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Extracorporeal Photopheresis versus Anticytokine Therapy as a Second-Line Treatment for Steroid-Refractory Acute GVHD: A Multicenter Comparative Analysis

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Article history:
Received 28 February 2013
Accepted 18 April 2013

Key Words:
Acute graft-versus-host disease
Steroid-refractory
Extracorporeal photopheresis
Allogeneic hematopoietic cell transplantation

A B S T R A C T

The optimal therapy for steroid-refractory (SR) acute graft-versus-host disease (aGVHD) is undefined. We studied patients with SR aGVHD, comparing extracorporeal photopheresis (ECP; n = 57) and anticytokine therapy (n = 41). In multivariate analyses, ECP, adjusted for steroid dose (odds ratio, 3.42; $P = .007$), and grade >II aGVHD (odds ratio, 68; $P < .001$) were independent predictors of response. ECP therapy, adjusted for conditioning regimen intensity and steroid dose, was associated with superior survival (hazard ratio [HR], 4.6; $P = .016$) in patients with SR grade II aGVHD. Grade >II aGVHD at onset of salvage therapy (HR, 9.4; $P < .001$) and lack of response to therapy (HR, 3.09; $P = .011$) were associated with inferior survival. These findings require validation in a prospective randomized study.

INTRODUCTION

Graft-versus-host disease (GVHD) remains an important complication of allogeneic stem cell transplantation (allo-SCT). Despite prophylaxis, International Bone Marrow Transplantation Registry severity index grade B-D acute GVHD (aGVHD) occurs in 39%-59% of patients undergoing T cell–replete related or unrelated donor allo-SCT [1]. Corticosteroids are the cornerstone of initial therapy for ≥grade II or grade B-D aGVHD [2-4], leading to complete response (CR) in 25%-69% of patients [5,6]. Patients not responding to steroids have a dismal prognosis, with poor survival [2,7].

Numerous agents for treating steroid-refractory (SR) aGVHD have been studied [7,8]. The French group published its experience in a cohort of 93 patients with SR aGVHD using either inolimumab or etanercept [9]. Single-center studies have suggested extracorporeal photopheresis (ECP) using UV-A irradiation of peripheral blood mononuclear cells after incubation with 8-methoxypsoralen as effective treatment for SR aGVHD [10-12]. The outcomes of ECP and anticytokine therapy have not been compared previously. In the present study, we performed a retrospective comparison of the efficacy of second-line therapy in 98 patients treated with either ECP (n = 57) or anticytokine therapy (n = 41).

METHODS

Consecutive patients undergoing allo-SCT after January 2005 and developing grade ≥II (according to modified Glucksberg criteria [13]) SR aGVHD (defined as progression after 3 days or no response after 7 days of initial therapy) and treated with ECP (Nashville, Tennessee, USA, n = 13; Nottingham, UK, n = 19; Vienna, Austria, n = 25) or with anticytokine therapy (Paris, France, n = 41) were included. Other inclusion criteria were corticosteroids at a dose of least ≥1 mg/kg/day alone as first-line therapy for aGVHD with continuation of calcineurin inhibitors. Anticytokine therapy consisted of inolimumab or etanercept (after 2003). Given that the ECP cohort was recruited after 2005, only a subset of patients from the French dataset (41 patients with SR aGVHD treated with inolimumab or etanercept after 2005) was included in the non-ECP group [9]. ECP was initiated at a frequency of 2-3 treatments per week on a weekly or biweekly basis. ECP therapy was stopped after maximal response was achieved (Austria and UK) or was tapered gradually (Tennessee, USA).

Response was defined as CR (disappearance of signs of GVHD from all organs involved), partial response (PR; any improvement in GVHD), or progressive disease (no response or worsening of GVHD in at least 1 organ). The use of additional immunosuppressive agents after ECP or anticytokine therapy for controlling aGVHD was considered progressive disease. Response was assessed at 4 weeks after anticytokine therapy or at the end of ECP (a median of 45 days after the start of ECP). Given the variability of response assessment and retrospective nature of the analyses, the primary focus of this analysis was overall survival (OS).

Descriptive statistics were calculated and groups were compared using the chi-squared test (nominal) and Wilcoxon rank-sum test (continuous) respectively. Two-proportion tests were used to compare stage of GVHD before and after therapy. OS was measured from the initiation of ECP or anticytokine therapy using Kaplan-Meier survival curves and compared

† M.J., H.G., E.D.-G., and G.S. contributed equally to this work.

Preliminary data from this study were presented at the Annual Meeting of the European Group for Blood and Marrow Transplantation in Geneva, Switzerland, April 1-4, 2012.

Financial disclosure: See Acknowledgments on page 1132.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.04.018

Table 1
Pretransplantation, aGVHD, and Outcome Characteristics, Univariate Analysis

Characteristic	Demographic Data, n (%)			Overall Response (CR+PR) to Therapy, n (%)				OS, Months, Median (95% CI)			
	ECP (n = 57)	Anticytokine (n = 41)	*P**	All Patients	ECP	Anticytokine	*P**	All Patients	ECP	Anticytokine	*P**
Age, yrs, median (range)	57 (16-67)	41 (5-64)	NS	—	—	—		—	—	—	
Recipient sex											
Male	34 (60)	25 (61)	NS	30 (51)	24 (71)	6 (24)	<.001	8.7 (0-43.5)	NR	3.6 (1.7-5.4)	.015
Female	23 (40)	16 (39)		21 (54)	14 (61)	7 (44)	NS	11.3 (0-36.2)	NR	5.6 (3.5-7.7)	.005
Donor type											
Related	12 (21)	9 (22)	NS	12 (57)	8 (67)	4 (44)	NS	9.8 (0-20.9)	NR	9.8 (0-27.1)	NS
Unrelated	45 (79)	32 (78)		39 (51)	30 (67)	9 (28)	.001	11.1 (0-42.9)	NR	3.9 (1.5-6.3)	<.001
Stem cell source											
Bone marrow	6 (11)	7 (17)	NS	8 (62)	4 (67)	4 (57)	NS	NR	NR	9.8 (0-22.3)	NS
Peripheral blood	48 (84)	28 (68)		38 (50)	32 (67)	6 (21)	NS	8.7 (0-29.9)	NR	3.6 (0.5-6.6)	<.001
Umbilical cord	3 (5)	6 (15)		5 (56)	2 (67)	3 (50)	NS	11.1 (0-32.2)	NR	3.8 (0-13.9)	NS
Regimen intensity[†]											
Ablative	32 (68)	20 (49)	NS	32[ε] (62)	26[ζ] (81)	6 (30)	.001	NR[ω]	NR	3.1 (0-9.7)	<.001
Reduced-intensity/nonmyeloablative	15 (32)	21 (51)		13[ε] (37)	7[ζ] (47)	6 (30)	NS	3.9[ω] (1.2-6.6)	1.9 (0-7.1)	3.9 (0.5-7.4)	NS
HLA match											
10/10	47 (83)	31 (76)	NS	40 (51)	31 (66)	9 (29)	.02	9.8 (0-24.2)	NR	4.9 (2.6-7.2)	.004
Other	10 (17)	10 (24)		11 (55)	7 (70)	4 (40)	NS	28.4 (0-37.5)	NR	3.8 (0-9.7)	.011
In vivo T cell depletion											
None	44 (77)	37 (90)	.028	42 (52)	30 (68)	12 (32)	.01	10.8 (0-34)	NR	4.9 (2.7-7.2)	<.001
Antithymocyte globulin/alemtuzumab	13 (23)	4 (10)		9 (53)	8 (62)	1 (25)	NS	20 (0-37)	NR	1.5 (0-10.6)	NS
Donor lymphocyte infusion–induced aGVHD	10 (18)	-	.005	5 (50)	-	-	-	NR	-	-	
aGVHD grade/stage at onset of salvage therapy											
Skin											
≤Stage 2	43 (75)	21 (51)	.013	38[η] (59)	30 (70)	8 (38)	.015	41.4 (3.1-79.7)	NR	5.4 (0-11)	.007
Stage 3-4	14 (25)	20 (49)		13[η] (38)	8 (57)	5 (25)	.05	8.4 (0-16.9)	NR	3.9 (2-5.8)	.019
Gastrointestinal											
≤Stage 2	31 (54)	26 (63)	NS	34 (60)	24 (77)	10 (39)	.03	20 (0-46)	NR	8.4[ς] (1.6-15.1)	.028
Stage 3-4	26 (46)	15 (37)		17 (42)	14 (54)	3 (20)	.034	3 (0-11.6)	NR	1.5[ς] (0.8-2.1)	.001
Liver											
≤Stage 2	43 (75)	40 (98)	.003	44 (53)	31 (72)	13 (33)	<.001	10.8 (0-38.6)	NR	4.9[μ] (2.8-7)	<.001
Stage 3-4	14 (25)	1 (2)		7 (47)	7 (50)	0	NS	20 (0-47)	20 (4.2-35.7)	0.1[μ] (–)	<.001
Overall grade											
≤Grade II	41 (72)	15 (37)	.001	48[λ] (86)	37[θ] (90)	11[ξ] (73)	NS	NR[ϵ]	NR[ϑ]	11.3[¶] (10.4-12.2)	.001
Grade 3-4	16 (28)	26 (63)		3[λ] (7)	1[θ] (6)	2[ξ] (8)	NS	1.5[ϵ] (0.9-2)	0.9[ϑ] (0.7-1.1)	1.9[¶] (0.2-3.6)	NS
Number of organs involved											
<3	44 (77)	39 (95)	.015	45 (54)	32 (73)	13 (33)	<.001	11.3 (0-42.5)	NR[γ]	5.4[δ] (2.9-7.9)	<.001
3	13 (23)	2 (5)		6 (40)	6 (46)	0	NS	3.6 (0-12.3)	8.7[γ] (0-29.9)	0.8[δ] (–)	NS
Steroid dose at salvage											
1 mg/kg	12 (21)	0	.02	10[π] (83)	-	-		NR	-	-	
≥2 mg/kg	45 (79)	41 (100)		40[π] (47)	27 (61)	13 (32)	.006	9.8 (4.3-15.2)	NR	4.9 (2.8-7.1)	.001
Duration of steroid use before salvage therapy, days, mean (range)	19.3 (4-82)	19.6 (2-60)		-	-	-		-	-	-	
Response status											
No response	-	-	-	47 (48)	19 (34)	28 (68)	.001	1.7[∈] (1.1-2.3)	1.1[ζζ] (0.4-1.7)	2.7[ππ] (0.3-5)	NS
Overall response (CR+PR)	-	-	-	51 (52)	38 (66)	13 (32)		NR[∈]	NR[ζζ]	12.7[ππ] (3.4-53.4)	.011
CR	-	-	-	39 (40)	31 (54)	8 (20)	.001	NR	NR	28.4 (1.5-55.2)	NS
PR	-	-	-	12 (12)	7 (12)	5 (12)	NS	41.4 (0-85.3)	41.4 (0-97.5)	5.6 (0-11.9)	NS

Survival										
Dead	23 (40)	31 (76)	.001	14[ψ] (26)	8[χ] (35)	6[ψ] (19)	NS	-	-	
Alive	34 (60)	10 (24)		37[ψ] (84)	30[χ] (88)	7[ψ] (70)	NS	-	-	
Survival, months, median (95% CI)	-	-		-	-	-		11.1 (0-37.5)	NR	4.9 (2.8-7.1) <.001
2-year survival, %	-	-		-	-	-		45	59	12
Cause of death										
GVHD	16 (70)	25 (81)	NS	-	-	-		-	-	-
Infection	4 (18)	6 (19)	NS	-	-	-		-	-	-
Other	1 (4)	0	NS	-	-	-		-	-	-
Disease relapse	2 (8)	0	NS	-	-	-		-	-	-

NS indicates not significant; NR, not reached.
P values for overall response within ECP and anticytokine subsets: [ζ]$P = .026$; [ξ]$P = .016$; [η]$P = .046$; [λ]$P < .001$; [θ]$P < .001$; ξ$P < .001$; [π]$P = .019$; [φ]$P < .001$; [χ]$P < .001$; [ψ]$P < .001$.
P values for OS within ECP and anticytokine subsets: [φ]$P = .001$; [ξ]$P = .008$; [μ]$P < .001$; [ζ]$P < .001$; [3]$P < .001$; [¶]$P < .001$; [γ]$P = .015$; [δ]$P = .011$; [€]$P < .001$; [ζζ]$P < .001$; [ππ]$P < .001$.
[*] *P* values comparing the ECP group with the anticytokine group.
[†] Post–donor lymphocyte infusion cases excluded (ECP, n = 47; non-ECP, n = 41).

using the log-rank test [14]. Multivariate analyses were performed using logistic regression or Cox proportional hazards regression. All statistical analyses were conducted using SPSS version 19 (IBM, Armonk, NY) or R version 2.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Table 1 provides the details on clinical and aGVHD characteristics and transplantation outcomes. The anticytokine therapy group had a higher proportion of patients receiving T cell–replete allo-SCT (90% versus 77%; $P = .028$), stage 3-4 skin aGVHD (49% versus 25%; $P = .013$), grade III-IV aGVHD (63% versus 28%; $P = .001$), and use of steroids at a dose $\geq$2 mg/kg (100% versus 79%; $P = .02$). The ECP group had a higher proportion of patients with stage 3-4 liver aGVHD (25% versus 2%; $P = .003$), and a higher proportion of patients with involvement of at least 3 organs (23% versus 5%; $P = .015$). All 10 patients with donor lymphocyte infusion–induced aGVHD were in the ECP group. ECP or anticytokine therapy was initiated at a median of 45 days (range, 8 to 99 days) after allo-SCT or donor lymphocyte infusion and after a median of 19 days (range, 2 to 82 days) of systemic corticosteroids for initial therapy for aGVHD. The median number of ECP treatments was 12 (range, 2 to 45) over a median duration of 45 days (range, 14 to 293 days).

Both overall response (CR+PR) and CR were significantly higher in the ECP group compared with the anticytokine group (66% versus 32%, $P = .001$; 54% versus 20%, $P = .001$). Figure 1 outlines patient responses to ECP and anticytokine therapy stratified by stage 3-4 organ involvement, grade III-IV aGVHD, and number of organs involved. Univariate analyses associated with response and survival are detailed in Table 1 for both groups, and Figure 2 presents a survival plot. In multivariate analyses, ECP, adjusted for steroid dose (1 mg/kg versus >1 mg/kg), was an independent predictor of response (odds ratio [OR], 3.42; 95% confidence interval [CI], 1.39-8.37; $P = .007$), as was grade of aGVHD (II versus >II), adjusted for ECP or anticytokine therapy and conditioning regimen intensity (OR, 68; 95% CI, 16-290; $P < .001$).

The median duration of follow-up of surviving patients after therapy was 30.2 months (range, 2.1 to 78 months; 37.9 months for the ECP group versus 17 months for the anticytokine group; $P < .001$), and the 2-year OS for all patients was 45.2%. In multivariate analysis, ECP therapy, adjusted for conditioning regimen intensity and steroid dose, was an independent predictor of superior survival (hazard ratio [HR], 2.12; 95% CI, 1.13-3.96; $P = .018$). Furthermore, ECP therapy, adjusted for conditioning regimen intensity and steroid dose, was associated with superior survival (HR, 4.6; 95% CI, 1.33-16.3; $P = .016$) in patients with SR grade II aGVHD. Grade >II aGVHD at the onset of salvage therapy (HR, 9.4; 95% CI, 4.73-18.8; $P < .001$) and lack of response to therapy (HR, 3.09; 95% CI, 1.2-7.4; $P = .011$), adjusted for conditioning regimen intensity and type of GVHD therapy, were associated with inferior survival.

In multivariate analyses, ECP therapy, adjusted for steroid dose, was associated with significantly lower nonrelapse mortality (NRM) (HR, 0.45; 95% CI, 0.23-0.87; $P = .018$). Grade >II aGVHD at onset of salvage therapy, adjusted for conditioning regimen intensity, type of GVHD therapy, and response to GVHD therapy (HR, 7.4; 95% CI, 2.6-21.2; $P < .001$), was associated with a higher NRM.

DISCUSSION

Acute GVHD is a complex interplay of donor T cells and host antigen-presenting cells and B cells. ECP has an

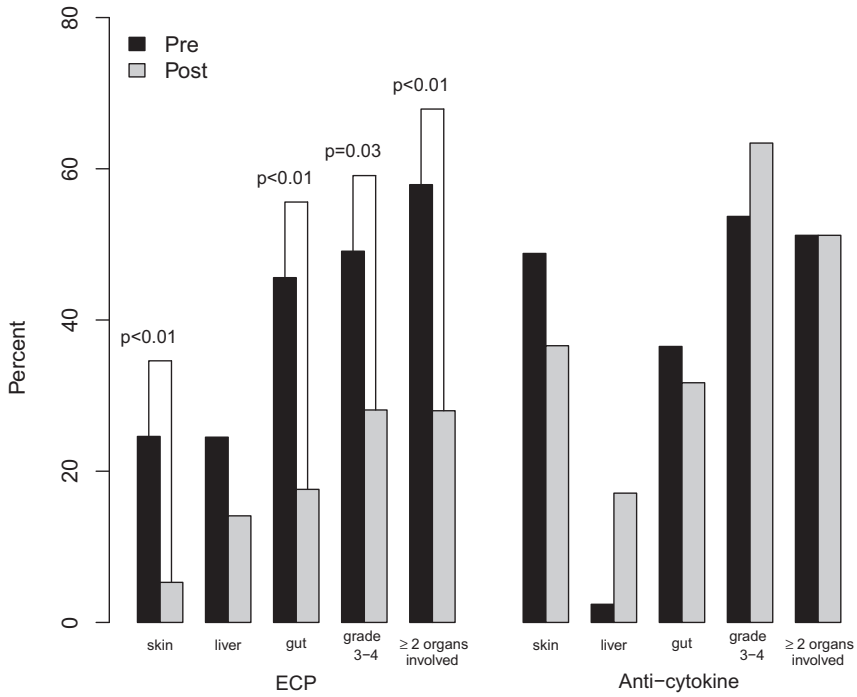

Figure 1. aGVHD before and after therapy in the ECP and anticytokine groups. Organ-specific involvement reflects stage III-IV aGVHD. *P* values reflect comparison of aGVHD incidence before and after therapy. Categories without *P* values were statistically nonsignificant.

immunomodulatory effect, possibly mediated by T regulatory cells, leading to decreased proinflammatory and increased anti-inflammatory cytokine production [15,16]. Our analysis suggests a significantly higher efficacy of ECP compared with anticytokine treatment directed at either IL-2R or TNF-α pathways in patients with SR grade II aGVHD, along with a significant survival advantage for patients receiving ECP.

This study has some limitations. First, the proportions of patients with grade III-IV aGVHD and those receiving 2 mg/kg steroids at onset of aGVHD were higher in the anticytokine therapy group compared with the ECP group. To account for this potential bias, all multivariate analyses were adjusted for steroid dose. Although 1 study reported that steroid dose might not influence the outcome of aGVHD, comparing 1 mg/kg and 2 mg/kg[3], the investigators did not specifically evaluate the outcome of SR patients given the 1 mg/kg dose. The impact of ECP on survival and NRM was most apparent in SR grade II aGVHD.

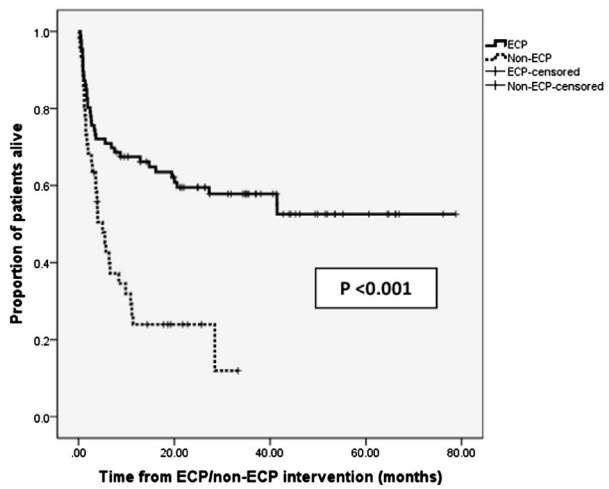

Figure 2. Overall survival (OS) stratified by treatment group. Survival is measured from onset of ECP or non-ECP intervention.

Other limitations of the present study are a lack of homogenous steroid tapering and ECP scheduling, and the potential differences in response assessment at the various centers. Although the timing of response assessment was variable in the 2 patient cohorts, optimal timing of response assessment for aGVHD therapy remains unclear, with recent data suggesting day 28 response or a 6-month freedom of failure from intervention as potential endpoints [17,18].

The optimal timing of intervention, frequency, duration, and tapering schedule of ECP in SR aGVHD remain important unanswered questions. ECP probably should be considered early in the course of SR aGVHD, before significant irreversible end organ damage has been established. The ability of ECP to spare steroids remains uncertain, but if validated could decrease steroid-induced complications, both acute and long-term. In the present study, the median duration of ECP was 50 days, suggesting that a prolonged course of ECP might not be necessary. This comprehensive multicenter analysis suggests that ECP could be an effective second-line regimen for SR aGVHD, offering a potential survival advantage. Given the limitations of this study, these observations remain to be validated in a well-designed risk-stratified multicenter prospective randomized study.

ACKNOWLEDGMENTS

The authors thank Carey Clifton, ACNP, Leigh Ann Vaughan, ACNP, Catherine Lucid, ACNP, and Karen Proctor, RN, of Vanderbilt University Medical Center.

Authorship statement: M.J., H.G., E.D.-G., and G. S. designed the study, analyzed the data, and wrote the manuscript. M.R. contributed to the data, reviewed and provided critical input during manuscript preparation. R.J. collected data at Vanderbilt University and reviewed the manuscript. B.S, B.E., A.K.,

R.K., and N.R. reviewed the manuscript and provided critical input. N.W. collected data at Medical University of Vienna, reviewed the manuscript, and provided critical input.

Financial disclosure: H.G. and G.S. have served as speakers at scientific meetings on behalf of Therakos Inc. The other authors have nothing to disclose.

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Salvage Bone Marrow Harvest in Patients Failing Plerixafor-Based Stem Cell Mobilization Attempt: Feasibility and Autologous Transplantation Outcomes

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Article history:
Received 22 April 2013
Accepted 22 April 2013

Inadequate mobilization of peripheral blood progenitor cells (PBPC) is sometimes a limiting factor to proceed with an autologous hematopoietic cell transplantation (auto-HCT), in an otherwise eligible patient. In such situations, a bone marrow harvest (BMH) procedure may be considered to achieve the CD34+ target dose for an autograft. Plerixafor-based mobilization has recently been shown to improve PBPC collection yields. However, the feasibility and outcomes of BMH in patients failing plerixafor-based mobilization is not known. We report here, 6 patients who underwent BMH after PBPC mobilization failure with plerixafor. The median CD34+ yield with plerixafor mobilization and BMH were 1.15 x 10^6/Kg (range, 0.2-1.7 × 10^6/Kg) and 0.32 (range, 0.12-0.38 × 10^6/Kg), respectively. Three patients proceeded to an auto-HCT, with only 1 patient receiving CD34+ cell dose of at least 2 × 10^6/Kg. While neutrophil recovery was seen, platelet recovery and red cell transfusion independence were delayed. All 3 autografted patients experienced disease progression by day +100. These data suggest, limited incremental benefit of a salvage BMH after plerixafor mobilization failure, cautioning against routine use of this strategy.

Peripheral blood stem and progenitor cell (PBPC) mobilization failure frequently prevents patients with hematological malignancies from undergoing a planned autologous hematopoietic cell transplantation (auto-HCT) procedure [1]. The combination of plerixafor and granulocyte colony-stimulating factor (G-CSF) has been shown to improve PBPC collection yield and potentially reduce mobilization failure rates in non-Hodgkin lymphoma and multiple myeloma compared with mobilization with G-CSF alone [2,3]. Limited data also suggest safety and feasibility of plerixafor salvage in patients who appear to be failing chemotherapy-based mobilization [4,5].

Financial disclosure: See Acknowledgments on page 1135.

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1083-8791/$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2013.04.019