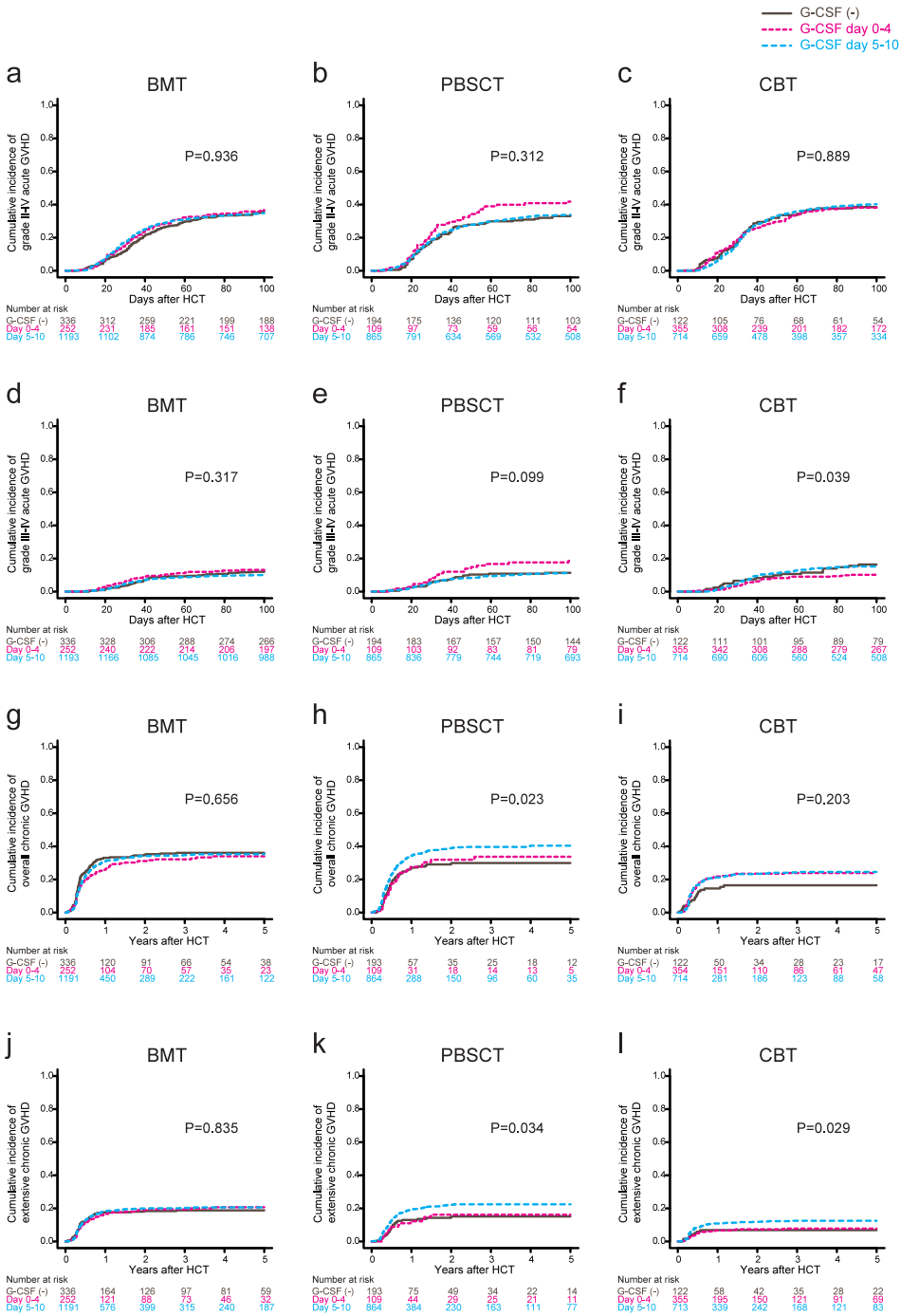

Figure 2. Effects of G-CSF administration and the timing of its initiation on grade II to IV acute GVHD, grade III to IV acute GVHD, and overall and extensive chronic GVHD according to graft type. The P-values are statistically significant ($< .0166$).

following PBSCT, but not BMT or CBT, in the multivariate analysis. Nevertheless, G-CSF administration and the timing of its initiation did not affect relapse, irrespective of graft type, even though G-CSF can induce blast cell proliferation in patients with MDS [10]. Furthermore, G-CSF administration and the timing of its initiation did not affect NRM despite accelerating neutrophil recovery, irrespective of graft type. Our current study suggests that late G-CSF initiation should be administered following PBSCT in adult patients with MDS.

The primary limitation of our study is that it is a registry-based retrospective analysis in Japan. Therefore, the types of G-CSF, such as filgrastim or lenograstim, and the route and dose of G-CSF administration were determined by the treating

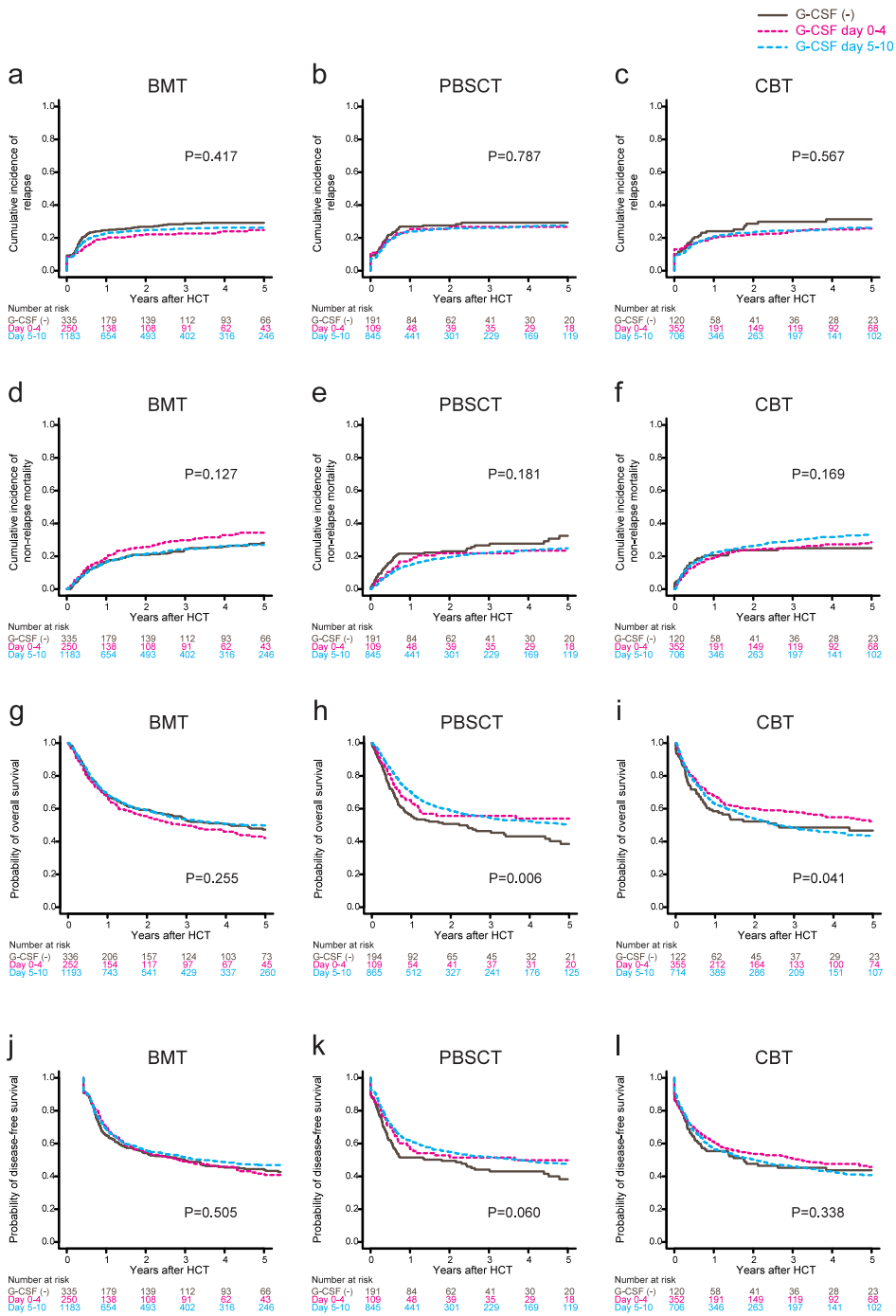

Figure 3. Effects of G-CSF administration and the timing of its initiation on relapse, non-relapse mortality, overall survival, and disease-free survival according to graft type. The P-values are statistically significant ($< .0166$).

physician's preference and their institution, which might have introduced some selection bias. Additionally, we could not explore the effect of planned G-CSF administration on documented infectious complications. Prospective studies are required to validate the present findings and determine the optimal timing of G-CSF initiation based on graft type for adult patients with MDS. Finally, the cost-effectiveness of G-CSF administration and initiation upon allogeneic HCT could also be assessed [4], although this was not investigated in our study.

In conclusion, our study demonstrates that G-CSF administration enhances neutrophil recovery following BMT, PBSCT, and CBT for MDS, but there is no benefit of early G-CSF initiation for neutrophil recovery. Late G-CSF initiation contributed to an increased incidence of overall chronic GVHD following PBSCT and CBT compared no administration of G-CSF. Late G-CSF initiation significantly

improved OS compared with no G-CSF administration only following PBSCT. Further studies are required to clarify the optimal timing of G-CSF initiation based on graft type in adult patients with MDS.

DATA AVAILABILITY

The data of this study are not publicly available due to ethical restrictions that it exceeds the scope of the recipient/donor's consent for research use in the registry. Data may be available from the corresponding author upon reasonable request and with permission of the JSTCT/JDCHCT.

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Conflict of interest statement: There are no conflicts of interest to report.

Authorship Statement: TK designed the research, analyzed the data, performed the statistical analysis, and wrote the first draft of the manuscript. All the other authors contributed to data collection. All authors approved the final version.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2025.03.010.

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