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Brief Article

Autologous Stem Cell Transplantation for Multiple Myeloma: Growth Factor Matters

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A B S T R A C T

Engraftment syndrome (ES) is a known complication of autologous hematopoietic stem cell transplant during neutrophil recovery. There is a limited amount of data available comparing the incidence of ES with post-transplant granulocyte colony-stimulating factor versus granulocyte macrophage colony-stimulating factor (GM-CSF), specifically in patients with multiple myeloma. Our retrospective review of 156 patients at a single center showed that GM-CSF was associated with a higher incidence of ES compared with G-CSF (32% versus 8% of patients, $P < .001$) and that development of ES was associated with a 32.9% ($P < .001$) longer hospital stay. This suggests that the choice of growth factor could possibly contribute to the development of ES and the associated costs of increased medical care.

INTRODUCTION

Engraftment syndrome (ES) is a constellation of symptoms during neutrophil recovery after autologous hematopoietic stem cell transplant (AHSCT). These symptoms are thought to be related to increased proinflammatory cytokines and capillary leak after neutrophil engraftment. Symptoms of ES include fever, rash, pulmonary infiltrates, hepatic or renal dysfunction, weight gain, and, rarely, transient encephalopathy.

Formal criteria for diagnosis of ES were initially proposed by Spitzer [1] in 2001 and later redefined by Maiolino et al. [2] in 2003. The occurrence of ES in AHSCT patients based on Maiolino and Spitzer criteria is approximately 10% to 20%, although other estimates from the literature using other definitions of ES put the incidence between 9% and 60% [2-5].

The development of ES has been associated with the use of post-AHSCT growth factors, type of pre-AHSCT treatment, cell dose, and rate of engraftment [3,6-9]. There is a limited amount of data available comparing the incidence of ES with post-AHSCT granulocyte colony-stimulating factor (G-CSF) versus granulocyte macrophage colony-stimulating factor (GM-CSF), specifically in patients with multiple myeloma (MM). In addition, the impact of plerixafor mobilization, which potentially affects CD34 cell dosing and rates of engraftment and graft composition, on post-AHSCT outcomes using G-CSF or GM-CSF is largely unknown. One study by Akasheh et al. [3] in 2003 investigated the effects of G-CSF compared with GM-CSF on ES. However, this study did not include plerixafor mobilized patients and had predominantly non-myeloma-related indications for transplant, including autologous stem cell rescue after high-dose chemotherapy for breast cancer.

We decided to focus solely on patients with MM who received a uniform conditioning regimen before AHSCT to reduce the number of possible confounding factors affecting development of ES. We also included patients who underwent stem cell mobilization with plerixafor. The purpose of this retrospective analysis of patients with MM was to compare the incidence of ES in a population of AHSCT recipients receiving G-CSF versus GM-CSF to possibly adjust clinical practice or to suggest further clinical trials.

METHODS

We reviewed 156 adult patients who underwent AHSCT for MM at Thomas Jefferson University Hospital (Philadelphia, Pennsylvania) between March 2008 and April 2016. The study was approved by the institutional

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review board of Thomas Jefferson University. Information on prior treatment with immunomodulators (lenalidomide and/or thalidomide), bortezomib, and/or cyclophosphamide was collected. Patients underwent peripheral stem cell mobilization before collection using 1 of 4 regimens: cyclophosphamide and G-CSF; cyclophosphamide, G-CSF, and plerixafor; G-CSF and plerixafor; or G-CSF only. All patients received conditioning with melphalan 200 mg/m^2 on the day before AHSCT. All patients also received either post-transplant GM-CSF or G-CSF starting on day 3 after AHSCT. Of note, as of September 2014, our institution used G-CSF exclusively post-transplant. Our primary endpoint was incidence of ES as defined by the Spitzer criteria and shown in Table 1 [5]. We chose the Spitzer criteria specifically because it was the ES definition used by Akasheh et al. [3] as well. Secondary endpoints included hospital length of stay and time to neutrophil engraftment. Time to neutrophil engraftment was measured from date of AHSCT to the first day of achieving an absolute neutrophil count $\geq$500/μL for at least 72 hours. Time to platelet engraftment was measured from date of AHSCT to the first day of achieving a platelet count $\geq$20,000/μL for at least 72 hours without platelet transfusions. Hospital length of stay (LOS) was measured from date of AHSCT to date of hospital discharge. We also assessed for the impact of incidence of ES and other factors on LOS.

Patient variables and outcomes were compared between patients who received G-CSF versus GM-CSF using Fisher's exact test or χ^2 test for binary and categorical variables, as well as 2-sample t test or Wilcoxon rank-sum test for continuous variables. Multivariate analyses were performed using logistic regression with linear model assumption and stepwise variable selection unless otherwise specified. Firth's bias-reduced logistic regression was used to assess factors contributing to ES development because of a low number of ES events for some patient factor groups [10]. All statistical analyses were carried out using the R statistical package [11].

RESULTS

Overall patient characteristics are shown in Table 2. Of a total 156 patients, 100 (64.1%) received post-transplant G-CSF and 56 (35.9%) received post-transplant GM-CSF. Patients in the GM-CSF group were more likely to have been previously treated with bortezomib, receive plerixafor mobilization, and receive a higher mean stem cell dose by 1.1×10^6 cells (5.9×10^6versus 4.8×10^6 cells).

The incidence of ES was higher in the post-transplant GM versus G-CSF group (32% versus 8% of patients, $P < .001$) with the mean overall incidence of 17%. These findings are consistent with a prior study by Akasheh et al. [3]. In a multivariable regression model, GM-CSF was associated with a higher risk of developing ES compared with G-CSF (odds ratio [OR], 4.245; P= .002). Male sex was also correlated with increased odds of developing ES (OR, 2.901; P= .032) compared with female sex. Pretransplant bortezomib treatment was also associated with a higher risk of ES (OR, 9.833; P = .040), and pretransplant cyclophosphamide treatment was associated with a lower risk of ES of borderline significance (OR, 0.397; P = .080). These findings are also described by Cornell et al. [6] and Gutierrez-Garcia et al. [12]. Factors affecting ES development, including age, sex, ethnicity, growth factor choice, mobilization regimen, pretransplant treatment, time to neutrophil engraftment, and CD34 dose, are summarized in Table 3.

Multivariable negative binomial regression using similar predictors, including ES, showed that development of ES was associated with 32.9% longer LOS ($P < .001$). Older age was also associated with a relative 0.7% longer LOS for every additional year of age (P = .004). Plerixafor use for mobilization was associated with a 12.5% decrease in LOS (P = .039). Pretransplant immunomodulator treatment was associated with a 13.5% decrease in LOS (P = .008) and pretransplant cyclophosphamide treatment was associated with a 11.5% decrease in LOS (P = .028). Factors affecting LOS are summarized in Table 4.

Table 1
Spitzer Criteria

Major criteria
Temperature over 38.3°C without infectious cause
Erythrodermatous rash involving >25% of body surface area and not attributable to medication
Noncardiogenic pulmonary edema, manifested by diffuse pulmonary infiltrates consistent with this diagnosis, and hypoxia
Minor criteria
Hepatic dysfunction with either total bilirubin >2 mg/dL or transaminase levels >2 times normal
Renal insufficiency (serum creatinine of >2 times baseline)
Weight gain >2.5% of baseline body weight
Transient encephalopathy unexplainable by other causes

Diagnosis established if all 3 major criteria met or 2 major criteria with 1 or more minor criteria met. Symptoms and signs should occur within 96 hours of neutrophil engraftment defined as absolute neutrophil count (ANC) >500/μL for 2 consecutive days.

DISCUSSION

Our study demonstrated a significant increase in the incidence of ES in patients who received post-transplant GM-CSF versus G-CSF to assist in neutrophil recovery. These findings are consistent with the study by Akasheh et al. [3], which also demonstrated a significant increase in the number patients who developed ES by Spitzer criteria if they received GM-CSF compared with G-CSF. In addition, the proportion of patients who developed ES in the 2 groups was similar between our study and Akasheh et al. [3]. One possible explanation for this finding is the upregulation of antigen-presenting cells with GM-CSF, which enhances cell-mediated cytotoxicity and secretion of cytokines such as IL-2 and TNF-α [13]. This might promote a proinflammatory state during immune reconstitution and subsequent neutrophil engraftment, increasing the risk of ES. Finally, our study also demonstrated that patients who developed ES had a 32.9% longer hospital LOS compared with those who did not develop ES. This suggests that reducing the development of ES is relevant and important to reducing health care costs and possible patient morbidity from increased risk of hospital-acquired complications.

Another possible explanation for the differences in ES risk may be caused by the use of plerixafor in combination with GM-CSF. Plerixafor has been shown to mobilize a more primitive population of CD34$^+$ cells, in addition to non-CD34$^+$ cells such as CD4$^+$ and CD8$^+$ T cells, natural killer (NK) cells, and dendritic cells. This may have also contributed to a proinflammatory state that was enhanced by growth factor use and subsequently increased ES risk [14]. Despite this, we found that plerixafor was associated with a decreased LOS, and we did not demonstrate an association between plerixafor and the development of ES. This may be caused by the relative infrequency of ES events in our study, with only 18 and 8 patients fulfilling Spitzer criteria in the GM-CSF and G-CSF groups, respectively. Therefore, this study may be underpowered to detect a statistical effect of factors other than growth factor on the development of ES. Of note, a recent study by Wangjam et al. [15] also did not demonstrate a significant effect of plerixafor on ES after AHSCT.

Our study also demonstrated that pretransplant immunomodulator and cyclophosphamide use were associated with a decreased LOS. Although these factors were not statistically significant with regard to ES, they do support earlier findings of Cornell et al. [6]. Pretransplant cyclophosphamide is thought to increase the regulatory T cell population, which would suppress postengraftment inflammation and reduce ES risk. This would lead to a lower LOS overall. A prior study by Partanen et al. [16] showed that a lenalidomide-based induction therapy led to an increased population of CD8$^+$ and NK cells during autologous stem cell collection. Although the data in

Table 2
Patient Demographics and Outcomes

Characteristic	Overall	G-CSF	GM-CSF	*P* Value
Post-AHSCT growth factor, n (%)	156 (100)	100 (64)	56 (36)	<.000
Age, mean (SD), yr	58.3 (9.9)	57.5 (10.2)	59.6 (9.3)	.202
Sex, n (%)				.865
Female	64 (41)	42 (42)	22 (39)	
Male	92 (59)	58 (58)	34 (61)	
Race, n (%)				.071
Caucasian	94 (60)	54 (54)	40 (71)	
Black	50 (32)	39 (39)	11 (20)	
Asian	5 (3)	3 (3)	2 (4)	
Hispanic	7 (5)	4 (4)	3 (5)	
Pretransplant therapy, n (%)				
Bortezomib	130 (83)	76 (76)	54 (96)	.001
Immunomodulator*	119 (76)	77 (77)	42 (75)	.778
Cyclophosphamide (prior†)	58 (37)	41 (41)	17 (30)	.187
Mobilization, n (%)				<.001
Cyclophosphamide/G-CSF	29 (19)	27 (27)	2 (4)	
Cyclophosphamide/G-CSF/plerixafor	8 (5)	5 (5)	3 (5)	
G-CSF/plerixafor	107 (68)	56 (56)	51 (91)	
G-CSF only	12 (8)	12 (12)	0 (0)	
Cyclophosphamide mobilization, n (%)	37 (24)	32 (32)	5 (9)	.001
Plerixafor mobilization, n (%)	115 (74)	61 (61)	54 (96)	<.001
CD34 dose, mean (SD), $\times 10^6$	5.2 (2.8)	4.8 (3.1)	5.9 (2.2)	<.001
Noninfectious fever, n (%)	76 (49)	37 (37)	39 (70)	<.001
ES by Spitzer criteria, n (%)	26 (17)	8 (8)	18 (32)	<.001
WBC engraftment,‡ mean (SD), d	11.8 (1.3)	11.4 (1.1)	12.6 (1.2)	<.001
Platelet engraftment, mean (SD), d	17.1 (4.2)	16.7 (4.1)	17.9 (4.2)	.311
Hospital LOS, mean (SD), d	19.8 (7.4)	19.2 (7.5)	20.8 (7.2)	.003

Patient variables and outcomes were compared between patients who received G-CSF versus GM-CSF using Fisher's exact test or χ^2 test for binary and categorical variables, as well as 2-sample *t* test or Wilcoxon rank-sum test for continuous variables.

* Immunomodulator = lenalidomide and/or thalidomide.

† (Prior) = for disease control before transplant.

‡ WBC engraftment = time to neutrophil engraftment.

Table 3
Predictors of ES

Characteristic	N (%)	Odds Ratio	95% Confidence Interval	*P* Value
ES by Spitzer criteria				
Male sex	92 (59)	2.901	1.095-8.628	.032
GM-CSF use	56 (36)	4.245	1.712-11.364	.002
Bortezomib pretransplant	130 (83)	9.833	1.087-1319.224	.040
Immunomodulator* pretransplant	119 (76)	0.421	0.151-1.165	.095
Cyclophosphamide (prior†)	58 (37)	0.397	0.122-1.110	.080

The endpoint of ES is analyzed using Firth's bias-reduced logistic regression with potential predictors of age, sex, ethnicity, post-transplant growth factor, pretransplant treatment, mobilization regimen, time to neutrophil engraftment, and CD34 dose.

* Immunomodulator = lenalidomide and/or thalidomide.

† (Prior) = for disease control before transplant.

autologous transplantation are limited, prior studies in allogeneic stem cell transplantation have demonstrated that a decreased NK cell population post-transplant is associated with a higher incidence of graft-versus-host disease and that infusions of activated NK cells decreased graft-versus-host disease in a murine model [17,18].

One unexpected result was the increased odds of ES in male versus female patients. Prior studies by Carreras et al. [4] and Edenfield et al. [8] have shown female predominance in ES. However, the study by Carreras et al. [4] included predominantly patients with lymphoma, and the study by Edenfield et al. [8] was primarily in female patients with breast cancer. Other studies have shown no correlation of ES with patient sex or have a heterogenous population of patients who had undergone AHSCT for other malignancies and thus are not directly comparable to our study [2,3,9,19,20].

Our study has some limitations because of the retrospective nature of the study and the heterogeneity of our patient groups, including variations in mobilization regimens and pretransplant induction therapy. Less patients in our study received GM than G-CSF (56 versus 100), which could skew our findings, but there were more absolute ES events with GM than G-CSF despite this discrepancy (18 versus 8). GM-CSF itself in other settings has also been associated with capillary leak syndrome [21], fevers [22], and rash [23]. A greater proportion of patients in the GM-CSF group received bortezomib

Table 4
Factors Affecting Hospital LOS

Characteristic	Mean Ratio	95% Confidence Interval	*P* Value
Hospital length of stay (mean: 19.8 days)			
Age	1.007	1.002-1.012	.004
GM-CSF versus G-CSF	1.021	0.916-1.138	.705
ES	1.329	1.173-1.505	<.001
Plerixafor mobilization	0.875	0.771-0.993	.039
Immunomodulator* pretransplant	0.865	0.777-0.963	.008
Cyclophos (prior†)	0.885	0.795-0.986	.028

The endpoint of LOS was analyzed using negative binomial regression model with potential predictors of ES, age, sex, ethnicity, post-transplant growth factor, pretransplant treatment, mobilization regimen, time to neutrophil engraftment, and CD34 dose.

* Immunomodulator = lenalidomide and/or thalidomide.

† (Prior) = for disease control before transplant.

compared with the G-CSF group. This can be explained by our use of G-CSF in the period before bortezomib approval for primary treatment in myeloma.

Prior studies have shown that AHSCT in elderly patients is safe with equivalent outcomes compared with younger patients [24,25]. However, our study demonstrated that older age was associated with a longer LOS, although not significant with regard to ES incidence. Belete et al. [26] previously demonstrated that older age (≥60 years) was associated with higher odds of grade 3 to 5 toxicities in AHSCT. Although ES was not specifically listed as a toxicity by Belete et al. [26], other ES-related side effects such as diarrhea and respiratory issues were higher in the older patient population. Also, although Muchtar et al. [25] demonstrated no difference in Progression-free survival (PFS) or overall survival (OS) when comparing younger versus older (>70 years) patients receiving AHSCT for MM, they did show that older patients had more frequent hospitalizations.

Also in contrast to our study's findings, there has been a recent study by Mori et al. [27] demonstrating decreased ES risk with pretransplant bortezomib therapy. This discrepancy could possibly be related to varying immunomodulatory effects from bortezomib in different patient populations. Also, our study did not differentiate as to whether patients received AHSCT after primary induction or in the relapsed/refractory MM setting. As bortezomib is frequently used in both settings for the treatment of MM, there might have been heavier pretreatment with bortezomib in the non-ES versus ES groups, which we did not document and would affect the interpretation of our results. Prior studies have shown that higher cumulative bortezomib doses improve long-term MM outcomes, which suggests that higher cumulative bortezomib dose could lead to long-term effects on the bone marrow microenvironment and could affect development of ES [28]. Larger studies with a more uniform, proteasome inhibitor-based induction therapy regimen could help elucidate these differences.

Another limitation of our study is that most centers no longer use GM-CSF to assist in count recovery post-AHSCT. GM-CSF was used predominantly between November 2011 and September 2014 because it was available at lower cost, although the cost savings might be negated by increased morbidity and hospitalization days related to higher rates of ES. There was also a significant difference in the CD34 cell dose between the two groups by 1.1×10^6 cells. This is likely caused by the greater proportion of patients in the GM-CSF group receiving plerixafor. Plerixafor is a potent immunostimulatory agent and was used preferentially to reduce the number of collections. There is also the possibility that our use of peripheral stem cell over bone marrow stem cell collection could increase the risk of ES, as described by Edenfield et al. [8], although use of bone marrow as the source of stem cells is now rarely done in the autologous setting. Our study also did not demonstrate any effect of CD34 cell dose on the incidence of ES, in contrast to prior studies [2,8,9]. However, these studies included varying indications for AHSCT such as for solid malignancies (breast cancer), as well as varying conditioning regimens such as carmustine, etoposide, cytarabine, and melphalan. Finally, the retrospective design of the study, along with lack of disease status and prior radiotherapy documentation, could lead to potential confounding and affect our findings.

Our study demonstrates that use of post-transplant growth factors such as GM-CSF may increase the risk of ES in patients with myeloma undergoing AHSCT and that development of ES is associated with a longer hospital LOS. Other factors that were associated with increased LOS included older age, whereas use of pretransplant immunomodulators, pretransplant cyclophosphamide, and plerixafor mobilization was associated with a reduced LOS. We also demonstrated an increased risk of ES with pretransplant bortezomib and a decreased risk with pretransplant cyclophosphamide. A recent study by Singh et al. [29] assessed the effects of early versus protocol-driven post-transplant G-CSF use on outcomes in AHSCT patients and found that there was an increased incidence of neutropenic fevers with ANC-driven G-CSF use but no difference in hospital LOS or survival. This suggests that unnecessary growth factor use can lead to preventable costs related to the medication itself and complications such as ES. To investigate this further, our institution is prospectively studying whether G-CSF is needed at all post-AHSCT and whether protocol-driven G-CSF use can reduce engraftment syndrome risk.

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