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Impact of Granulocyte Colony-Stimulating Factor (G-CSF) on Clinical Outcomes in Allogeneic Hematopoietic Cell Transplantation: Does Speeding Up Neutrophil Engraftment Make a Difference?

Ahmed Alnughmush, MD,[1,2,3] Ayman Sayyed, MD,[1,2,4] Mats Remberger, PhD,[5] Eshrak AL-Shaibani, MD,[1,2] Carol Chen,BSc,[2] Caden Chiarello,[2] Ivan Pasic, MD,[1,2] Igor Novitzky-Basso, MD,[1,2] Arjun Datt Law, MD,[1,2] Wilson Lam, MD,[1,2] Dennis (Dong Hwan) Kim, MD,[1,2] Armin Gerbitz, MD,[1,2] Auro Viswabandya, MD,[1,2] Rajat Kumar, MD,[1,2] Fotios V. Michelis, MD,[1,2] and Jonas Mattsson, MD, PhD[1,2,6]

Background. Despite decades of post–allogeneic hematopoietic cell transplantation (HCT) growth factor utilization, its role remains undefined, leading to ongoing debates and research. The theoretical impacts of growth factors have been challenged in numerous studies. **Methods.** In this retrospective cohort study conducted at the Princess Margaret Cancer Centre, we analyzed the clinical outcomes of 509 patients who underwent allogeneic HCT between May 1, 2019, and May 31, 2022. This study aimed to assess the impact of granulocyte colony-stimulating factor (G-CSF) administration posttransplantation on neutrophil and platelet engraftment, incidence of bloodstream infections (BSIs), graft-versus-host disease, engraftment syndrome (ES), and survival metrics including overall survival, nonrelapse mortality, and graft-versus-host disease–free/relapse-free survival. **Results.** Our findings indicate that G-CSF administration expedited neutrophil engraftment (16 versus 18 d, $P = 0.009$) and was associated with a decreased incidence of BSI (9.4% versus 31.3%, $P = 0.014$). However, this benefit was counterbalanced by a significant delay in platelet engraftment (21 versus 17 d, $P < 0.001$). Multivariate logistic regression analysis identified mismatched donors (odds ratio, 1.72; 95% confidence interval, 1.03-2.88; $P = 0.038$) and the duration of G-CSF therapy (odds ratio, 1.04; 95% confidence interval, 1.00-1.09; $P = 0.038$) as independent predictors for the development of ES. Despite these hematological impacts, there was no observed advantage in overall survival, nonrelapse mortality, or graft-versus-host disease–free/relapse-free survival among patients who received G-CSF compared with those who did not. **Conclusions.** Although G-CSF post-HCT expedited neutrophil engraftment and reduced BSI risk, it did not result in a survival advantage. The association with ES necessitates careful consideration.

(*Transplantation Direct* 2025;11: e1753; doi: 10.1097/TXD.0000000000001753.)

Allogeneic hematopoietic cell transplantation (HCT) represents a potentially curative intervention for a wide spectrum of hematologic malignancies. Despite decades of growth factor use, such as granulocyte colony-stimulating factor (G-CSF) after allogeneic HCT, conflicting findings have made it a subject of ongoing debate and research.[1] The practice of using G-CSF post-HCT varies widely between transplant physicians and centers. One of the earlier prospective

Received 18 November 2024

Accepted 18 November 2024.

[1] Department of Medicine, University of Toronto, Toronto, ON, Canada.

[2] Hans Messner Allogeneic Transplant Program, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada.

[3] Department of Hematology, Stem Cell Transplant and Cellular Therapy, Oncology Centre, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

[4] Division of Clinical Sciences, Department of Internal Medicine, Northern Ontario School of Medicine, Sudbury, ON, Canada.

[5] KFUE, Uppsala University Hospital, and IMV, Uppsala University, Uppsala, Sweden.

[6] Gloria and Seymour Epstein Chair in Cell Therapy and Transplantation, Department of Medicine, University of Toronto, Toronto, ON, Canada.

The authors declare no funding or conflicts of interest.

All authors listed contributed, reviewed, and edited the article.

The authors declare that data supporting the findings of this study are available within the article.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantationdirect.com).

Correspondence: Jonas Mattsson, MD, PhD, Division of Medical Oncology and Hematology, University Health Network, OPG Building, 700 University Ave, Toronto, ON M5G 1X6, Canada. (jonas.mattsson@uhn.ca).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001753

randomized trials that tried to challenge the effect of G-CSF found no differences in hematological recovery as well as other transplant outcomes such as graft-versus-host disease (GVHD) and survival when G-CSF was given at different time points posttransplant.[2] This was followed by multiple randomized control trials that tested the effect of G-CSF versus placebo or observation, which found no favorable outcome apart from improvement in neutrophil engraftment by 1–4 d in the G-CSF group.[3-6] In addition to the absence of significant clinical benefits, earlier research has highlighted concerns about an increased occurrence of GVHD after the administration of G-CSF after allogeneic HCT.[7,8] These observations emphasize the necessity for a meticulous evaluation of the use of G-CSF posttransplantation. However, it is important to note that prior registry-based studies and randomized controlled trials did not confirm the potential association between G-CSF use and the risk of GVHD.[4,5,9,10] The impact of G-CSF administration after allogeneic HCT on patient outcomes remains an area requiring further exploration, particularly in the context of the increasingly frequent use of potent GVHD prophylaxis regimens (such as posttransplant cyclophosphamide [PTCy] and antithymocyte globulin [ATG]), as well as the expanding range of transplant indications. We aim to investigate further the role of post–allogeneic HCT G-CSF administration in the presented study.

PATIENTS AND METHODS

Patients

We retrospectively analyzed data from a total of 509 consecutive adult patients (older than 18 y) who underwent allogeneic HCT from May 1, 2019, to May 31, 2022, at the Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada. The cohort consisted of patients undergoing their first allogeneic HCT during this period, regardless of transplant indication, performance status, donor type, or stem cell source. Data were collected from electronic patient records and the Hans Messner Allogeneic Transplant Program database. The study was reviewed and approved by the University Health Network Research Ethics Board. At our center, G-CSF was routinely administered starting on day +7 posttransplant until engraftment to most patients before May 1, 2021. After May 1, 2021, the routine use of G-CSF posttransplant was discontinued and left to the discretion of the attending physicians. We aimed to compare the outcomes of allogeneic HCT patients with and without G-CSF support.

Variables

Variables collected included patient sex, age, transplant indication, HCT comorbidity index (HCT-CI), Karnofsky performance status (KPS), disease risk index (DRI), donor type and age, $CD34^+$ cell dose, conditioning regimen intensity, and GVHD prophylaxis regimen. Posttransplant events documented included time to neutrophil and platelet engraftment, engraftment syndrome (ES), duration of immunosuppressive therapy, bloodstream infections (BSIs), acute GVHD (aGVHD), chronic GVHD, disease relapse, graft failure (GF), and survival status at the time of last follow-up.

Conditioning Regimen

Reduced-intensity conditioning regimens included (1) administration of fludarabine at a dose of 35 mg/m² daily for 4 d, starting from day –5, combined with total body irradiation (TBI) of 2 Gy on day –1; (2) fludarabine at 35 mg/m² daily for 4 d and treosulfan at 10 or 14 g/m² daily for 3 d; (3) fludarabine at 30 mg/m² daily for 4 d, starting from day –5, cyclophosphamide 60 mg/kg for 2 d, starting from day –5, with TBI of 2 Gy on day –1; and (4) fludarabine at 30 mg/m² daily for 5 d, starting from day –6, cyclophosphamide 14.5 mg/kg for 2 d, starting from day –6, ATG 4.5 mg/kg for 3 d starting from day –9 with TBI of 2 Gy on day –1. Myeloablative conditioning (MAC) regimens involved various protocols, including (1) fludarabine at 35 mg/m² daily for 4 d, beginning on day –5, and busulfan at 3.2 mg/kg daily for 4 d, starting from day –5, with or without TBI of 4 Gy on day –1; (2) fludarabine at 40 mg/m² daily for 3 d, beginning on day –5, combined with TBI of 2 Gy administered twice daily for 3 d, starting on day –3; and (3) etoposide at 60 mg/kg administered once on day –5, along with TBI of 2 Gy administered twice daily for 3 d, starting on day –3.

GVHD Prophylaxis

GVHD prophylaxis included any of the following regimens: (1) ATG 2 mg/kg or 4.5 mg/kg, posttransplant cyclophosphamide (PTCy) at 50 mg/kg for 2 d starting on day +3, cyclosporine A (CsA) at 2.5 mg/kg q12h starting on day +5; (2) PTCy at 50 mg/kg for 2 d starting on day +3, mycophenolate mofetil at 15 mg/kg q8h starting on day +5, and CsA at 2.5 mg/kg every 12 h starting on day +5; (3) ATG at 2 mg/kg combined with methotrexate at 15 mg/m² on day +1 and 10 mg/m² on days +3 and +6, and CsA at 2.5 mg/kg every 12 h starting on day –1; (4) CsA at 2.5 mg/kg every 12 h starting on day –1 and mycophenolate mofetil at 15 mg/kg q8h starting on day +1; (5) alemtuzumab (SC) at 60 mg on day –3, followed by CsA at 2.5 mg/kg q12h starting on day +5; and (6) CsA at 2.5 mg/kg every 12 h starting on day –1 and methotrexate at 15 mg/m² on day +1 and 10 mg/m² on days +3 and +6.

Infectious Prophylaxis

Infectious prophylaxis consisted of ciprofloxacin 500 mg orally daily starting on day –6 until neutrophil engraftment, micafungin 50 mg IV daily or caspofungin 70 mg IV loading dose then 50 mg IV daily starting on day +1 until engraftment, valacyclovir 500 mg twice daily starting on day +1 until 1 y posttransplant, posaconazole 300 mg orally daily starting at engraftment until day +100, and Pneumocystis prophylaxis starting at engraftment or day +28 until 1 y posttransplant. Beginning in February 2020, patients who were considered at high risk for cytomegalovirus reactivation received letermovir once daily starting on day +21 and for up to 100 d.[11]

Outcomes

The primary outcome of the study was to determine the incidence and timing of neutrophil and platelet engraftment among patients who received G-CSF support versus those who did not. Timing of neutrophil engraftment is defined as the period from stem cell infusion to the day of neutrophil engraftment, which is recognized as the first of 3 consecutive days when the absolute neutrophil count is $\geq 0.5 \times 10^9$/L. Platelet engraftment is defined as the interval from stem cell infusion to platelet engraftment, which is the first of 3 consecutive days with a platelet count $\geq 20 \times 10^9$/L without platelet transfusion in the preceding 7 d.[12] Secondary

endpoints of interest include overall survival (OS), nonrelapse mortality (NRM), length of hospital stay, occurrence of infections, cumulative incidence of GVHD, GVHD-free/relapse-free survival (GRFS), GF, and ES.[12] ES in our cohort was defined using Spitzer's criteria.[13] ES was diagnosed by the presence of either all 3 major criteria or 2 major criteria plus ≥1 minor criteria within 96 h of engraftment. Major criteria include (1) a temperature of ≥38.3 °C with no identifiable infectious source, (2) erythematous rash involving >25% of body surface area not related to medication, and (3) noncardiogenic pulmonary edema and hypoxia. The minor criteria include (1) hepatic dysfunction with either bilirubin ≥2 mg/dL or transaminase levels ≥2 times normal, (2) renal insufficiency, (3) weight gain ≥2.5% of baseline body weight, and (4) transient encephalopathy unexplained by other causes.

Statistical Analysis

The baseline characteristics and outcomes of patients were compared between those who routinely received G-CSF posttransplant and those who did not or who received it at the discretion of the attending physician, using appropriate statistical tests. A 2-sided P value of ≤0.05 was considered statistically significant. Statistical analysis was conducted using Statistica software, version 14. Categorical variables were compared using the χ^2 test or the Fisher exact test (depending on the number of data entrances). Descriptive statistics were used to report clinical characteristics. GRFS and OS were estimated with the Kaplan-Meier method, and differences in survival between subgroups were assessed using the log-rank test. Multivariate survival analysis was performed with the Cox regression model, adjusting for independent variables. NRM and GVHD were estimated using the cumulative incidence method, considering relapse as a competing risk for NRM. Cox proportional hazards regression was used to assess the impact of covariates of interest on outcomes.

RESULTS

Baseline Characteristics

Patient details and baseline characteristics are summarized in Table 1. A total of 509 patients were reviewed: 298 patients received G-CSF before May 1, 2021, 117 patients did not receive G-CSF, and 94 patients received G-CSF after this date. The median duration of G-CSF administration before May 2021 was 10 d (range, 1–28 d). The median age of G-CSF recipients was 58 y, whereas nonrecipients had a median age of 54 y (P = 0.015). The median donor age was 31 y, with no significant difference between groups (P = 0.97).

Approximately two-thirds of patients received matched related donor or matched unrelated donor transplants (22.2% and 47%, respectively). Alternative donor transplants, including haploidentical and mismatched (MM) unrelated donor transplants, comprised about one-third of the cohort (21.2% and 9.6%, respectively).

The primary graft source for the majority of our cohort was peripheral blood stem cells. A significantly higher median $CD34^+$ cell dose of 7.1×10^6 cells/kg (P = 0.007) was observed in patients who underwent transplantation before May 2021. This is because the $CD34^+$ dose at our center was capped at 8×10^6 cells/kg after May 2021 and at 5×10^6 cells/kg for haploidentical stem cell transplantation. Hematological malignancies were the main indication for transplant, with acute myeloid leukemia being the most common. Reduced-intensity conditioning was used in approximately 60% of patients who received G-CSF before May 2021, compared with 50% of patients who did not receive G-CSF (P = 0.03).

The most common GVHD prophylaxis regimen was PTCy combined with ATG (66.4%), more common among G-CSF recipients before May 2021 compared with nonrecipients (74.2% versus 37.6%, P < 0.001). ATG without PTCy was less common among G-CSF recipients (6.4% versus 47%, P < 0.001). No significant differences were found in performance status (P = 0.40), high comorbidity index (P = 0.09), or DRI (P = 0.97) between the groups.

G-CSF Group After May 2021

In the G-CSF group post-May 2021 (N = 94), the median duration of G-CSF administration was 2 d (range, 1–26 d). The median neutrophil engraftment time was 21 d compared with 18 d in the non-G-CSF group. The hospital stay was longer at 35 d, and the GF rate was 9.7%, both significantly higher than in the comparative group. G-CSF was administered on median day +19 posttransplant. Due to inherent biases related to poor graft function and delayed engraftment, potentially confounding the outcomes of G-CSF use, this group was excluded from further analysis.

Hematological Recovery

The G-CSF group experienced faster neutrophil engraftment with median times of 16 d (range, 11–22 d) compared with 18 d (range, 10–26 d) for those who did not receive G-CSF (P = 0.009; Figure 1A). However, platelet engraftment was delayed in G-CSF recipients, with a median time of 21 versus 17 d for those without G-CSF (P < 0.001; Figure 1B). Multivariate analysis (MVA) for neutrophil engraftment showed that G-CSF use (hazard ratio [HR], 1.46; 95% confidence interval [CI], 1.15-1.85; P = 0.002) and higher CD34 cell dose (HR, 1.11; 95% CI, 1.05-1.16; P < 0.001) were associated with faster neutrophil engraftment. In contrast, posttransplant cyclophosphamide (HR, 0.66; 95% CI, 0.51-0.86; P = 0.002) and female-to-male donor-recipient pairing (HR, 0.74; 95% CI, 0.57-0.97; P = 0.03) were associated with delayed engraftment.

GVHD (Acute and Chronic)

The incidence of grade II–IV acute GVHD in the G-CSF group was 26.2% (95% CI, 21.3%-31.3%) compared with 27.4% (95% CI, 19.6%-35.7%) in the non-G-CSF group (P = 0.38). Additionally, there was no significant difference in the incidence of grade III–IV acute GVHD between the 2 groups (8.7% versus 9.4%, respectively; P = 0.71). The cumulative incidence of chronic GVHD at 1 y was 31.7% (95% CI, 26.3%-37.3%) in the G-CSF group versus 33.6% (95% CI, 24.8%-42.7%) in the non-G-CSF group (P = 0.80). MVA identified several factors associated with the risk of developing acute GVHD. For grade II–IV aGVHD, systemic steroid use for ES (HR, 1.77; 95% CI, 1.09-2.87; P = 0.02) and increasing donor age per decade (HR, 1.14; 95% CI, 1.02-1.26; P = 0.02) were significant risk factors. For grade III–IV aGVHD, increasing recipient age per decade (HR, 1.21; 95% CI, 1.00-1.43; P < 0.05) and the use of PTCy (HR, 0.51; 95% CI, 0.27-0.97; P = 0.04) were significant. However, steroid use for ES was not statistically significant (HR, 1.98; P = 0.08).

TABLE 1.

Baseline characteristics

Characteristics	All patients (N = 509)	G-CSF before May 2021 (N = 298)	G-CSF after May 2021 (N = 94)	No G-CSF (N = 117)	*P*
Days with G-CSF	10 (1–28)	10 (1–28)	2 (1–26)	–	
Diagnosis					0.18
AML	231 (45.4)	147 (49.3)	35 (37.2)	49 (41.9)	
ALL	57 (11.2)	26 (8.7)	15 (16.0)	16 (13.7)	
MPAL	12 (2.4)	11 (3.7)	1 (1.1)	0	
MDS	84 (16.5)	44 (14.8)	19 (20.2)	21 (17.9)	
Lymphoma	28 (5.5)	16 (5.4)	6 (6.4)	6 (5.1)	
CML/CLL	19 (3.7)	10 (3.3)	4 (4.2)	5 (4.3)	
CMML	14 (2.8)	11 (3.7)	2 (2.1)	1 (0.9)	
MF	33 (6.5)	20 (6.7)	7 (7.4)	6 (5.1)	
Other malignant	4 (0.8)	2 (0.7)	1 (1.1)	1 (0.9)	
Nonmalignant	27 (5.3)	11 (3.7)	4 (4.3)	12 (10.3)	
Age, y	58 (18–76)	58 (18–76)	59 (18–74)	54 (18–73)	**0.03**
Sex (M/F)	282/227	158/140	61/33	63/54	0.12
FtoM	91 (17.9)	46 (15.4)	20 (21.3)	25 (21.4)	0.23
Donor age	31 (13–72)	31 (17–70)	32 (14–72)	32 (13-66)	0.99
BMSC/PBSC	22/487	12/286	4/90	6/111	0.88
CD34 dose	6.9 (0.3–13.7)	7.1 (0.3-13.7)	6.3 (1.2–10.2)	6.6 (1.3–11.3)	**0.008**
Donor					
MRD	113 (22.2)	58 (19.4)	17 (18.1)	38 (32.5)	**0.007**
MUD	239 (47.0)	137 (46.0)	45 (47.9)	57 (48.7)	0.69
Haplo	108 (21.2)	69 (23.1)	26 (27.7)	13 (11.1)	**0.008**
MM URD	49 (9.6)	34 (11.4)	6 (6.4)	9 (7.7)	0.35
Frozen graft	129 (25.3)	69 (23.1)	25 (26.6)	35 (29.9)	0.35
RIC/MAC	301/208	182/116	62/32	57/60	**0.02**
Letermovir prophylaxis	188 (45.3)	123 (41.3)	65 (55.6)	–	**0.01**
GVHD prophylaxis					
ATG	79 (15.5)	19 (6.4)	5 (5.3)	55 (47.0)	**<0.001**
Other	15 (2.9)	3 (1.0)	4 (4.3)	8 (6.8)	**0.003**
PTCy	77 (15.1)	55 (18.5)	12 (12.8)	10 (8.5)	**0.02**
PTCy+ATG	338 (66.4)	221 (74.2)	73 (77.7)	44 (37.6)	**<0.001**
KPS <90	96 (18.9)	53 (17.8)	27 (28.7)	16 (13.6)	0.40
HCT-CI ≥3	173 (34.0)	92 (30.9)	33 (35.1)	48 (41.0)	0.19
DRI					
Low	21 (4.1)	13 (4.4)	3 (3.2)	5 (4.3)	0.47
IM	381 (74.9)	230 (77.2)	68 (72.3)	83 (70.9)	
High to very high	74 (14.5)	42 (14.1)	17 (18.1)	15 (12.8)	
Engraftment syndrome	74 (14.5)	49 (16.4)	9 (9.6)	16 (13.7)	0.25

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BMSC, bone marrow stem cell; CML/CLL, chronic myeloid leukemia/chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; DRI, disease risk index; FtoM, female donor to male recipient; G-CSF, granulocyte colony-stimulating factor; GVHD, graft-versus-host disease; Haplo, haploidentical donor; HCT-CI, hematopoietic cell transplant comorbidity index; IM, intermediate risk; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM URD, mismatched unrelated donor; MPAL, mixed phenotype acute leukemia; MRD, matched related donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cell; PTCy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning.We have bolded the significant P-values to enhance readability and draw the reader's attention.

Bloodstream Infection

By day +30 posttransplant, the incidence of BSIs was significantly lower in the G-CSF group at 9.4% (95% CI, 6.4-13) versus 31.3% (95% CI, 23-39.9) in the non-G-CSF group ($P = 0.014$). This marked difference in risk persisted up to day +100 posttransplant (25.8% versus 41.7%, respectively; Figure 2A). Further analysis differentiated the timelines for those who did not receive G-CSF before and after May 2021. It was found that the risk of BSI in patients (N = 50) who did not receive G-CSF before May 2021 was not statistically significant compared with those who did receive G-CSF (16% versus 9.4%, $P = 0.12$; Figure 2B). However, patients (N = 67) who did not receive G-CSF after May 2021 showed a significant reduction in BSI, favoring the G-CSF group (9.4% versus 43.1%, $P = 0.025$; Figure 2C). Furthermore, MVA revealed that G-CSF use significantly reduced the risk of BSI (HR, 0.68; 95% CI, 0.50-0.93; $P = 0.01$), whereas a KPS of <90 was associated with a higher risk (HR, 1.57; 95% CI, 1.03-2.39; $P = 0.04$). We also examined the correlation between the day of engraftment and the risk of early BSI (within 30 d). In univariate analysis, delayed neutrophil engraftment was significantly associated with early BSI (HR, 1.08; 95% CI, 1.01-1.15; $P = 0.02$). However, this significance was lost in MVA, where the effect of G-CSF overruled the impact of engraftment timing. In the multivariate model, the day of engraftment had an HR of 1.07 (95% CI, 0.99-1.15; $P = 0.06$). Gram-positive organisms predominated in both groups, accounting for 54% of the BSI in the non-G-CSF

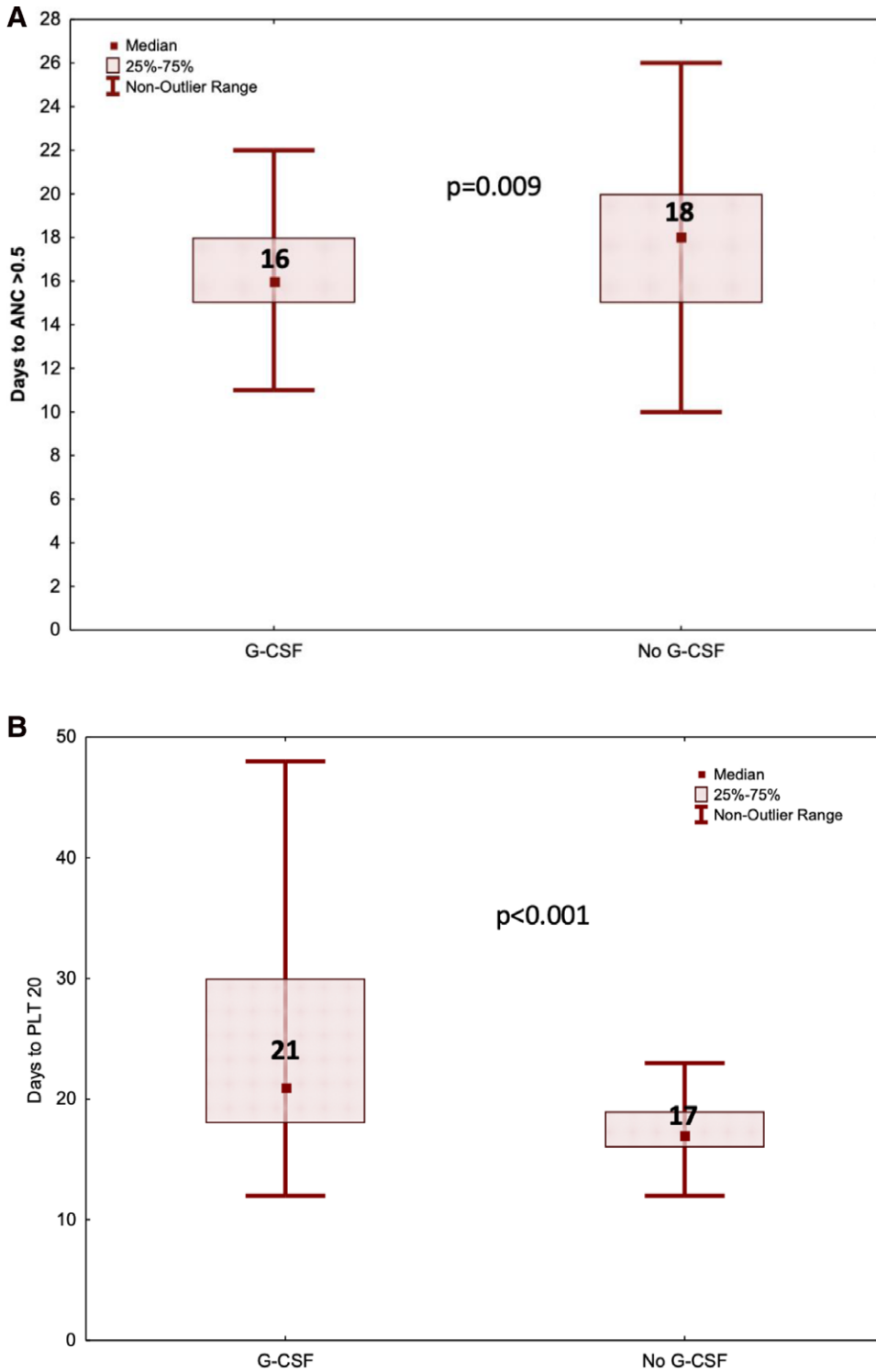

FIGURE 1. Hematological recovery. A: Neutrophil engraftment, B: Platelet engraftment. ANC, absolute neutrophil count; PLT, platelet.

group and 60.2% in the G-CSF group. Coagulase-negative Staphylococcus was the most frequently isolated organism in both cohorts. Gram-negative organisms constituted 23.4% of BSIs in the G-CSF group and 20.6% in the non-G-CSF group. Polymicrobial infections were observed in both groups, with an incidence of 16.4% in the G-CSF group and 23.8% in the non-G-CSF group (**Table S1, SDC,** http://links.lww.com/TXD/A730).

Engraftment Syndrome

As previously highlighted, the incidence of ES was similar across groups. Nevertheless, after excluding those who received G-CSF after May 2021, we identified a subset of 65 patients who developed ES, 49 (75%) of whom had received G-CSF (Table 2). Within the cohort that received G-CSF, there was a trend for those who received G-CSF for a longer period to develop ES (median 11 versus 10 d), although this was not

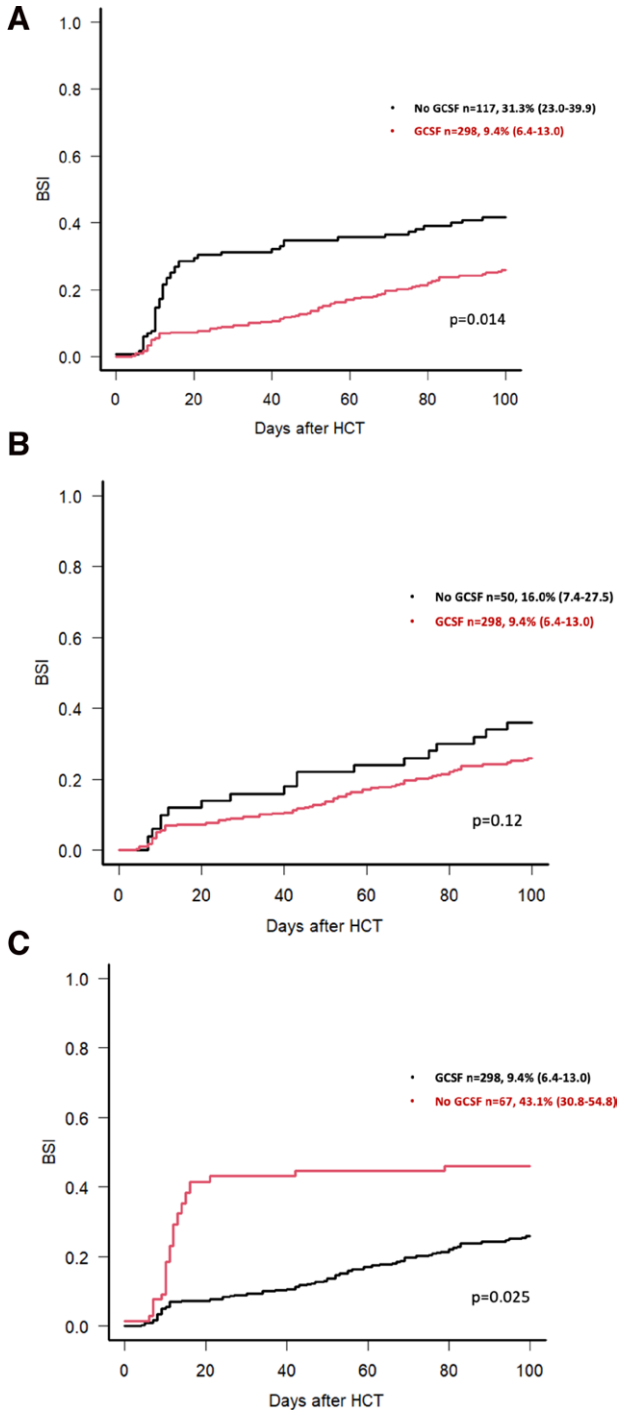

FIGURE 2. Day 30 incidence of bloodstream infection. A: G-CSF before May 2021 vs. no G-CSF before or after May 2021, B: G-CSF before May 2021 vs. no G-CSF before May 2021, C: G-CSF before May 2021 vs. no G-CSF after May 2021. BSI, bloodstream infection; G-CSF, granulocyte colony-stimulating factor; HCT, hematopoietic cell transplant.

statistically significant ($P = 0.08$; Figure 3A). Multivariate logistic regression analysis identified MM donors (OR, 1.72; 95% CI, 1.03-2.88; $P = 0.038$) and the duration of G-CSF therapy (OR, 1.04; 95% CI, 1.00-1.09; $P = 0.038$) as independent predictors for the development of ES. Assessing the effect of ES on engraftment revealed that those on G-CSF who developed ES experienced a significant delay in platelet engraftment (median 26 d, $P < 0.001$) with a minor effect observed on neutrophil engraftment (Figure 3B and C).

Survival Outcomes and Length of Stay

The median length of stay at initial admission and by 100 d posttransplant was 30 d for both the G-CSF group and the non-G-CSF group ($P = 0.15$) and 33 d for both groups ($P = 0.27$), respectively. However, MVA revealed the following factors to be associated with an extended length of stay: treatment with G-CSF (HR, 1.10; 95% CI, 1.0-1.21; $P = 0.05$), ES (HR, 1.10; 95% CI, 1.0-1.21; $P = 0.06$), HLA-mismatch; HR, 1.15; 95% CI, 1.05-1.27; $P = 0.005$), and KPS score (<90; HR, 2.08; 95% CI, 1.16-3.70; $P = 0.01$).

The 1-y OS was 77.2% in the G-CSF group versus 79.5% in the non-G-CSF group ($P = 0.84$; Figure 4A). The incidence of NRM was comparable between groups: 14.1% for G-CSF versus 12.8% for non-G-CSF ($P = 0.93$; Figure 4B). Given that hematological malignancies constituted the majority of our cohort (N = 287 G-CSF and N = 105 no G-CSF), we analyzed the 1-y GRFS between the 2 groups, which was similar (60.6% G-CSF versus 59% no G-CSF; $P = 0.30$). MVA for overall mortality showed that a high HCT-CI score (≥3; HR, 1.48; 95% CI, 1.04-2.09; $P = 0.03$) and high DRI (HR, 1.67; 95% CI, 1.09-2.55; $P = 0.02$) were significantly associated with increased overall mortality. Age at transplant showed a trend but did not reach statistical significance (HR, 1.12; 95% CI, 0.99-1.25; $P = 0.06$). Regarding NRM, MVA identified increasing age at transplant per decade (HR, 1.29; 95% CI, 1.10-1.48; $P = 0.002$) as a significant factor for increased NRM, whereas MM donor status approached significance (HR, 1.61; 95% CI, 0.99-2.59; $P = 0.05$).

GF rates showed no cases of primary GF and 1 case of secondary graft failure (0.9%) in the non-G-CSF group, whereas the G-CSF group had 7 cases of primary graft failure (2.3%) and 8 cases of secondary graft failure (2.7%). The retransplantation rate was 7.4% (22/298) in the G-CSF group compared with 3.4% (4/117) in the non-G-CSF group ($P = 0.20$).

DISCUSSION

It is essential to note the diversity in practices concerning the after allogeneic HCT administration of G-CSF. Notably, authority guidelines, such as those from the American Society of Clinical Oncology, have classified the recommendation for its use as weak, attributing this position to the limited quality of available evidence.[14] The results of our report align with earlier studies, demonstrating that G-CSF promotes rapid neutrophil engraftment but is associated with a notable postponement in platelet engraftment.[8,10,15] This delay in platelet engraftment could be attributed to the G-CSF-induced enhancement of platelet aggregation and consumption.[1,16] Alternatively, it has been proposed that this effect might stem from the selective expansion of myeloid progenitor cells.[17] Furthermore, thrombocytopenia has been observed in some donors taking G-CSF for stem cell donation.[18,19]

In our study cohort, G-CSF administration did not increase the incidence of acute and chronic GVHD, although it is noteworthy that our follow-up for chronic GVHD was limited to 1 y. Our cohort is particularly distinctive, with many patients undergoing dual T-cell depletion strategies involving PTCy combined with ATG for those undergoing matched unrelated donor or haploidentical stem cell transplantation, a combination for which there is an increasing body of data.[20] Despite the inclusion of this potent GVHD prophylaxis combination, we did not observe significant changes in engraftment in the

TABLE 2.

Characteristic of patients who developed engraftment syndrome compared with those who did not

Characteristics	ES (N = 65)	No ES (N = 350)	*P*
G-CSF	49 (75.4)	249 (71.1)	
Diagnosis			0.49
AML	24 (36.9)	172 (49.1)	
ALL	8 (12.3)	34 (9.7)	
MPAL	1 (1.5)	10 (2.9)	
MDS	9 (13.8)	56 (16.0)	
Lymphoma	5 (7.7)	17 (4.9)	
CML/CLL	1 (1.5)	14 (4.0)	
CMML	5 (7.7)	7 (2.0)	
MF	5 (7.7)	21 (6.0)	
Other malignant	1 (1.5)	2 (0.6)	
Nonmalignant	6 (9.2)	17 (4.9)	
Age	60 (18–71)	57 (18–76)	0.31
Sex (M/F)	36/29	185/165	0.81
FtoM	11 (16.9)	60 (17.1)	0.89
Donor age	33 (18–70)	31 (13–69)	0.96
BMSC/PBSC	4/61	14/336	0.65
CD34 dose	7.1 (2.1–10.7)	7.0 (0.3–13.7)	0.59
Donor			0.19
MRD	11 (16.9)	85 (24.2)	
MUD	27 (41.5)	167 (47.7)	
Haplo	19 (29.2)	63 (18.0)	
MM URD	8 (12.3)	35 (10.0)	
HLA-match/MM	38/27	252/98	**0.04**
Frozen graft	19 (29.2)	85 (24.3)	0.49
RIC/MAC	44/21	195/155	0.10
GVHD prophylaxis			0.66
ATG	13 (20.0)	61 (17.4)	
Other	1 (1.5)	10 (2.9)	
PTCy	11 (16.9)	54 (15.4)	
PTCy + ATG	40 (61.5)	225 (64.3)	
KPS <90	11 (16.9)	58 (16.6)	0.91
HCT-CI ≥3	19 (29.2)	121 (34.6)	0.68
DRI			
Low	3 (4.6)	15 (4.3)	0.96
IM	45 (69.2)	268 (76.6)	
High to very high	9 (13.8)	48 (13.7)	

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ATG, antithymocyte globulin; BM, bone marrow stem cell; CML/CLL, chronic myeloid leukemia/chronic lymphocytic leukemia; CMML, chronic myelomonocytic leukemia; DRI, disease risk index; ES, engraftment syndrome; FtoM, female donor to male recipient; G-CSF, granulocyte colony-stimulating factor; GVHD, graft-versus-host disease; Haplo, haploidentical donor; HCT-CI, hematopoietic cell transplant comorbidity index; IM, intermediate risk; KPS, Karnofsky performance status; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MF, myelofibrosis; MM URD, mismatched unrelated donor; MPAL, mixed phenotype acute leukemia; MRD, matched related donor; MUD, matched unrelated donor; PBSC, peripheral blood stem cell; PTCy, posttransplant cyclophosphamide; RIC, reduced-intensity conditioning.

context of G-CSF use when compared with previous reports using other conventional GVHD prophylaxis regimens.

Previous studies have shown a potential increase in the risk of GVHD for patients receiving G-CSF.[8,21] An earlier report suggested that the use of G-CSF, even in the context of bone marrow grafts, can increase the risk of GVHD. Ringden et al[15] further demonstrated that this risk is significantly higher in recipients of bone marrow grafts who received G-CSF than in those who did not. Conversely, the administration of G-CSF to stem cell donors may differentially affect the GVHD risk. Previous studies have indicated that G-CSF can alter donor T-cell polarization and induce immune tolerance, potentially mitigating GVHD.[22,23] Nonetheless, evidence from multiple randomized controlled trials and meta-analyses has demonstrated that there is no significant increase in the incidence of GVHD among G-CSF recipients.[6,24-26]

Our findings interestingly demonstrate that the incidence of BSIs was significantly reduced in the G-CSF group (9.4% versus 31.3%, $P = 0.014$) by day +30, with results persistently favoring G-CSF even at day +100. This benefit may be attributed to accelerated neutrophil engraftment observed in the G-CSF group. Furthermore, an investigation conducted at our center on risk factors influencing BSI identified PTCy in the GVHD prophylaxis regimen as an independent risk factor, prompting speculation regarding the potential role of G-CSF in this setting.[27]

In our study population, we observed a 14.5% incidence of ES. The reported incidence of this complication in literature is highly variable, ranging from 8% to 77%.[28-30] This variability may be attributable to the diverse criteria used to define ES.[13,31,32] Our analysis specifically investigated the risk of ES in the setting of G-CSF administration, a correlation

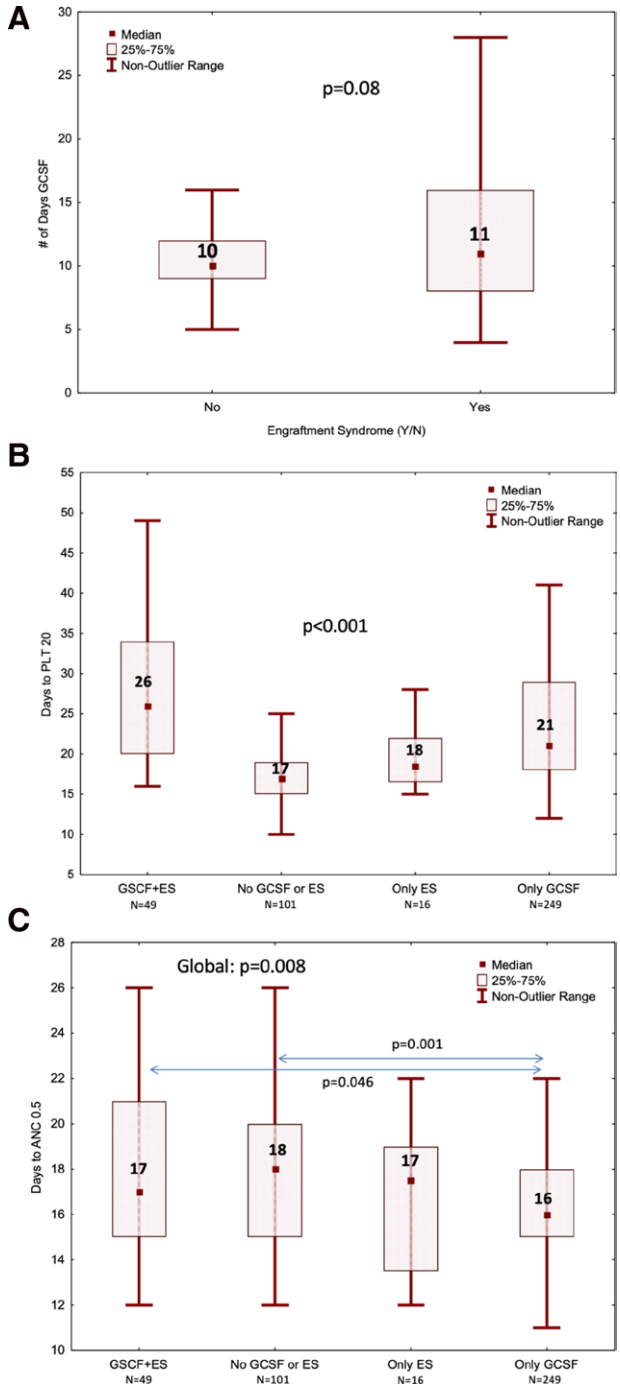

FIGURE 3. Risk of ES and its effect on hematological recovery. A: Incidence engraftment syndrome and correlation with number of G-CSF days including only recipients of G-CSF, B: Effect of engraftment syndrome on platelet engraftment with and without G-CSF, C: Effect of engraftment syndrome on neutrophil engraftment with and without G-CSF. ES, engraftment syndrome; G-CSF, granulocyte colony-stimulating factor.

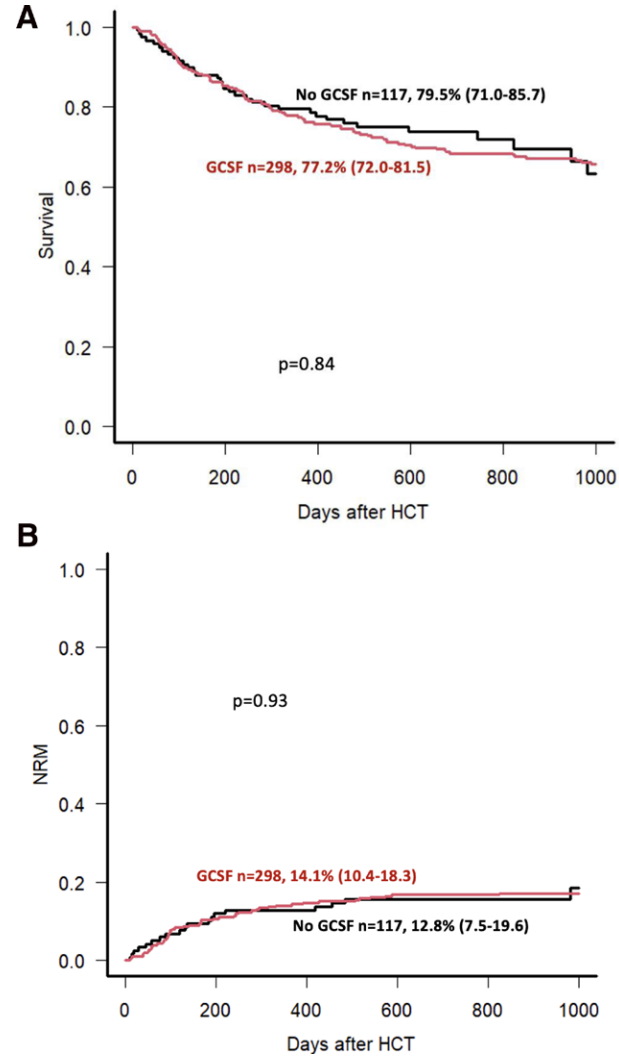

FIGURE 4. Overall survival and NRM. A: Overall survival, B: Nonrelapse mortality. G-CSF, granulocyte colony-stimulating factor; HCT, hematopoietic cell transplant; NRM, nonrelapse mortality.

that has not been extensively reported in prior studies. The incidence of ES did not differ significantly between groups. However, interesting observations were noted regarding ES and G-CSF use. Platelet engraftment was significantly delayed in patients who developed ES in the G-CSF subgroup, suggesting a potential compound detrimental effect associated with the use of G-CSF and the occurrence of ES. Additionally, our MVA identified G-CSF therapy duration as an independent predictor of ES development.

Our data indicated that G-CSF administration did not increase the incidence of posttransplant relapse in our cohort. This outcome is consistent with the findings of several previous studies.[25,26] Notably, an older study has reported that G-CSF administration demonstrated efficacy comparable with donor lymphocyte infusion in the treatment of post–stem cell transplantation relapse.[33]

In the G-CSF treated cohort, despite the observed benefits of faster neutrophil engraftment and a decreased incidence of BSIs, these improvements did not translate into statistically significant clinical outcomes, namely OS, NRM, and length of hospital stay. This equivalence in the length of hospital stay might be attributed to the counterbalancing effect of ES, which may negate the clinical benefits of more rapid neutrophil recovery.

A major limitation of our study is that the predominant indication for transplantation was hematological malignancy; consequently, our ability to evaluate the impact of G-CSF on nonmalignant conditions is constrained. To determine whether divergent outcomes exist, further research that

includes a broader variety of nonmalignant conditions is warranted. Moreover, another major limitation of our study is its retrospective design, which inherently restricts the capacity to establish causation owing to potential biases and unmeasured confounders. Prospective studies, especially in the era of PTCy use in GVHD prophylaxis, are needed to confirm our findings and allow for a more controlled and systematic investigation of the variables of interest.

REFERENCES

1. Ringdén OTH, Le Blanc K, Remberger M. Granulocyte and granulocyte-macrophage colony-stimulating factors in allografts: uses, misuses, misconceptions, and future applications. *Exp Hematol*. 2005;33:505–512.
2. Hägglund H, Ringdén O, Man SO¨, et al. A prospective randomized trial of Filgrastim (r-MetHuG-CSF) given at different times after unrelated bone marrow transplantation. 1999;24:831–836.
3. Stinson TJ, Adams JR, Bishop MR, et al. Economic analysis of a phase III study of G-CSF vs placebo following allogeneic blood stem cell transplantation. *Bone Marrow Transplant*. 2000;26:663–666.
4. Bishop MR, Tarantolo SR, Geller RB, et al. A randomized, double-blind trial of Filgrastim (granulocyte colony-stimulating factor) versus placebo following allogeneic blood stem cell transplantation. *Blood*. 96:80–85.
5. Przepiorka D, Smith TL, Folloder J, et al. Controlled trial of Filgrastim for acceleration of neutrophil recovery after allogeneic blood stem cell transplantation from human leukocyte antigen-matched related donors. *Blood*. 2001;97(11):3405-3410.
6. Ernst P, Bacigalupo A, Ringdén O, et al. A phase 3, randomized, placebo-controlled trial of filgrastim in patients with haematological malignancies undergoing matched-related allogeneic bone marrow transplantation. *Arch Drug Inf*. 2008;1:89–96.
7. Remberger M, Naseh N, Aschan J, et al. G-CSF given after haematopoietic stem cell transplantation using HLA-identical sibling donors is associated to a higher incidence of acute GVHD II-IV. *Bone Marrow Transplant*. 2003;32:217–223.
8. Ringden O, Hassan Z, Karlsson H, et al. Granulocyte colony-stimulating factor induced acute and chronic graft-versus-host disease. *Transplantation*. 2010;90:1022–1029.
9. Khoury HJ, Loberiza FR, Ringdén O, et al. Impact of posttransplantation G-CSF on outcomes of allogeneic hematopoietic stem cell transplantation. *Blood*. 2006;107:1712–1716.
10. Orfali N, Zhang MJ, Allbee-Johnson M, et al. Planned granulocyte colony-stimulating factor adversely impacts survival after allogeneic hematopoietic cell transplantation performed with thymoglobulin for myeloid malignancy. *Transplant Cell Ther*. 2021;27:993.e1–993.e8.
11. Pang I, Chen P, Trinh GV, et al. Letermovir prophylaxis for cytomegalovirus reactivation in allogeneic hematopoietic cell transplant recipients: single center Canadian data. *Eur J Haematol*. 2024;112:301–309.
12. Sureda A, Carpenter PA, Bacigalupo A, et al. Harmonizing definitions for hematopoietic recovery, graft rejection, graft failure, poor graft function, and donor chimerism in allogeneic hematopoietic cell transplantation: a report on behalf of the EBMT, ASTCT, CIBMTR, and APBMT. *Bone Marrow Transplant*. 2024;59:832–837.
13. Spitzer T. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant*. 2001;27:893–898.
14. Smith TJ, Bohlke K, Lyman GH, et al; American Society of Clinical Oncology. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology Clinical Practice Guideline update. *J Clin Oncol*. 2015;33:3199–3212.
15. Ringdén O, Labopin M, Gorin NC, et al. Treatment with granulocyte colony-stimulating factor after allogeneic bone marrow transplantation for acute leukemia increases the risk of graft-versus-host disease and death: a study from the acute leukemia working party of the European group for blood and marrow transplantation. *J Clin Oncol*. 2004;22:416–423.
16. Shimoda K, Okamura S, Inaba S, et al. Granulocyte colony-stimulating factor and platelet aggregation. *Lancet*. 1993;341:633.
17. Kumar Gupta A, Meena JP, Haldar P, et al. Review article impact of G-CSF administration post-allogeneic hematopoietic stem-cell transplantation on outcomes: a systematic review and meta-analysis. 2021;11:544–563.
18. Li Y, Guo R, Wang L, et al. G-CSF administration results in thrombocytopenia by inhibiting the differentiation of hematopoietic progenitors into megakaryocytes. *Biochem Pharmacol*. 2019;169:113624.
19. Minelli O, Falzetti F, Di Ianni M, et al. G-CSF-induced thrombocytopenia in a healthy donor. *Bone Marrow Transplant*. 2009;43:263–264.
20. Duléry R, Brissot E, Mohty M. Combining post-transplant cyclophosphamide with antithymocyte globulin for graft-versus-host disease prophylaxis in hematological malignancies. *Blood Rev*. 2023;62:101080.
21. Singh V, Jang H, Kim S, et al. G-CSF use post peripheral blood stem cell transplant is associated with faster neutrophil engraftment, shorter hospital stay and increased incidence of chronic GVHD. *Leuk Lymphoma*. 2021;62:446–453.
22. Pan L, Delmonte J, Jalonen CK, et al. Pretreatment of donor mice with granulocyte colony-stimulating factor polarizes donor T lymphocytes toward type-2 cytokine production and reduces severity of experimental graft-versus-host disease.
23. Chang YJ, Zhao XY, Huang XJ. Granulocyte colony-stimulating factor-primed unmanipulated haploidentical blood and marrow transplantation. *Front Immunol*. 2019;10:2516.
24. Ben Othman T, Ghedira H, Ben Abdejlil N, et al. Filgrastim following HLA-identical allogeneic bone marrow transplantation: long-term outcomes of a randomized trial. *Biol Blood Marrow Transplant*. 2018;24:2459–2465.
25. Dekker A, Bulley S, Beyene J, et al. Meta-analysis of randomized controlled trials of prophylactic granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor after autologous and allogeneic stem cell transplantation. *J Clin Oncol*. 2006;24:5207–5215.
26. Ho VT, Mirza NQ, del Junco D, et al. The effect of hematopoietic growth factors on the risk of graff-vs-host disease after allogeneic hematopoietic stem cell transplantation: a meta-analysis. *Bone Marrow Transplant*. 2003;32:771–775.
27. Carreira AS, Salas MQ, Remberger M, et al. Bloodstream infections and outcomes following allogeneic hematopoietic cell transplantation: a single-center study. *Transplant Cell Ther*. 2022;28:50.e1–50.e8.
28. Grant A, Chapman LRM, Mitchell R, et al. Engraftment syndrome following hematopoietic stem cell transplant: a review of the literature. *Clin Transplant*. 2020;34:e13875.
29. Schmid I, Stachel D, Pagel P, et al. Incidence, predisposing factors, and outcome of engraftment syndrome in pediatric allogeneic stem cell transplant recipients. *Biol Blood Marrow Transplant*. 2008;14:438–444.
30. Maqbool S, Nadeem M, Shahroz A, et al. Engraftment syndrome following Hematopoietic stem cell transplantation: a systematic approach toward diagnosis and management. *Med Oncol*. 2022;40:36.
31. Patel KJ, Rice RD, Hawke R, et al. Pre-engraftment syndrome after double-unit cord blood transplantation: a distinct syndrome not associated with acute graft-versus-host disease. *Biol Blood Marrow Transplant*. 2010;16:435–440.
32. Maiolino A, Biasoli I, Lima J, et al. Engraftment syndrome following autologous hematopoietic stem cell transplantation: definition of diagnostic criteria. *Bone Marrow Transplant*. 2003;31:393–397.
33. Bishop MR, Tarantolo SR, Pavletic ZS, et al. Filgrastim as an alternative to donor leukocyte infusion for relapse after allogeneic stem-cell transplantation. *J Clin Oncol*. 2000;18:2269–2272.