Biol Blood Marrow Transplant 19 (2013) 1368–1373

Divergent Effects of Novel Immunomodulatory Agents and Cyclophosphamide on the Risk of Engraftment Syndrome after Autologous Peripheral Blood Stem Cell Transplantation for Multiple Myeloma

Robert Frank Cornell [1,2], Parameswaran Hari [1,2], Mei-Jie Zhang [3], Xiabao Zhong [3], Jonathan Thompson [1], Timothy S. Fenske [1,2], Mary M. Horowitz [1,2], Richard Komorowski [4], Jeanne Palmer [1,2], Marcelo C. Pasquini [1,2], J. Douglas Rizzo [1,2], Wael Saber [1,2], Mathew Thomas [1], William R. Drobyski [1,2,*]

[1] *Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[2] *Bone Marrow Transplant Program, Medical College of Wisconsin, Milwaukee, Wisconsin*
[3] *Department of Biostatistics, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin*

Article history:
Received 2 May 2013
Accepted 18 June 2013

Key Words:
Autologous graft-versus-host disease
Engraftment syndrome
Multiple myeloma
Autologous peripheral stem cell transplantation

A B S T R A C T

Engraftment syndrome (ES) is an increasingly observed and occasionally fatal complication after autologous peripheral blood stem cell transplantation (PBSCT). In this study, we demonstrate that the incidence of ES is significantly increased in patients undergoing autologous PBSCT for multiple myeloma in comparison to patients with non-Hodgkin lymphoma or Hodgkin lymphoma. Multivariate analysis revealed that age > 60 (hazard ratio [HR], 1.71; 95% confidence interval [CI], 1.12 to 2.62; $P = .013$) and transplantation for multiple myeloma (HR, 2.80; 95% CI, 1.60 to 4.90; $P = .0003$) were associated with an increased risk of this complication. When stratified for myeloma patients only, age > 60 (HR, 1.80; 95% CI, 1.13 to 2.87; $P = .013$) and prior treatment with both lenalidomide and bortezomib (HR, 1.83; 95% CI, 1.11 to 3.04; $P = .0001$) were associated with an increased incidence of ES. Conversely, lack of exposure to cyclophosphamide from either chemomobilization or as a component of the pretransplantation therapeutic regimen increased the risk of this complication (HR, 3.05; 95% CI, 1.91 to 4.87; $P < .0001$). These studies demonstrate that the pretransplantation exposure of multiple myeloma patients to novel immunomodulatory agents and cyclophosphamide significantly affects the subsequent risk of developing ES.

INTRODUCTION

Autologous peripheral blood stem cell transplantation (PBSCT) remains a cornerstone of the therapeutic armamentarium for patients with multiple myeloma (MM) and lymphoma [1,2]. Treatment-related mortality and morbidity after autologous PBSCT are typically low because of rapid reconstitution of immunity and hematopoietic function [3]. Some patients, however, develop an engraftment syndrome (ES), commonly characterized by fever, skin rash, and diarrhea and, less frequently, by hepatic dysfunction, transient encephalopathy, and a capillary leak syndrome [4-7]. Although the syndrome is mild and self-limited in most patients, a subset can develop serious complications [8,9], often characterized by inflammation in the gastrointestinal tract [10-13], which can be fatal [12,14,15]. Recent evidence indicates that this complication is increasing in recipients of autologous PBSCT [4,16], although the precise explanation for this increased incidence and why it may be higher in patients with MM [12] has remained elusive. In this study, we reviewed 591 consecutive autologous PBSCTs for MM, non-Hodgkin lymphoma, or Hodgkin lymphoma between 2001 and 2010 to define risk factors for the development of ES.

MATERIAL AND METHODS

Patients

The clinical records of 591 consecutive autologous PBSCTs for treatment of MM, non-Hodgkin lymphoma, or Hodgkin lymphoma at the Medical College of Wisconsin between 2001 and 2010 were reviewed to determine the incidence of ES. The patient demographics, disease characteristics, stem cell mobilization therapy, and treatments administered to patients before and at the time of transplantation are shown in Table 1. The PBSC mobilization method was evaluable in all 591 transplantations. Patients were mobilized by filgrastim (16 mcg/kg) alone in 26% (n = 155); filgrastim and plerixafor (.24 mg/kg) in 5% (n = 27); filgrastim (10 mcg/kg) and chemotherapy in 65% (n = 386); filgrastim (16 mcg/kg) and sargramostim (granulocyte-macrophage colony stimulating factor) (500 mcg/m^2) in 3% (n = 15); and filgrastim, chemotherapy, and plerixafor in 1% (n = 8). All patients received postgrafting treatment with either filgrastim (n = 560, 95%) or pegylated filgrastim (n = 31, 5%) to accelerate myeloid engraftment. Patients were maintained on antimicrobial prophylaxis with fluconazole and acyclovir. Ciprofloxacin was begun prophylactically when patients became neutropenic. Patients were diagnosed with ES using minor modifications of previously published criteria [7,8]. Specifically, patients were deemed to have ES when presenting with a noninfectious fever and 1 other symptom (ie, diarrhea, skin rash, pulmonary infiltrates, and hepatic dysfunction), or a combination of rash, diarrhea, and pulmonary infiltrates during the peri-engraftment period, which was defined as up to 3 days prior and 10 days after the day of engraftment. A noninfectious fever was defined as a temperature > 100.4°F (38°C) without microbiological culture positive infection and no documented response to antibiotic administration. Diarrhea was considered 2 or more episodes of liquid defecations per day

Financial disclosure: See Acknowledgments on page 1372.

* Correspondence and reprint requests: William R. Drobyski, MD, Bone Marrow Transplant Program, 8701 Watertown Plank Road, Milwaukee, WI 53226.
E-mail address: wdrobysk@mcw.edu (W.R. Drobyski).

1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.06.017

Table 1
Patient and Treatment Characteristics of Patients with and without ES

	ES	No ES	*P* Value
Number of transplantations	131	460	
Age at transplantation, median (range), yr	61 (26 to 77)	56 (18 to 79)	.002
18 to 50	22 (17)	135 (29)	
50 to 60	33 (25)	156 (34)	
60 to 70	61 (47)	125 (27)	
70 to 80	15 (11)	44 (10)	
Gender			.36
Male	75 (57)	285 (62)	
Female	56 (43)	175 (38)	
Year of transplantation			<.001
2001 to 2005	19 (15)	150 (33)	
2006 to 2010	112 (85)	310 (67)	
Multiple myeloma	114 (87)	307 (67)	<.001
Non-Hodgkin lymphoma	14 (11)	102 (22)	.003
Hodgkin lymphoma	3 (2)	51 (11)	.001
Conditioning regimen[*]			<.001
BEAM	11 (8)	147 (32)	
Melphalan alone	114 (87)	304 (66)	
Others	6 (5)	9 (2)	
Outpatient transplantations	9 (7)	24 (5)	.52
Disease status before transplantation[†]			<.001
CR	30 (23)	130 (28)	
PR	77 (59)	171 (37)	
SD	4 (3)	16 (3)	
Prog/rel	15 (11)	121 (27)	
Missing	5 (4)	22 (5)	
Lines of therapy before PBSCT			.70
1	54 (41)	198 (43)	
2	40 (31)	159 (35)	
>2	37 (28)	103 (22)	
Growth factor support after transplantation[‡]			
Filgrastim	123 (94)	431 (95)	.65
Pegylated filgrastim	8 (6)	23 (5)	.66
No. $CD34^+$ cells $\times 10^6$/kg, median (range)	5.0 (2 to 30)	4.0 (2 to 34)	.05
Myeloma pre-PBSCT chemotherapy[§]			
Lenalidomide-based	52 (40)	75 (16)	<.001
Bortezomib-based	79 (60)	145 (32)	<.001
Thalidomide-based	28 (21)	90 (20)	.71
Lenalidomide + bortezomib	41 (30)	55 (12)	<.001
Cytotoxic chemotherapy	29 (25)	106 (35)	.06
Cyclophosphamide exposure (chemotherapy and/or mobilization)	62 (51)	237 (78)	<.001
Mobilization method			
Cytokine-based[‖]	69 (53)	129 (28)	<.001
Chemotherapy-based[¶]	63 (47)	341 (72)	<.001
Time from transplantation to discharge, median (range), d	17 (13 to 157)	15 (7 to 42)	<.001
Time to ANC > 500 x 10^9/L, median (range), d	12 (10 to 29)	12 (7 to 40)	.52
Time to plts > 20 x 10^9/L, median (range), d	22 (7 to 82)	21 (7 to 395)	.15

Data are presented as n (%) unless otherwise indicated.
ES indicates engraftment syndrome; CR, complete remission; PR, partial remission; SD, stable disease; Prog/Rel, progressive disease/relapse; ANC, absolute neutrophil count; plts, platelets.

[*] Conditioning regimens: Mel (melphalan 200 mg/m^2); BEAM (carmustine 300 mg/m^2, cytarabine 400 mg/m^2, etoposide 200 mg/m^2, melphalan 140 mg/m^2), Others (ES): Cyclophosphamide + TBI (n = 2), TBI + Etoposide (n = 1), unspecified (n = 3); (No ES): Cyclophosphamide + TBI (n = 1), Busulfan + Cyclophosphamide (n = 1), Cyclophosphamide + Cisplatin (n = 1), Cyclophosphamide + TBI + Etoposide (n = 3), TBI (n = 1), unspecified (n = 2).

[†] Disease status before ASCT was defined according to the international working group criteria for MM and lymphoma [28,29].

[‡] Growth factor support post-transplantation was with either filgrastim at a dose of 5 mcg/kg beginning day +5 or pegylated filgrastim at a dose of 6 mg starting on day +1.

[§] Total of numbers in parentheses for each cohort exceed 100% because some patients received therapeutic regimens that contained multiple agents.

[‖] Cytokine-based mobilization consisted of regimens that employed the following agents: filgrastim (16 mcg/kg), plerixafor (.24 mg/kg), and sargramostim (500 mcg/m^2).

[¶] Chemotherapy-based mobilization was with cyclophosphamide plus filgrastim, or cyclophosphamide plus filgrastim and plerixafor.

without evidence of infectious etiology. Skin rash was defined as maculopapular exanthema covering > 25% of the body surface area and not due to a drug reaction or underlying infection. Pulmonary infiltrates were confirmed by chest x-ray or computed tomography scans of the chest and not secondary to infectious or cardiopulmonary etiologies. Transient encephalopathy was defined as confusion not secondary to any other etiology. Hepatic dysfunction was defined as a total bilirubin ≥ 2 mg/dL or transaminase levels ≥ 2 times the upper limit of normal. The day of neutrophil engraftment was denoted as the first of 3 consecutive days with an absolute neutrophil count > 0.5 x 10^9/L. This retrospective cohort study was approved by the institutional review board of the Medical College of Wisconsin.

Statistical Analysis

Patient-related factors were compared between patients with and without ES using the Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. Forty-three patients received a second autologous PBSCT, and 1 patient underwent 3 transplantations. Therefore, a total of 591 observations occurred from 547 patients to identify risk factors associated with developing ES. A random effect logistical regression model was used to adjust for repeated measures. The variables considered in the regression model building were age, gender, diagnosis, pretransplantation mobilization method, pretransplantation disease status, pretransplantation induction chemotherapy, including novel agents, cyclophosphamide and other cytotoxic chemotherapy, posttransplantation