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Revisiting the Utility of Granulocyte Colony-Stimulating Factor Post-Autologous Hematopoietic Stem Cell Transplantation for Outpatient-Based Transplantations

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A B S T R A C T

The use of granulocyte colony-stimulating factor (G-CSF) after autologous stem cell transplantation (ASCT) has been shown to reduce the time to neutrophil engraftment, as well as the duration of hospitalization post-transplantation. However, prior studies have focused on inpatient-based ASCT, where patients are routinely admitted for conditioning and frequently remain hospitalized until signs of neutrophil recovery. Given improvements in post-transplantation care, an increasing number of patients, particularly those receiving ASCT for multiple myeloma, are now undergoing transplantation in an outpatient setting. We hypothesized that the routine use of G-CSF for outpatient-based ASCT might not result in the same benefit with respect to a reduced duration of hospitalization and thus should be reconsidered in this setting. We performed a retrospective cohort study of 633 consecutive patients with multiple myeloma (MM; n = 484) or non-Hodgkin lymphoma (NHL; n = 149) who underwent ASCT between September 2018 and February 2023. Outpatient ASCT comprised 258 (53%) of combined MM and NHL cases. Starting in September 2021, post-transplantation G-CSF was incorporated into the supportive care regimen for all ASCTs. A total of 410 patients (309 with MM, 101 with NHL) underwent ASCT during the pre-G-CSF policy period and 223 (175 with MM, 48 with NHL) did so in the post-G-CSF policy period. The primary outcome focused on the duration of hospitalization within the first 30 days following graft infusion. As expected, after implementation of the G-CSF policy, the time to neutrophil engraftment was reduced in the patients with MM (mean, -2.8 days; $P < .0001$) and patients with NHL (mean, -2.9 days; $P < .0001$). However, among the patients with MM, roughly one-half of whom underwent outpatient-based ASCT, the inpatient duration during the first 30 days was not reduced after G-CSF implementation ($P = .40$). Comparatively, the inpatient duration (mean, -1.8 days; $P = .030$) was reduced among patients with NHL, all of whom were electively admitted for ASCT. For patients with MM at an outpatient-based transplant center, incorporation of G-CSF post-ASCT resulted in reduced time to neutrophil engraftment but did not significantly reduce the time spent in the inpatient setting through day +30.

INTRODUCTION

Autologous hematopoietic stem cell transplantation (ASCT) following chemotherapy is used to treat multiple myeloma (MM) and non-Hodgkin lymphoma (NHL), but the associated prolonged neutropenia contributes to morbidity [1–3]. The use of granulocyte colony-stimulating factor (G-CSF) after ASCT has been shown to reduce both the time to neutrophil engraftment and the duration of hospitalization, leading to its adoption in guidelines and routine use in transplant centers despite no clear benefit in long-term ASCT outcomes [4–6]. However, prior studies of G-CSF focused primarily on electively admitted patients, for whom the duration of admission may depend on the time to engraftment, and often included populations with heterogeneous diagnoses [5,7-18]. Given advances in mobilization techniques, monitoring, and infectious disease management and the increasing number of ASCTs performed in the outpatient setting, we revisited the utility of routine G-CSF use with a focus on inpatient duration in relation to the underlying diagnosis and initial care setting (ie, inpatient or outpatient).

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Historically, the Fred Hutchinson Cancer Center (FHCC) has not used G-CSF in ASCT, owing in part to the frequency of outpatient transplantations performed, as well as institutional data suggesting that G-CSF may impair platelet engraftment in patients receiving a lower $CD34^+$ cell dose [19]. Starting in September 2021, a revised standard operating procedure (SOP) went into effect whereby G-CSF is given starting on day +5 post-ASCT for all patients with MM and NHL, excluding patients at elevated risk of adverse events. Using data from patients who underwent ASCT between September 2018 and February 2023, we evaluated the impact of the policy change on short-term outcomes, including time to hematopoietic recovery, duration of hospitalization, and infectious complications.

METHODS

Patients and Treatment Plan

The study was approved by FHCC's Institutional Review Board based on federal regulations and the ethical standards of the FHCC Human Research Protection Program. All patients provided informed consent allowing for the collection of medical information for research. The cohort for analysis comprised adult patients (age $\geq$18 years) with a diagnosis of MM or NHL. Eligible patients were divided into 2 groups for analysis: before implementation of the G-CSF policy (pre-SOP; September 2018 to August 2021) and after implementation of the G-CSF policy (post-SOP; September 2021 to February 2023).

Standard G-CSF administration was given to patients who underwent ASCT after September 1, 2021. G-CSF was given at 5 μg/kg s.c. daily starting on day +5 post-transplantation, in accordance with guidelines [4,5], to all adult patients in both the inpatient and outpatient settings until absolute neutrophil cell (ANC) recovery, defined as $\geq .5 \times 10^9$ cells/L for 3 consecutive days). Exclusions were made for patients with concurrent amyloid and POEMS syndrome, owing to the risk of engraftment syndrome, and for those with a history of autoimmune disease, owing to the risk of disease exacerbation. Patients with a history of cardiac comorbidities were excluded according to provider preference, owing to theoretical concerns about inducible ischemic injury and arrhythmias [20,21].

Supportive Care

Patients had a central venous catheter implanted for administration of chemotherapy, stem cell infusion, antibiotics, transfusions, fluids, total parenteral nutrition, and other medications. Packed RBCs were transfused for hematocrit <26%, and platelets were transfused for a platelet count $<11 \times 10^9$/L or where clinically indicated. Prophylactic antimicrobial therapy included acyclovir or valacyclovir, fluconazole, and levofloxacin according to institutional standards. Patients requiring inpatient care were admitted to single-occupancy rooms in a dedicated blood and marrow transplantation unit. Broad-spectrum i.v. antibiotics were initiated for neutropenic fever (NF) in accordance with institutional guidelines. In the absence of a serious allergy to penicillin or cephalosporin, empiric treatment with cefepime was provided for NF. Indications for the addition of empiric vancomycin included skin soft tissue infection, clinically apparent catheter-related infection, positive blood culture with gram-positive bacteria before susceptibility results, and a history of methicillin-resistant *Staphylococcus aureus*. Total parenteral nutrition was provided if oral nutrition became insufficient. Discharge from the hospital was not contingent on achievement of a specific ANC value.

Definitions

The time to neutrophil engraftment was defined as the number of days from ASCT graft infusion (day 0) until an ANC $\geq .5 \times 10^9$/L for 3 days, and the time to platelet engraftment was defined as the number of days from day 0 until a platelet count of $\geq 50 \times 10^9$/L without platelet transfusion for 7 days. The total number of inpatient days was collected from day +1 through day +30. A body temperature $\geq$38 °C was considered fever, and an ANC $<.5 \times 10^9$/L defined neutropenia. The SOP adherence rate was defined as the proportion of patients initiating G-CSF by day +5 without a documented contraindication.

Statistical Analysis

The primary outcome was the total number of inpatient days from the first day of graft reinfusion to day +30. Secondary outcomes included the times to platelet and neutrophil engraftment, incidence and duration of NF, and antibiotic receipt and duration.

Among the patients with MM and NHL, the sample sizes studied yielded 84% power and 81% power, respectively, to observe a statistically significant (at a 2-sided significance level of .05) difference in the mean number of inpatient days between the pre-SOP and post-SOP groups under the following assumptions: a true difference of .84 hospital days between the pre-SOP (n = 309) and post-SOP (n = 175) groups for MM, with a common standard deviation of 3 days and a true difference of 1.5 hospital days between the pre-SOP (n = 101) and post-SOP (n = 48) groups for NHL, with a common standard deviation of 3 days.

Continuous variables were compared using the Student *t* test, and proportions were compared using the chi-square or Fisher exact tests. Point estimates of overall survival (OS) and progression-free survival (PFS) were obtained using the Kaplan-Meier method. The probability of engraftment as a function of time was summarized using cumulative incidence estimates. The median time for each outcome was estimated as the time that the Kaplan-Meier or cumulative incidence estimate reached or crossed 50%. Unadjusted comparisons of OS, PFS, and engraftment were obtained using the log-rank test, and Cox regression was used to estimate the cause-specific hazard ratio (HR) of the event appropriate to each outcome. Linear and logistic regression were performed for continuous variables and binary variables, respectively. Multivariable models adjusted for age, sex, $CD34^+$ cell dose, conditioning, and pretransplantation disease status. Pretransplantation measures of disease status included metabolic response (ie, complete metabolic response, partial metabolic response, or progressive disease) for NHL and cytogenetic risk (ie, standard risk versus high risk as defined by the presence of 17p deletion, t(4;14), t(4;16), t(4;20), or amp 1q) and International Myeloma Working Group response (ie, stringent complete response/complete response, very good partial response, partial response, or progressive disease) for MM [22,23].

An as-treated analysis was performed among those compliant with the policy, excluding patients in the pre-SOP and post-SOP periods who did and did not receive G-CSF, respectively.

RESULTS

Patient Characteristics

Among the 633 patients identified for inclusion, 484 (76.5%) had MM and 149 (23.5%) had NHL. There were 410 and 223 patients in the pre-SOP group (September 2018 to August 2021) and 223 patients in the post-SOP group (September 2021 to February 2023). All 149 NHL patients (100%) and

Table 1
Baseline Characteristics of Patients in the Pre- and Post-G-CSF Policy Periods

Characteristic	MM Patients		NHL Patients	
	Pre-SOP (N = 309)	Post-SOP (N = 175)	Pre-SOP (N = 101)	Post-SOP (N = 48)
Sex, n (%)				
Male	177 (57)	103 (59)	66 (65)	33 (69)
Female	132 (43)	72 (41)	35 (35)	15 (31)
Age, yr, median (range)	61 (36-78)	63 (32-75)	61 (24-75)	61 (27-79)
CD34 cells $\times 10^6$/kg, median (IQR)	5.34 (4.32-6.45)	5.02 (4.31-5.94)	6.09 (5.00-8.50)	6.63 (4.91-7.67)
CMV serostatus positive, n (%)	183 (59)	98 (56)	58 (57)	17 (35)
Conditioning, n (%)				
L-PAM	309 (100)	175 (100)		
L-PAM, ARA-C, BCNU, VP-16			77 (76)	39 (81)
BU, CY, TEPA			20 (20)	6 (12)
BU, TEPA			3 (3.0)	3 (6.2)
L-PAM, TEPA, ARA-C,VP-16			1 (1.0)	0 (0)
L-PAM dose, mg/m^2, n (%)				
200	285 (92)	161 (92)		
140	24 (7.8)	14 (8.0)	78 (100)	39 (100)
Elective admission, n (%)	137 (44)	89 (51)	101 (100)	48 (100)

L-PAM indicates melphalan; ARA-C, cytarabine; BCNU, carmustine; VP-16, etoposide; BU, busulfan; CY, cyclophosphamide; TEPA, thiotepa.

226 MM patients (46.7%) were electively hospitalized for ASCT. The patients' baseline characteristics are listed in Table 1. Notably, 1 MM patient in the post-SOP group received a CD34$^+$ cell dose $<2.5 \times 10^6$/kg.

SOP Adherence

All comparisons are presented as pre-G-CSF versus post-G-CSF policy implementation. Both the proportion of patients who received G-CSF by day +5 (MM: 2.3% versus 65.1%; NHL: 14.9% versus 75%) and the median number of G-CSF doses administered (MM: .4 versus 5.2; NHL: 1.7 versus 5.1) were increased. Reasons for withholding G-CSF (n = 55; 24.7%) included cardiac disorders (ie, atrial fibrillation [n = 14], other arrhythmias [n = 3], congestive heart failure [n = 2]), autoimmune disorders (n = 13), intolerance (n = 6), gout (n = 6), chronic kidney disease (n = 5), amyloid (n = 3), and attending preference (n = 3). G-CSF by day +5 was administered less frequently among MM patients who were admitted electively (73.3% versus 57.3; P = .040). In the post-SOP period, G-CSF was administered appropriately (ie, given by day +5 without a documented exclusion) in 90.5% (202 of 223).

Engraftment

In the pre-SOP versus post-SOP periods, the estimated median time to neutrophil engraftment was 15 days versus 12 days ($P < .0001$) for MM patients and 12 days versus 10 days ($P < .0001$) for NHL patients (Figure 1). The estimated median time to platelet engraftment in the 2 periods was 15 days versus 15 days (P = .70) for MM and 15 days versus 13 days (P = .002) for NHL. The probabilities of neutrophil and platelet engraftment as functions of time are depicted in Supplementary Figures S1 and S2, respectively. Table 2 presents unadjusted and adjusted regression results.

All patients achieved neutrophil engraftment. Eleven patients failed to achieve platelet engraftment; 1 patient died (an NHL patient in the pre-SOP group) and 10 patients were discharged from FHCC (8 NHL patients and 2 MM patients in the pre-SOP group) without achieving platelet engraftment.

Admissions

The mean total duration of inpatient admission in the pre-SOP versus post-SOP groups was 10.4 days versus 10.9 days (P = .36) for MM and 14.7 days versus 12.9 days (P = .015) for NHL (Supplementary Figure S2, Table 2). Among MM patients electively admitted for ASCT, the total inpatient duration in the 2 groups was 14.8 days versus 14.8 days (P = .92), with a mean difference of .06 (95% confidence interval [CI], -1.2 to 1.4; P = .92) and an adjusted mean difference of -.19 (95% CI, -1.5 to 1.1; P = .8). Among MM patients not electively admitted, the proportion requiring admission was 75.0% versus 75.6% ($P > .99$), and the total inpatient duration was 6.9 days versus 6.8 days, with a mean difference of -.08 (95% CI, -1.5 to 1.4; $P > .9$) and an adjusted mean difference of -.08 (95% CI, -1.5 to 1.4; $P > .9$). The proportion of NHL patients requiring readmission was 24.8% versus 4.2% (P = .004) with an odds ratio (OR) of .14 (95% CI, .02 to .50; P = .009) and an adjusted OR (aOR) of .13 (95% CI, .02 to .49; P = .009), and the duration of the primary admission was 12.8 days versus 13.0 days (P = .79; Supplementary Figure 3A). Reasons for readmission of NHL patients are shown in Supplemental Figure 3B. The proportion of NHL patients who were neutropenic at their initial discharge was 37.6% versus 12.5% (OR, .24; 95% CI, .08 to .57; P = .003; aOR, .19; 95% CI, .06 to .49; P = .001), and the proportion readmitted for NF was 11.9% versus 0% (P = .025).

Notably, the 1 patient with NHL who underwent ASCT in the pre-SOP period died before day +30 and was admitted through day +27. This patient's inpatient duration was counted as 27 days.

Fever and Infectious Disease

The proportion of patients who developed NF was 56.0% in the pre-SOP group versus 50.3% in the post-SOP for MM (P = .21) and 89.1% versus 87.5% (P = .95) for NHL. The mean number of febrile days was 2.7 days versus 3.0 days for MM (P = .23) and 4.1 days versus 3.3 days for NHL (P = .064) (Supplementary Figure S3, Table 2).

The proportion of patients who received cefepime in the 2 groups was 52.1% versus 57.1% (P = .27) for MM and 86.1%

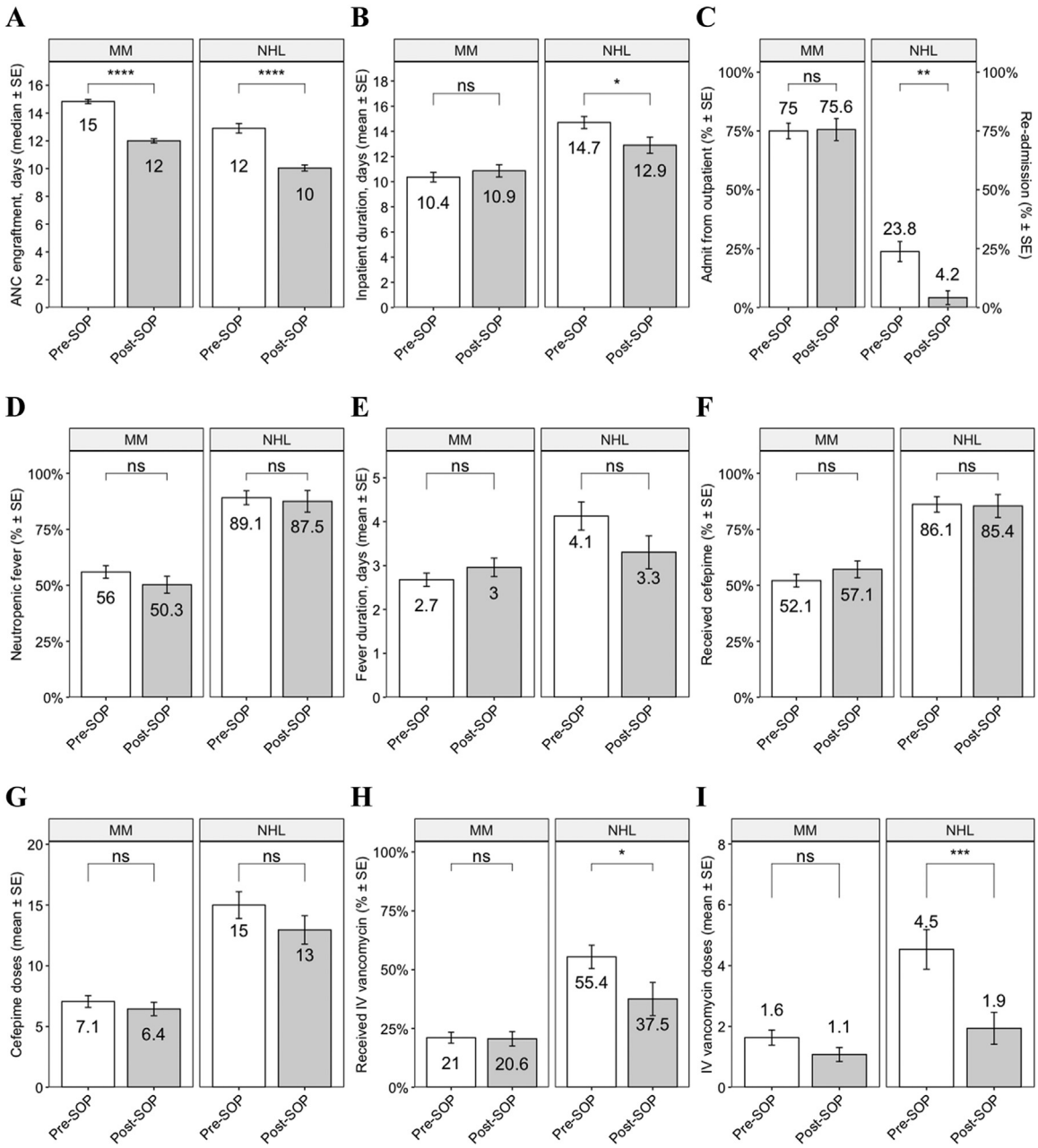

Figure 1. Time to neutrophil engraftment (A), duration of inpatient admission (B), proportion of patients admitted from the outpatient setting among patients with MM or readmitted postdischarge with NHL (C), proportion of patients who developed NF (D), total number of days in which fever was detected (E), proportion of patients who received cefepime (F), number of cefepime doses administered (G), proportion of patients who received i.v. vancomycin (H), and number of i.v. vancomycin doses administered (I). ns, not significant; $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$; $^{****}P < .0001$.

versus 85.4% ($P > .99$) for NHL. The mean number of cefepime doses administered was 6.4 versus 7.1 ($P = .35$) for MM and 15 versus 13 ($P = .15$) for NHL (Supplementary Figure S4). Among MM patients, the proportion who received i.v. vancomycin was 21.0% versus 20.6% ($P = .98$), and the mean number of doses administered was 1.6 versus 1.1 ($P = .056$). On the other hand, among NHL patients, the proportion who received i.v. vancomycin was 55.4% versus 37.5% ($P = .038$), and the mean number of doses administered was 4.5 versus 1.9 ($P = .0003$). The proportion of patients with ≥1 positive blood culture was 13.9% versus 11.4% ($P = .47$) for MM and 25.7% versus 12.5% ($P = .078$) for NHL.

Survival

Among survivors, the median duration of follow-up was 19 months for MM patients and 14 months for NHL patients. Neither median OS nor median PFS was reached in either group.

In both the pre-SOP and post-SOP periods, the 100-day OS was excellent: 99.0% versus 98.5% ($P = .70$) for MM patients and 95.9% versus 96.9% ($P = .80$) for NHL patients. The 100-day PFS in the 2 groups was 98.6% versus 98.5% ($P = .92$) for MM patients and 81.8% versus 96.9% ($P = .0028$) for NHL patients. The 1-year OS was 97.6% versus 95.2% ($P = .31$) for MM patients and 85.0% versus 96.9% ($P = .014$) for NHL patients, and the 1-year PFS was 96.2% versus 95.2% ($P = .69$) for MM patients

Table 2
Summary of Linear, Cox, and Logistic Regression Analyses of all Patients in the Post-G-CSF versus Pre-G-CSF Policy Periods

Variable	MM Patients						NHL Patients					
	Univariate Analysis			Multivariable Analysis			Univariate Analysis			Multivariable Analysis		
	Beta	**95% CI**	***P* Value**	**Beta**	**95% CI**	***P* Value**	**Beta**	**95% CI**	***P* Value**	**Beta**	**95% CI**	***P* Value**
Inpatient days	.51	-.72 to 1.7	.4	-.11	-1.1 to .86	.8	-1.8	-3.4 to -.17	.030	-1.7	-3.4 to -.03	.045
Febrile days	.28	-.23 to .79	.3	.18	-.34 to .70	.5	-.82	-1.9 to .24	.13	-.95	-2.0 to .13	.083
Antibiotic doses												
Cefepime	-.62	-2.1, to .89	.4	-.89	-2.4 to .63	.2	-2.0	-5.6 to 1.5	.3	-1.6	-5.3 to 2.1	.4
Vancomycin	-.56	-1.3 to .18	.14	-.61	-1.4 to .14	.11	-2.6	-4.6 to -.60	.011	-2.2	-4.3 to -.21	.031
	HR	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Engraftment												
Neutrophils	3.11	2.56-3.78	<.001	3.31	2.71-4.05	<.001	3.48	2.38-5.09	<.001	5.07	3.27-7.88	<.001
Platelets	1.03	.85-1.24	.8	1.15	.95-1.39	.15	1.69	1.18-2.41	.004	1.60	1.10-2.32	.014
	OR	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
NF	.8	.55-1.15	.2	.77	.53-1.13	.2	.86	.30-2.63	.8	.75	.23-2.63	.6
Antibiotic receipt												
Cefepime	1.23	.84-1.78	.3	1.18	.81-1.73	.4	.94	.36-2.65	>.9	1.19	.44-3.54	.7
Vancomycin	.97	.61-1.53	>.9	.91	.57-1.44	.7	.48	.24-.97	.042	.55	.26-1.15	.11
≥1 positive blood culture	.8	.45-1.39	.4	.74	.41-1.32	.3	.41	.14-1.02	.072	.38	.12-1.02	.069

Beta represents mean difference.

and 81.8% versus 96.9% ($P = .0028$) for NHL patients. Multivariable Cox regression analysis did not show an independent impact of the post-SOP period on PFS (MM: adjusted HR [aHR], 1.23; 95% CI, .43 to 3.51, $P = .7$; NHL: aHR, .30; 95% CI, .04 to 2.29; P = .2) or OS (MM: aHR, 1.78; 95% CI, .59 to 5.37; $P = .3$; NHL: aHR, .37; 95% CI, .05 to 2.90; $P = .3$).

As-Treated Analysis

Baseline characteristics of as-treated patients are listed in Supplementary Table S1. Results from univariate and multivariable regression analyses for the as-treated patients in the pre-SOP group versus post-SOP group are compared in Supplementary Table S2. In the pre-SOP and post-SOP groups, the estimated median time to neutrophil engraftment was 15 days versus 11 days ($P < .0001$) for MM patients and 13 days versus 10 days ($P < .0001$) for NHL patients (Supplementary Figure S4). Among as-treated NHL patients, the mean duration of inpatient admission was 14.7 days versus 12.8 days ($P = .033$) and the readmission rate was 26.7% versus 5.6% ($P = .012$), with an OR of .16 (95% CI, .02 to .59; $P = .017$) and an aOR of .18 (95% CI, .03 to .71; $P = .031$). Among as-treated MM patients, the mean duration of inpatient admission was 10.3 days versus 9.3 days ($P = .12$).

DISCUSSION

This retrospective study of patients with MM and NHL was undertaken to evaluate the impact of implementing a policy of starting G-CSF on day +5 post-ASCT at a center that routinely and preferentially performs outpatient-based transplantations. Adherence was excellent, with G-CSF administered appropriately to 90.5% of patients, with an average of 5 doses administered per patient. Post-SOP, neutrophil engraftment was accelerated by 3 days on average, and platelet engraftment was not compromised, findings consistent with prior reports [4,7,8,10,11,13,15,16,24-28]. These results were supported by an exploratory as-treated analysis.

To assess the impact on key outcomes according to the transplantation diagnosis and initial care setting, we analyzed outcomes of patients before and after implementation of the G-CSF policy with a focus on inpatient duration, NF, and infectious complications. Prior reports have observed conflicting outcomes regarding the impact of post-ASCT G-CSF on the incidence and duration of NF [7-14,16,25,29]. In our study, the proportions of MM and NHL patients who developed NF were numerically similar, and the total number of febrile days was not definitively different. Some studies have reported fewer days of i.v. antibiotic use in patients receiving post-ASCT G-CSF [7,10,25,29]. We found little evidence that the proportions of MM and NHL patients in our study who required cefepime was reduced, though the as-treated analysis suggested less cefepime use among G-CSF-treated MM patients. The use of i.v. vancomycin was not definitively lower among MM patients; however, there was a decrease in the proportion of NHL patients who received i.v. vancomycin and a reduction in the number of doses administered in the post-SOP group, findings supported by the as-treated analysis.

We also evaluated the impact of the G-CSF policy on the total number of inpatient hospital days over the course of ASCT. Some prior studies have observed a benefit [7,9-12,16,25,29,30], whereas others have not [8,11,13,14,26-28,31]. At our center, the total number of inpatient days was reduced in NHL patients, all of whom underwent inpatient-based transplantation, a finding in agreement with most prior studies involving a homogeneous population of NHL patients [9,12,29]. Several findings suggest that this decrease in total inpatient duration was driven by a reduction in the readmission rate: fewer patients were discharged while neutropenic, there were no readmissions for NF or infection, and the duration of the primary hospitalization was not definitively changed. Among MM patients, however, the inpatient duration was similar in those who underwent ASCT in either an inpatient or an outpatient setting in both the pre-SOP and post-SOP groups. Among those who underwent outpatient-based ASCT, the proportion of patients requiring admission was not obviously different. It is possible that the NHL patients derived greater benefit from accelerated neutrophil engraftment owing to a greater risk of complications from more toxic conditioning regimens, such as BEAM (carmustine, etoposide, cytarabine, and melphalan) [32].

Our analysis has implications for the stewardship of supportive care resources. A G-CSF biosimilar currently used at our center, filgrastim-aafi (Nivestym), costs approximately $219 for a 300 μg syringe and $350 for a 480 μg syringe, based on wholesale pricing information [33]. As the majority of G-CSF doses administered were 480 μg (913 of 1458; 62.6%), the weighted average cost of filgrastim-aafi was approximately $300 per dose. This figure does not account for the cost of dispensing and administering the drug. Thus, the added cost of implementing the post-ASCT G-CSF policy was at least $1440 per transplantation for MM patients and $1020 per transplantation for NHL patients. The estimated inpatient costs associated with ASCT across US hospitals are $2408/day for MM patients and $2755/day for NHL patients, based on a recent analysis of data extracted from the Nationwide Inpatient Sample [34]. Therefore, the intervention resulted in a net reduction in expenses of roughly $3938 per patient among those who underwent ASCT for NHL, who had a 1.8-day reduction in inpatient duration and a 20.6 percentage point decrease in readmission rate. These benefits were not seen in MM patients, in whom the intervention did not appear to be cost-effective.

This study has several limitations, including (1) its retrospective nature, (2) limited sample size, (3) data collected from a single center, (4) withholding of G-CSF administration to patients with specific comorbidities, and (5) lack of patient-level cost data. Furthermore, the study period was punctuated by the Coronavirus disease 2019 pandemic, with the SOP taking effect roughly 1.5 years into the pandemic, although we examined 3 years of pre-SOP data to take this into account. Because we are reporting on 1.5 years of data after the G-CSF policy implementation, a limited number of transplantations were performed during this period, limiting the power of our statistical analyses. Given that these data come from a single center, it would be of interest to assess whether our findings are generalizable to other institutions, particularly because ASCT is increasingly being performed in the outpatient setting. Finally, G-CSF was not administered to patients considered at high risk of adverse events from the intervention. The presence of cardiac comorbidities was the dominant reason for exclusion. Thus, the impact of the policy on such patients is unknown.

CONCLUSION

The implementation of routine post-ASCT G-CSF administration in patients with NHL and MM was found to accelerate neutrophil engraftment without compromising platelet engraftment yet resulted in a differential effect on the duration of hospitalization. Among NHL patients, all of whom were electively admitted for ASCT, the inpatient duration and readmission rate were reduced, as was the use of i.v. antibiotics. Among MM patients, however, many of whom initiated and completed ASCT in the outpatient setting, there was insufficient evidence to support definitive reductions in inpatient duration, admission rate, infectious complications, or antibiotic use. At our center, post-ASCT G-CSF was clearly beneficial for patients with NHL but not for those with MM. The latter finding remains to be confirmed in a prospective, multicenter, randomized control trial.

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Data availability statement: The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.08.021.

REFERENCES

1. Mossad SB, Longworth DL, Goormastic M, Serkey JM, Keys TF, Bolwell BJ. Early infectious complications in autologous bone marrow transplantation: a review of 219 patients. *Bone Marrow Transplant*. 1996;18:265–271.
2. Afessa B, Peters SG. Major complications following hematopoietic stem cell transplantation. *Semin Respir Crit Care Med*. 2006;27:297–309. https://doi.org/10.1055/s-2006-945530.
3. Smith LA, Wright-Kanuth MS. Complications and risks in hematopoietic stem cell transplant patients. *Clin Lab Sci*. 2001;14:118–124.
4. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol*. 2006;24:3187–3205. https://doi.org/10.1200/JCO.2006.06.4451.
5. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of WBC growth factors: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2015;33:3199–3212. https://doi.org/10.1200/JCO.2015.62.3488.
6. Trivedi M, Martinez S, Corringham S, Medley K, Ball ED. Optimal use of G-CSF administration after hematopoietic SCT. *Bone Marrow Transplant*. 2009;43:895–908. https://doi.org/10.1038/bmt.2009.75.
7. Klumpp TR, Mangan KF, Goldberg SL, Pearlman ES, Macdonald JS. Granulocyte colony-stimulating factor accelerates neutrophil engraftment following peripheral-blood stem-cell transplantation: a prospective, randomized trial. *J Clin Oncol*. 1995;13:1323–1327. https://doi.org/10.1200/JCO.1995.13.6.1323.
8. McQuaker IG, Hunter AE, Pacey S, Haynes AP, Iqbal A, Russell NH. Low-dose filgrastim significantly enhances neutrophil recovery following autologous peripheral-blood stem-cell transplantation in patients with lymphoproliferative disorders: evidence for clinical and economic benefit. *J Clin Oncol*. 1997;15:451–457. https://doi.org/10.1200/JCO.1997.15.2.451.
9. Faber E, Pytlik R, Slabý J, et al. Individually determined dosing of filgrastim after autologous peripheral stem cell transplantation in patients with malignant lymphoma: results of a prospective multicentre controlled trial. *Eur J Haematol*. 2006;77:493–500. https://doi.org/10.1111/j.1600-0609.2006.00741.x.

10. Schmitz N, Ljungman P, Cordonnier C, et al. Lenograstim after autologous peripheral blood progenitor cell transplantation: results of a double-blind, randomized trial. *Bone Marrow Transplant*. 2004;34:955–962. https://doi.org/10.1038/sj.bmt.1704724.
11. Hornedo J, Solá C, Solano C, et al. The role of granulocyte colony-stimulating factor (G-CSF) in the post-transplant period. *Bone Marrow Transplant*. 2002;29:737–743. https://doi.org/10.1038/sj.bmt.1703539.
12. Lee SM, Radford JA, Dobson L, et al. Recombinant human granulocyte colony-stimulating factor (filgrastim) following high-dose chemotherapy and peripheral blood progenitor cell rescue in high-grade non-Hodgkin's lymphoma: clinical benefits at no extra cost. *Br J Cancer*. 1998;77:1294–1299. https://doi.org/10.1038/bjc.1998.216.
13. Ojeda E, Garcia-Bustos J, Aguado M, et al. A prospective randomized trial of granulocyte colony-stimulating factor therapy after autologous blood stem cell transplantation in adults. *Bone Marrow Transplant*. 1999;24:601–607. https://doi.org/10.1038/sj.bmt.1701972.
14. Piccirillo N, Sica S, Laurenti L, et al. Optimal timing of G-CSF administration after $CD34^{+}$ immunoselected peripheral blood progenitor cell transplantation. *Bone Marrow Transplant*. 1999;23:1245–1250. https://doi.org/10.1038/sj.bmt.1701795.
15. Shimazaki C, Oku N, Uchiyama H, et al. Effect of granulocyte colony-stimulating factor on hematopoietic recovery after peripheral blood progenitor cell transplantation. *Bone Marrow Transplant*. 1994;13:271–275.
16. Valteau-Couanet D, Faucher C, Aupérin A, et al. Cost effectiveness of day 5 G-CSF (Lenograstim) administration after PBSC transplantation: results of a SFGM-TC randomised trial. *Bone Marrow Transplant*. 2005;36:547–552. https://doi.org/10.1038/sj.bmt.1705097.
17. Richard S, Schuster MW. Stem cell transplantation and hematopoietic growth factors. *Curr Hematol Rep*. 2002;1:103–109.
18. National Comprehensive Cancer Network (NCCN). Hematopoietic growth factors (version 4.2021, May 20, 2021). Available at: https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. Accessed June 14, 2021.
19. Bensinger W, Appelbaum F, Rowley S, et al. Factors that influence collection and engraftment of autologous peripheral-blood stem cells. *J Clin Oncol*. 1995;13:2547–2555. https://doi.org/10.1200/JCO.1995.13.10.2547.
20. Hill JM, Syed MA, Arai AE, et al. Outcomes and risks of granulocyte colony-stimulating factor in patients with coronary artery disease. *J Am Coll Cardiol*. 2005;46:1643–1648. https://doi.org/10.1016/j.jacc.2005.01.067.
21. Wolfram O, Jentsch-Ullrich K, Wagner A, et al. G-CSF-induced mobilization of CD34(+) progenitor cells and proarrhythmic effects in patients with severe coronary artery disease. *Pacing Clin Electrophysiol*. 2007;30 (suppl 1)):S166–S169. https://doi.org/10.1111/j.1540-8159.2007.00630.x.
22. Barrington SF, Kluge R. FDG PET for therapy monitoring in Hodgkin and non-Hodgkin lymphomas. *Eur J Nucl Med Mol Imaging*. 2017;44(suppl 1):97–110. https://doi.org/10.1007/s00259-017-3690-8.
23. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20:1467–1473. https://doi.org/10.1038/sj.leu.2404284.
24. Ozcan M, Ustün C, Akçağlayan E, et al. Recombinant human granulocyte colony-stimulating factor (rh-G-CSF) may accelerate hematopoietic recovery after HLA-identical sibling allogeneic peripheral blood stem cell transplantation. *Bone Marrow Transplant*. 2001;27:499–505. https://doi.org/10.1038/sj.bmt.1702816.
25. Demirer T, Ayli M, Dagli M, et al. Influence of post-transplant recombinant human granulocyte colony-stimulating factor administration on peritransplant morbidity in patients undergoing autologous stem cell transplantation. *Br J Haematol*. 2002;118:1104–1111. https://doi.org/10.1046/j.1365-2141.2002.03762.x.
26. Dunlop DJ, Fitzsimons EJ, McMurray A, et al. Filgrastim fails to improve haemopoietic reconstitution following myeloablative chemotherapy and peripheral blood stem cell rescue. *Br J Cancer*. 1994;70:943–945. https://doi.org/10.1038/bjc.1994.425.
27. Osma MM, Ortuño F, Lozano ML, et al. Administration of post-autologous PBSCT rhG-CSF is associated with long-term low concentrations of bone marrow hematopoietic progenitor cells. *Bone Marrow Transplant*. 2001;27:1287–1292. https://doi.org/10.1038/sj.bmt.1703079.
28. Vey N, Molnar S, Faucher C, et al. Delayed administration of granulocyte colony-stimulating factor after autologous bone marrow transplantation: effect on granulocyte recovery. *Bone Marrow Transplant*. 1994;14:779–782.
29. Tarella C, Castellino C, Locatelli F, et al. G-CSF administration following peripheral blood progenitor cell (PBPC) autograft in lymphoid malignancies: evidence for clinical benefits and reduction of treatment costs. *Bone Marrow Transplant*. 1998;21:401–407. https://doi.org/10.1038/sj.bmt.1701104.
30. Brice P, Divine M, Marolleau JP, et al. Comparison of autografting using mobilized peripheral blood stem cells with and without granulocyte colony-stimulating factor in malignant lymphomas. *Bone Marrow Transplant*. 1994;14:51–55.
31. Cortelazzo S, Viero P, Bellavita P, et al. Granulocyte colony-stimulating factor following peripheral-blood progenitor-cell transplant in non-Hodgkin's lymphoma. *J Clin Oncol*. 1995;13:935–941. https://doi.org/10.1200/JCO.1995.13.4.935.
32. Veeraputhiran M, Jain T, Deol A, et al. BEAM conditioning regimen has higher toxicity compared with high-dose melphalan for salvage autologous hematopoietic stem cell transplantation in multiple myeloma. *Clin Lymphoma Myeloma Leuk*. 2015;15:531–535. https://doi.org/10.1016/j.clml.2015.05.008.
33. Pfizer. Information for Colorado prescribers of prescription drugs. Nivestym (filgrastim-aafi). February 10, 2022.
34. Jones JA, Qazilbash MH, Shih YT, Cantor SB, Cooksley CD, Elting LS. In-hospital complications of autologous hematopoietic stem cell transplantation for lymphoid malignancies: clinical and economic outcomes from the Nationwide Inpatient Sample. *Cancer*. 2008;112:1096–1105. https://doi.org/10.1002/cncr.23281.