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The effect of G-CSF use on hospital length of stay after an allogeneic hematopoietic cell transplantation: a retrospective multicenter cohort study

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Abstract

Granulocyte colony stimulating factor (G-CSF) is administered after allogeneic hematopoietic cell transplantation (HCT) to aid with neutrophil recovery. We compared the effect of empiric G-CSF administration on duration of index inpatient hospitalization stay after HCT for patients aged ≥18 years with hematologic malignancy. G-CSF was considered empiric if administered between day −3 to day +6 in relation to infusion of the graft. We studied 3562 transplants (N=1487 HLA-matched sibling and N=2075 HLA-matched unrelated donor) between 2007 to 2016. Three hundred and thirteen (21%) recipients of HLA-matched sibling and 417 (20%) recipients of HLA-matched unrelated donor HCT received empiric G-CSF. The effect of G-CSF on index hospitalization stay was examined in general linear models (GLM) with adjustment for other patient, disease and transplant characteristics and acute graft-versus-host disease and infection post-transplant. Length of index hospitalization by treatment group did not differ for HLA-matched sibling HCT but was shorter with G-CSF (15 vs. 19 days, $p<0.001$) for HLA-matched unrelated donor HCT. GLM models confirmed shorter hospitalization with use of G-CSF for HLA-matched unrelated donor HCT ($p=0.01$). G-CSF was not associated with early survival for either donor type. There is no benefit or disadvantage of giving G-CSF to promote neutrophil recovery.

Keywords

G-CSF; Allogeneic hematopoietic cell transplant; length of stay

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INTRODUCTION

Hematopoietic growth factors such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have been shown to promote faster neutrophil recovery after hematopoietic cell transplantation (HCT) [1,2]. An earlier study from the Center for International Blood and Marrow Transplant Research (CIBMTR) in adults with leukemia observed shortening of the neutropenic period post transplantation [3]. In that study, G-CSF was administered within 7 days of infusion of the graft and duration of hospitalization was similar between groups receiving G-CSF for both peripheral blood and bone marrow grafts) [3]. The study also did not observe differences in early treatment related mortality, acute and chronic graft-versus-host disease (GVHD), relapse, leukemia free or overall survival [3]. Results of two meta analyses failed to demonstrate an effect of empiric G-CSF use on treatment related mortality and GVHD [4,5]. One of the meta-analysis also compared the effect of G-CSF on duration of hospitalization and found a three-day reduction in hospitalization in the group that received G-CSF [5].

Since the publication of the above-mentioned reports there have been several changes in the field of HCT. Increasing numbers of patients over 60 years are undergoing HCT, there has been an increase in the use of reduced intensity and non-myeloablative conditioning regimens to extend transplantation to those with co-morbidities, an increase in 8/8 HLA matched unrelated donor transplants and the near universal use of peripheral blood graft. In the current era of escalating healthcare costs, resource utilization is a priority for transplant centers [6]. A report from the Agency for the Healthcare Research and Quality (AHRQ) noted that HCT ranked among the top 10 procedures with the most rapid increase in hospital costs in the US [7]. The median cost of an HCT (based on data from 2007-2009) in the first 100 days was $203,026 (IQR, $141,742–316,426) with more than 75% of costs attributable to inpatient stay[8]. As G-CSF use promotes faster neutrophil recovery, this could potentially be used as a tool to reduce duration of inpatient stay and thus healthcare costs. Thus, the current analysis sought to study the effect of empiric G-CSF on the duration of inpatient hospitalization in the first 100 days after HLA-matched sibling and 8/8 HLA matched unrelated peripheral blood transplants for acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) and myelodysplastic syndrome (MDS).

METHODS

Patients

The CIBMTR is a group of over 300 transplant centers worldwide that contribute data prospectively on consecutive transplants performed at each individual center and patients are followed longitudinally until death or lost to follow-up. Included are patients aged 18 year and older with AML, ALL, or MDS, received peripheral blood grafts and planned to be admitted to the hospital for transplantation. Transplants occurred between 2007 and 2016 in the United States. Patients received grafts from an HLA-matched sibling or unrelated donor, matched at the allele-level at HLA-A, -B, -C, -DRB1. G-CSF administration was considered empiric if date of onset was between day −3 to day +6 in relation to the date of infusion of the graft. Forty-two patients admitted for transplantation died prior to discharge and were excluded. Recipients of out-patient transplants were excluded. Other exclusions included

transplantation with CD34 selected graft, *ex vivo* and *in vivo* T-cell depletion, HLA-mismatched relative or unrelated donors, GM-CSF for neutrophil recovery and post-transplant cyclophosphamide for graft-versus-host disease (GVHD) prophylaxis. Patients provided written informed consent for research. The Institutional Review Board of the National Marrow Donor Program approved this study.

Outcomes

The primary outcome was duration of index inpatient hospitalization for transplantation. The duration was calculated from date of transplant to date of first discharge from hospital. Neutrophil recovery was defined as achieving an absolute neutrophil count (ANC) of ≥ 0.5 x 10^9/L for 3 consecutive days. Acute grade II-IV GVHD were based on reports from each transplant center and using standard criteria [9]. Death from any cause was considered an event and surviving patients were censored at last follow-up.

Statistical analysis

Patient, disease, and transplantation characteristics of those that received empiric G-CSF and those who did not were compared using the Chi-square test for categoric variables and the Wilcoxon test for continuous variables. The probability for overall survival were estimated using the Kaplan-Meier estimator [10]. The day-28 incidence of neutrophil recovery was calculated using the cumulative incidence estimator to accommodate competing risks [11]. As donor type is a significant predictor for overall survival, analyses on transplant outcomes were studied separately for HLA-matched sibling and HLA-matched unrelated donor transplants.

We used a multivariable generalized linear model (GLM) with duration of index inpatient hospital days as the outcome variable to study the effect of empiric G-CSF, 3-months after transplantation [12]. Variables tested included empiric G-CSF administration, age, sex, race, ethnicity, performance status, hematopoietic cell transplantation-comorbidity index (HCT-CI), cytomegalovirus serostatus, interval from diagnosis to transplant, disease-risk index (DRI; composite of disease, disease status and cytogenetic risk), conditioning regimen intensity, GVHD prophylaxis, transplant period, grade II-IV acute GVHD and systemic bacterial, viral and fungal infections. A Cox regression model was built to study the effect of empiric G-CSF administration on 3-month survival, adjusted characteristics described above [13]. A stepwise model building approach was adopted and variables that attained a p-value <0.05 (two-sided) were retained in the final model with the exception of G-CSF administration, which was held in all steps of model building regardless of level of significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient, disease and transplant characteristics

Of the 1487 patients who received their graft from their HLA matched sibling, 21% (313 of 1487) received empiric G-CSF (Table 1). The characteristics of those who received and did not receive G-CSF were similar expect those who received G-CSF were more likely to be male, non-Caucasians, receive reduced intensity conditioning regimens and calcineurin

inhibitor with mycophenolate for GVHD prophylaxis. Of the 2075 patients who their graft from an HLA matched unrelated donors 20% (417 of 2075) received empiric G-CSF (Table 2). Characteristics of the treatment groups were similar except patients who received G-CSF were more likely to have performance scores less than 90, more likely to receive reduced intensity conditioning regimens and less likely to receive G-CSF in the period 2012 - 2016.

Index inpatient hospitalization

We did not observe a difference in length of index hospitalization between those who received and did not receive G-CSF after HLA-matched sibling. The median length of hospitalization was 17 days (interquartile range [IQR] 14-21) in those who received G-CSF and 18 days (IQR 15-22) in those who did not receive G-CSF (p=0.06). Among recipients of HLA-matched unrelated donor transplant, index length of hospitalization was shorter for those who received G-CSF (median 15 days [IQR 12-21) compared to those who did not receive G-CSF (median 19 days [IQR 15-22), p<0.001. Multivariate analysis confirmed shorter index hospitalization for those who received G-CSF compared to those who did not receive G-CSF after HLA-matched unrelated donor transplant (Table 3).

Neutrophil recovery and overall survival

Among recipients of HLA-matched sibling transplants, the median time to neutrophil recovery was faster at 12 days (10-14) for patients who received G-CSF compared to 15 days (IQR, 13 – 17) for those who did not receive G-CSF (p<0.001). Nevertheless, by day-28, incidence of neutrophil recovery did not differ between treatment groups, 98% (95% confidence interval [CI], 96-99) and 98% (95% CI, 98-99), with and without G-CSF (p=0.32). The corresponding 3-month probability of survival was 92% (95% CI 89-95) and 94% (95% CI 93-96), p=0.17. Multivariate analysis confirmed absence of a difference in overall survival by treatment group (Table 4).

Among recipients of HLA-matched unrelated donor transplants, the median time to neutrophil recovery was also faster at 11 days (IQR, 10- 13) for patients who received G-CSF compared to 15 days (IQR, 13-17) for those who did not receive G-CSF (p<0.001). The day-28, incidence of neutrophil recovery did not differ between treatment groups, 97% (95% CI, 95-98) and 98% (95% CI, 97-98), with and without G-CSF (p=0.38). The corresponding 3-month probability of survival was 88% (95% CI 85-91) and 91% (95% CI 90-92), p=0.09. Multivariate analysis confirmed absence of a difference in overall survival by treatment group (Table 4).

DISCUSSION

The role of G-CSF has been extensively evaluated in allogeneic transplantation with some studies suggesting higher risks for acute GVHD and treatment related mortality after bone marrow transplantation [14,15]. However, none of the studies have shown an advantage with G-CSF other than faster neutrophil recovery which has not resulted in better survival [3,5]. Correspondingly, guidelines from the American Society of Clinical Oncology do not have a strong recommendation for G-CSF use after an allogeneic transplantation other than acknowledge faster neutrophil recovery [16]. Yet data reported to the CIBMTR, an

observational registry for HCTs suggest G-CSF is used empirically for ~20% of HLA-matched related and HLA-matched unrelated donor transplantations in the US for adults with acute leukemia and MDS. This prompted the current analysis with its focus on index length of hospitalization. The period of neutropenia was shorter in patients who received G-CSF after HLA-matched sibling and HLA-matched unrelated donor transplantation. However, index length of hospitalization was shorter for recipients of HLA-matched unrelated donor transplantations but not HLA-matched sibling transplantations. Thus, in the setting of HLA-matched sibling transplantation these data do not support empiric G-CSF for adults with acute leukemia and MDS. The findings in the setting of HLA-unrelated donor transplantation may be relevant in the current economic situation knowing time spent as an inpatient is a major driver of early costs associated with transplantation. Others have shown early transplantation cost account for 75-90% of total cost associated with transplantation [17-19]. The findings from our generalized linear model adjusted for other patient, disease and transplant characteristics associated with unrelated donor transplantation showed a reduction in index hospitalization by 1.7 days. Drug purchasing contracts vary between hospitals and the monetary advantage from an approximate reduction in 2 days of hospitalization must be considered in the context of G-CSF administration over a 2-3 week period. As the data in the current analysis was obtained from a registry we did not have access to costs associated with the transplantations and acknowledge our limitation.

There are several other measures that have been instituted to lower cost associated with transplantation including outpatient transplants [6,20,21]. In fact, one study that examined costs associated with transplantation observed a substantial increase in cost with readmissions within the first 100 days after HCT [21]. In our population, approximately 65% of recipients of HLA-matched sibling and HLA-matched unrelaetd donor transplantations was readmitted within the first 100 days but the proportion of readmissions did not differ by whether G-CSF was given. In a multivariate analysis, considering the length of hospitalization within the first 100 days, we did not observe a significant difference between those who received and did not receive empiric G-CSF after HLA-matched sibling (coefficient=0.93, p=0.26) and HLA-matched unrelated donor (coefficient=0.82, p=0.28) transplants. We did not observe differences in survival and our findings are consistent with all reports on G-CSF administration [1-5]. We did not observe differences in grade II-IV acute GVHD by G-CSF administration after HLA-matched sibling and HLA-matched unrelated donor transplantation (data not shown). These findings are consistent with that of others.

There are several limitations. Our study is an analysis of an existing cohort rather than a prospective design which is considered the “ideal” when evaluating treatments. A prospective study in which patients are randomly assigned empiric G-CSF or not is unlikely considering the prohibitive costs associated with prospective studies. We do not know why G-CSF was administered and may reflect physician preference, institutional practice or an unknown or unmeasured factor. Our models adjusted for known characteristics and confirmed a reduction in index hospitalization by 1.7 days in recipients of HLA-matched unrelated donor transplantation. However, considering over 60% of patients required at least one re-admission we do not know whether early discharge (no greater than 2 days) offer a monetary advantage. Further, we only considered G-CSF and not GM-CSF. In the meta-

analysis by Dekker and colleagues, infections were substantially lower in patients who received GM-CSF but not G-CSF [5]. We also excluded umbilical cord blood and haploidentical donor transplantations and use of post-transplant cyclophosphamide for GVHD prophylaxis.

In summary, these data do not support use of empiric G-CSF for HLA-matched sibling transplantation for adults with acute leukemia and MDS. For HLA-matched unrelated donor transplantation we observed shorter index hospitalization but without differences in readmission within the first 100 days or overall survival. This observation merits further investigation which is beyond the scope of this analysis or the available data in the registry.

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Highlights

1. Empiric G-CSF shortens length of in-patient stay after HLA-matched unrelated donor transplant
2. Empiric G-CSF does not shorten length of in-patient stay after HLA-matched sibling transplant
3. Empiric G-CSF is not associated with early survival

Table 1.

HLA-matched sibling transplant: patient, disease and transplant characteristics

Characteristic	No G-CSF	G-CSF	P value
No. of patients	1174	313	
Age, years			0.47
18- 30	113 (10%)	26 (8%)	
31- 40	127 (11%)	25 (8%)	
41- 50	240 (20%)	61 (19%)	
51- 60	381 (32%)	118 (38%)	
61- 70	283 (24%)	75 (24%)	
> 70	30 (3%)	8 (3%)	
Gender			0.04
Male	649 (55%)	193 (62%)	
Female	525 (45%)	120 (38%)	
Race			< 0.001
Caucasian	1023 (87%)	252 (81%)	
African American	48 (4%)	29 (9%)	
Asian and other races	103 (9%)	32 (10%)	
Ethnicity			0.21
Non-Hispanic	1019 (87%)	263 (84%)	
Hispanic	155 (13%)	50 (16%)	
Performance score			0.25
90-100	709 (60)	177 (57%)	
<90	465 (40)	136 (43%)	
Hematopoietic cell transplantation- comorbidity index			0.59
0-2	680 (58%)	176 (56%)	
3+	494 (42%)	137 (44%)	
Donor-recipient cytomegalovirus serostatus			0.86
Positive / Positive	478 (41%)	120 (38%)	
Positive / Negative	156 (13%)	42 (13%)	
Negative / Positive	292 (25%)	84 (27%)	
Negative / Negative	248 (21%)	67 (21%)	
Disease			0.96
Acute myeloid leukemia	636 (54%)	167 (53%)	
Acute lymphoblastic leukemia	202 (17%)	55 (18%)	
Myelodysplastic syndrome	336 (29%)	91 (29%)	
Disease risk index			0.70
Low	58 (5%)	12 (4%)	
Intermediate	712 (61%)	190 (61%)	
High and Very High	404 (34%)	111 (35%)	
Time to transplant from diagnosis			0.40
Less than one year	886 (75%)	229 (73%)	

Characteristic	No G-CSF	G-CSF	P value
More than one year	288 (25%)	84 (27%)	
Conditioning regimen intensity			<0.001
Myeloablative, total body irradiation containing	369 (31%)	73 (23%)	
Myeloablative, non- total body irradiation containing	406 (35%)	112 (36%)	
Reduced intensity, total body irradiation containing	70 (6%)	44 (14%)	
Reduced intensity, non- total body irradiation containing	329 (28%)	84 (27%)	
GVHD prophylaxis			< 0.001
Calcineurin inhibitor + mycophenolate	250 (21%)	95 (30%)	
Calcineurin inhibitor + methotrexate	715 (61%)	178 (57%)	
Calcineurin inhibitor + other	209 (18%)	40 (13%)	
Transplant period			0.37
2007-2011	537 (46%)	152 (49%)	
2011-2016	637 (54%)	161 (51%)	
Median follow up in months (Min-Max)	62.8(3-125)	70.9 (12-123)	

Table 2.

HLA-matched unrelated donor transplant: patient, disease and transplant characteristics

Characteristic	No G-CSF	G-CSF	P value
No. of patients	1658	417	
Age, years			0.28
18- 30	168 (10%)	31 (7%)	
31- 40	161 (10%)	36 (9%)	
41- 50	258 (16%)	57 (14%)	
51- 60	408 (25%)	104 (25%)	
61- 70	544 (33%)	158 (38%)	
> 70	119 (7%)	31 (7%)	
Sex			0.25
Male	958 (58%)	254 (61%)	
Female	700 (42%)	163 (39%)	
Race			0.78
Caucasian	1527 (92%)	382 (92%)	
African American	45 (3%)	14 (3%)	
Asian and other races	86 (5%)	21 (5%)	
Ethnicity			0.36
Non-Hispanic	1555 (94%)	386 (93%)	
Hispanic	103 (6%)	31 (7%)	
Performance score			0.007
90-100	1003 (60%)	205 (49%)	
<90	655 (40%)	212 (51%)	
Hematopoietic cell transplantation- comorbidity index			0.34
0-2	906 (55%)	217 (52%)	
3+	752 (45%)	200(48%)	
Donor-recipient cytomegalovirus serostatus			0.07
Positive / Positive	411 (25%)	94 (23%)	
Positive / Negative	179 (11%)	59 (14%)	
Negative / Positive	577 (35%)	126 (30%)	
Negative / Negative	491 (30%)	138 (33%)	
Disease			0.92
Acute myeloid leukemia	854 (52%)	212 (51%)	
Acute lymphoblastic leukemia	209 (13%)	51 (12%)	
Myelodysplastic syndrome	595 (36%)	154 (37%)	
Disease risk index			0.87
Low	66 (4%)	15 (4%)	
Intermediate	932 (56%)	231 (55%)	
High and Very High	660 (40%)	171 (41%)	
Time to transplant from diagnosis			0.64
Less than one year	1196 (72%)	296 (71%)	

Characteristic	No G-CSF	G-CSF	P value
More than one year	462 (28%)	121 (29%)	
Conditioning regimen intensity			<0.001
Myeloablative, total body irradiation containing	335 (20%)	60 (14%)	
Myeloablative, non- total body irradiation containing	565 (34%)	122 (29%)	
Reduced intensity, total body irradiation containing	144 (9%)	37 (9%)	
Reduced intensity, non- total body irradiation containing	614 (37%)	198 (47%)	
GVHD prophylaxis			0.25
Calcineurin inhibitor + mycophenolate	421 (25%)	115 (28%)	
Calcineurin inhibitor + methotrexate	953 (57%)	244 (59%)	
Calcineurin inhibitor + other	284 (17%)	58 (14%)	
Transplant period			<0.001
2007-2011	590 (36%)	195 (47%)	
2011-2016	1068 (64%)	222 (53%)	
Median follow up in months (Min-Max)	59.1(3-125)	63.2 (11-123)	

Table 3.

Linear model (GLM) with coefficients showing differences in length of hospitalization during the index hospitalization.

	Matched Sibling Donor		Matched Unrelated Donor	
Characteristics	**Coefficient**	**P value**	**Coefficient**	**P value**
G-CSF	0.18	0.78	−1.9	0.02
Gender: Male	0.9	0.10	0.3	0.59
Race: Caucasian	−2.8	0.003	−2.1	0.16
Race: African American	−2.5	0.09	−0.4	0.86
Ethnicity: Hispanic (vs non- Hispanic)	1.8	0.02	3.5	0.008
Performance score <90	1.1	0.05	2.7	<.001
HCT-comorbidity index ≥3	0.5	0.35	0.8	0.23
CMV Positive/Negative	1.3	0.12	−0.2	0.83
CMV Negative/Positive	0.4	0.50	−0.2	0.82
CMV Negative/Negative	0.7	0.35	0.2	0.77
Disease: AML	−0.7	0.29	−0.8	0.33
Disease: ALL	−0.8	0.44	−0.7	0.60
High/very high disease risk index	2.2	0.10	−0.2	0.86
Intermediate disease risk index	2.6	0.04	−0.7	0.65
Time to transplant from diagnosis(< 1 year)	−0.6	0.31	−0.2	0.72
Period of transplant 2007-2011	1.3	0.03	1.4	0.04
TBI containing myeloablative regimen	1.4	0.04	1.9	0.04
TBI containing reduced intensity regimen	−2.0	0.10	−1.9	0.17
Non TBI containing reduced intensity regimen	0	0.97	−1.0	0.22
Calcineurin inhibitor + Mycophenolate	−0.7	0.43	−5.3	<0.001
Calcineurin inhibitor + methotrexate	−1.0	0.19	−4.7	<0.001
Acute GVHD Grade 2-4	4.0	<0.001	4.6	<0.001
Viral infection	0.1	0.82	0.6	0.34
Bacterial infection	1.7	0.002	2.1	0.002
Fungal infection	0	0.98	1.9	0.14

Baseline variables for the model (categorical variables):

Gender: Female; Race: Asian and others; Ethnicity: Non-Hispanic; Performance score: 90-100; HCT-CI:0-2; CMV status: Positive/Positive; Disease: MDS; Time from transplant to diagnosis: > 1 year; Period of transplant: 2012-2016;

Conditioning regimen: Non TBI containing myeloablative regimen; GVHD Prophylaxis: calcineurin inhibitor + others

Table 4.

Cox proportional hazard model for overall survival.

Characteristics	Hazard ratio (95% CI)	P value
Matched Sibling Donor		
G-CSF	1.10(0.94-1.30)	0.23
Performance status	1.20(1.04-1.39)	0.009
HCT-CI (≥3)	1.37(1.19-1.57)	<0.001
High and very high DRI	2.10(1.42-3.09)	<0.001
GVHD(Grade2-4)	1.72(1.43-2.05)	<0.001
Bacterial infection	1.33(1.16-1.54)	<0.001
Viral infection	1.18(1.16-1.37)	0.028
Matched unrelated donor		
G-CSF	1.06(0.92-1.23)	0.35
Performance status	1.27(1.13-1.43)	<0.001
HCT-CI (≥3)	1.37(1.22-1.54)	<0.001
High and very high DRI	2.58(1.76-3.78)	<0.001
Intermediate DRI	1.66(1.13-2.43)	0.009
GVHD(Grade2-4)	2.04(1.77-2.36)	<0.001
Bacterial infection	1.17(1.04-1.32)	0.007
Fungal infection	1.60(1.30-1.96)	<0.001