European Journal of Haematology ISSN 0902-4441

ORIGINAL ARTICLE

Peripheral blood stem cell transplant for POEMS syndrome is associated with high rates of engraftment syndrome

Angela Dispenzieri[1], Martha Q. Lacy[1], Suzanne R. Hayman[1], Shaji K. Kumar[1], Francis Buadi[1], David Dingli[1], Mark R. Litzow[1], Dennis A. Gastineau[1], David J. Inwards[1], Michelle A. Elliott[1], Ivana N. Micallef[1], Stephen M. Ansell[1], William J. Hogan[1], Luis F. Porrata[1], Patrick A. Johnston[1], Bekele Afessa[2], Alan Bryce[1], Robert A. Kyle[1], Morie A. Gertz[1]

[1]Division of Hematology, [2]Division of Pulmonary and Critical Care Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA

Abstract

Polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (POEMS) syndrome is a devastating syndrome, characterized by peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma cells, skin changes, papilledema, volume overload, sclerotic bone lesions, thrombocytosis and high vascular endothelial growth factor (VEGF). High-dose chemotherapy with autologous peripheral blood stem cell transplantation (ASCT) ultimately yields excellent clinical responses, but there can be considerable peritransplant morbidity. We have treated 30 POEMS patients with ASCT at Mayo Clinic, Rochester. During transplant period, patients had high rates of fever, diarrhea, weight gain and rash (93%, 77%, 53% and 43%, respectively). Only 13% remained outpatient, and median time to discharge from hospital was transplant day 17 (range 0–175). Splenomegaly was the baseline factor that best predicted for a complicated peritransplant course. Depending on the definition used, ~50% of patients satisfied criteria for engraftment syndrome. Earlier and more aggressive use of corticosteroids may be associated with less complicated post-transplant courses. Median overall survival has not been reached; the treatment-related mortality was 3%. In addition, important clinical improvements and reductions in plasma VEGF levels can occur in the absence of significant decrease in the monoclonal protein. Unraveling the mechanisms of the syndrome both in the context of ASCT and in general are challenges for the future.

Key words POEMS syndrome; monoclonal gammopathy; osteosclerotic myeloma; Castleman disease; transplantation; complications; cytokines

Correspondence Angela Dispenzieri, MD, Division of Hematology, Mayo Clinic, 200 First Street S.W., Rochester, MN 55905, USA. Tel: +1 507 284 2479; Fax: +1 507 266 4972; e-mail: dispenzieri.angela@mayo.edu

Accepted for publication 2 January 2008 doi:10.1111/j.1600-0609.2008.01037.x

Background

Polyneuropathy, organomegaly, endocrinopathy, M protein and skin changes (POEMS) syndrome, also known as osteosclerotic myeloma, Crow–Fukase syndrome or Takasuki syndrome, is an incompletely understood paraneoplastic syndrome resulting from an underlying plasmaproliferative disorder. Effective treatment of the underlying plasma cell disorder controls the disease and results in dramatic reversal of symptoms. Historically, irradiation of a solitary sclerotic plasmacytoma or low-dose alkylator along with steroids had been the mainstay of treatment (1), but in the past decade, the treatment repertoire has expanded to include high-dose melphalan with autologous peripheral blood stem cell transplant (ASCT), as well as novel myeloma therapies (thalidomide, lenalidomide) and anti-vascular endothelial growth factor (VEGF) antibodies (bevacizamib). To date ~31 cases of transplant for POEMS have been published (2–7), 16 of which have been from the Mayo Clinic (8). Consistently, authors have demonstrated that ASCT is effective therapy for these patients with improvement of the neuropathy, skin changes, pulmonary function tests,

VEGF levels, etc. However, we were impressed by the unexpected, excessive morbidity of the procedure in this cohort of patients. We have therefore updated our experience with ASCT in patients with POEMS syndrome with an emphasis on treatment-related morbidity.

Methods

Patients

Between March 1999 and August 2007, 30 patients with POEMS syndrome have undergone ASCT at Mayo Clinic, Rochester, 11 of them have been reported in part previously. Peripheral blood stem cells were collected using either cyclophosphamide and growth factor ($n = 5$) or growth factor alone ($n = 25$). The median number of CD34 cells infused was 4.46×10^6/kg (range 2.39–15.7). Ten patients were conditioned using melphalan 140 mg/m^2, 19 received melphalan 200 mg/m^2 (Table 1). One patient received carmustine, etoposide, cytarabine and melphalan. Half of the patients had scheduled sargramostim beginning on day +6 post-transplantation.

Standard supportive care with prophylactic antibiotics was provided to all patients. Data were retrospectively collected on patients with approval from the Mayo Clinic Institutional Review Board and in accordance with Minnesota state law. Charts were reviewed by AD.

Definitions

A diagnosis of POEMS syndrome is predicated on the following: (i) polyneuropathy; (ii) monoclonal plasma cell proliferative disorder; (iii) sclerotic bone lesions, elevations in VEGF, or Castleman disease and (iv) at least one of the other characteristic features (9).

Bacteremia was defined as a positive blood culture for any organism, except for coagulase-negative staphylococci, skin coryneforms and *Lactobacillus* species, for which at least two consecutive positive blood cultures were considered significant.

Two published definitions for engraftment syndrome (ES) were initially used. The first was that of Spitzer (10), who has developed major and minor criteria for the syndrome. The major criteria are: temperature >38.3°C with no identifiable infectious etiology; erythroderma involving more than 25% of body surface area and not attributable to a medication and non-cardiogenic pulmonary edema and hypoxia. The minor criteria are: hepatic dysfunction as characterized by a bilirubin >2 mg/dL or a doubling of the transaminases; a doubling of the serum creatinine; weight gain ≥2.5% over baseline body weight or transient encephalopathy. To be classified as ES, all three major criteria or two major and one minor criterion are required within 96 h of neutrophil engraftment [absolute neutrophil count (ANC) 0.5×10^9/L]. The second published definition for ES used was that by Maiolino *et al.* (11), which requires fever within 24 h of first appearance of neutrophil along with any of the following: cutaneous rash, pulmonary infiltrates or diarrhea. A third engraftment entity examined was the periengraftment respiratory distress syndrome (PERDS). This is

Table 1 Patient characteristics

	n	%	Median	Range
Age	30		48.5	20–70
Gender, M	20	67		
Race				
Caucasian	25	83		
African-American	2	7		
Hispanic	2	7		
Other	1	3		
ECOG PS 2/3	9/10	30/33		
Polyneuropathy	30	100		
Organomegaly	21	70		
Endocrinopathy	24	80		
Monoclonal PCD	30	100		
Skin involvement	24	80		
Extravascular volume overload	29	97		
VEGF elevated, $n = 16$	15	94		
Sclerotic bone lesions	27	90		
Castleman's disease	5	17		
Immunoglobulin heavy chain isotype				
IgA/IgG	18/7	60/23		
IgM/none	1/4	3/13		
DLCO	30		64.5	36–109
RSVP, mmH_2O	20		38	21–68
Prior regimens	25		2	0–6
Alkylator based	4	13		
Thalidomide or lenalidomide	4	13		
Corticosteroids	23	77		
Radiation therapy	5	17		
Intravenous gamma globulin	13	43		
Plasmapheresis	9	30		
Time to transplant from diagnosis, months	30		4	1–57
Time to transplant from symptoms, months	30		23.5	7–66
Year SCT				
2006–2007	11	37		
1999–2005	19	63		
Mobilization				
CTX/G	5	17		
G-alone	25	83		
Conditioning				
Mel200/BEAM	20	67		
Mel140	10	33		
CD34, $\times 10^6$	30		4.46	2.39–15.7
MNC, $\times 10^8$	30		6.86	1.21–21.6
Growth factor post-transplant	15	50		
Corticosteroid maintenance	13	43		

defined as fever >38.3°C and evidence of pulmonary injury in the form of hypoxia and/or pulmonary infiltrates on chest radiographs (CXRs) in the absence of clinical cardiac dysfunction that has to occur within 5 d of neutrophil engraftment (12).

Corticosteroid use was converted into daily 'prednisone equivalents'. Dexamethasone was considered to be sevenfold more potent than prednisone and cortisone one-fifth as potent as prednisone. Intravenous methylprednisolone was considered 1.2-fold more potent than oral prednisone.

Hematologic responses were defined according to the International Uniform Response Criteria (13). These criteria include a complete response as the disappearance of monoclonal protein in the serum and urine by immunofixation as well as fewer than 5% bone marrow plasmacytosis. A very good partial response (PR) was also included as a hematological response category, and included patients who no longer had a measurable monoclonal protein in the serum or urine, but were immunofixation positive (or did not have immunofixation performed to verify complete response). A PR includes a 50% reduction in the monoclonal protein in the serum and urine in the absence of any additional evidence of progressive myeloma.

Statistics

Endpoints for the analyses included: ES, need for intubation, corticosteroid bolus during transplant course and time to hospital discharge. Time to hospital discharge relative to peripheral blood stem cell transplantation (ASCT) was the preferred endpoint over duration of hospitalization because the latter was partially confounded by early hospitalization for disability related to neuropathy rather than treatment-related toxicity.

Demographic and baseline clinical and laboratory data between groups were compared using the Kruskal–Wallis test (14). Except where stated, continuous variables were treated as continuous variables. Fisher's exact test was used to test differences in categorical variables (15). The pretreatment characteristics used to test outcomes are those listed in patient characteristics (Table 1). For the purpose of outcomes' analyses, transplant-related events included radiographic changes, fever, weight gain, diarrhea, positive blood cultures, admission to the intensive care unit (ICU) and administration of bolus corticosteroids. Survival was calculated from the time of transplant and survival curves were constructed according to the Kaplan–Meier method (16). Multivariate analyses were performed with the use of a stepwise forward regression model with an entry probability for each variable set at 0.05. All analyses were done using JMP 6.0.0 Statistical Discovery™ from SAS (Cary, NC, USA).

Results

Patient characteristics

Of the 30 patients, 67% were male (Table 1). The median age of the cohort was 48.5 (range 20–70). Time to transplant from onset of symptoms was 23.5 months and from diagnosis was 4 months. Most patients had received prior therapy, most commonly corticosteroids ($n = 23$), intravenous gammaglobulin ($n = 13$), plasmapheresis ($n = 9$), but only 40% ($n = 12$) had received chemotherapy (cyclophosphamide or IMiDs) or radiation therapy ($n = 3$). Eastern cooperative group performance score was 3 in 33%. Pulmonary function showed decreased diffusion capacity for carbon monoxide (DLCO < 70%) in 57%.

Going into transplant, 13 patients were receiving corticosteroids, either a taper from chronic use or adrenal replacement. Pretransplant characteristics of this group were the same as compared with their non-chronic steroid using counterparts with the exceptions that they had more prior therapy (three regimens vs. two regimens, $P = 0.02$) and lower DLCOs (57% vs. 73% of expected, $P = 0.02$).

Engraftment

Patients had slow neutrophil engraftment, with a median time to ANC 0.5×10^9/L of 16 d [interquartile range (IQR) 15–18], with 10% reaching an ANC of 0.5×10^9/L by day 13. The time to platelets 20×10^9/L and 50×10^9/L were 14.5 d (IQR 11–22) and 19.5 d (IQR 15–39), respectively. The median number of platelet and erythrocyte transfusions was 5 aphesis units (IQR 2.0–10) and 6 units (IQR 2.5–8.5), respectively.

Treatment-related toxicity

All but four patients were hospitalized during their transplant course (patient no. 9, 13, 18 and 26). Rates of fever, diarrhea, weight gain ≥3% of baseline and rash were high, occurring in 93%, 77%, 53% and 43% of patients, respectively. Three patients required temporary dialysis (no. 3, 15 and 20). Twelve patients required supplemental oxygen (no. 3, 4, 5, 7, 15, 16, 17, 20, 21, 22, 23 and 24). Five patients had a bronchoalveolar lavage performed (no. 3, 4, 15, 16 and 20). One patient had hemosiderin laden macrophages (patient no. 21). Seven patients were admitted to the ICU and five required endotracheal intubation (patient no. 3, 4, 15, 16 and 20).

Eleven patients had positive blood cultures during their course (Table 2), including two who had *Micrococcus* and coagulase-negative *Staphylococcus* while another patient had *Acinetobacter* growing from one catheter

Table 2 Positive blood cultures

Patient no.	Positive blood cultures (BCx)	Positive BCx relative to day 0	First negative BCx	Growth after (d)	BCx (positive/total)	Bottles (positive/total)
24	*Staphylococcus* coagulase-negative	−4	+4	1	2/2	5/6
26	*Acinetobacter*[1]	−2	0[2]	1	1/2	1/3
3	Capnocytophaga	+8	+9[2]	4	1/3	–
22	*Micrococcus*, 1 lumen[1]	+8	+10[2]	2	1/3	1/4
	Corynebacterium[1]			2	1/3	1/4
29	*Staphylococcus* coagulase-negative[1]	+8	+9[2]	2	1/3	1/4
	Micrococcus[1]			2	1/3	1/4
30	*Staphylococcus* coagulase-negative	+10	+16	2	3/3	9/10
9	*Staphylococcus* coagulase-negative	+11	+14[2]	1	2/3	–
5	*Escherichia coli*	+15	+19[2]	1	3/3	–
17	*Staphylococcus* coagulase-negative	+30	+33[3]	1	2/2	2/5
4	*Pseudomonas aeruginosa*	+33	+35[2]	1	2/3	–
15	*Enterococcus faecalis, Bacteroides vulgatus*	+81	+84[2]	1	1/3	1/3
	Also, CMV viremia day +125			1	1/3	1/3

[1]Considered a contaminant.
[2]First redraw.
[3]1/3 cultures still positive (line only), so line removed and cultures not rechecked.

lumen on one occasion (designated contaminants). One patient had coagulase-negative *Staphylococcus* growing from the long-term central venous catheter on day –4, which had cleared by day +4 post-transplant. Four of the instances of bacteremia occurred at days 30, 33 and 81. Overall, there were only five patients with clinically significant bacteremia from days 2–29 post-ASCT.

The median time to hospital discharge was day 17 (IQR 14.7–25) post-transplant, with the longest hospitalization exceeding 170 d. The median number of days post-ASCT to dismissal from transplant center was 26 (IQR 20–42). Pretransplant characteristics that were associated with delayed hospital dismissal, defined as greater than the median of 17 d, included increased age ($P = 0.04$) and splenomegaly ($P = 0.01$), but only splenomegaly was associated with longer hospitalizations on multivariate analysis. Transplant events that predicted for longer hospitalizations included radiographs with infiltrates and/or effusions 7–17 d post-transplant ($P < 0.0001$), fever ($P = 0.03$), weight gain >3% of baseline ($P = 0.02$), receipt of bolus corticosteroids ($P = 0.0005$) and any admission to the ICU ($P < 0.001$). On multivariate analysis, only ICU admission predicted for prolonged hospitalization.

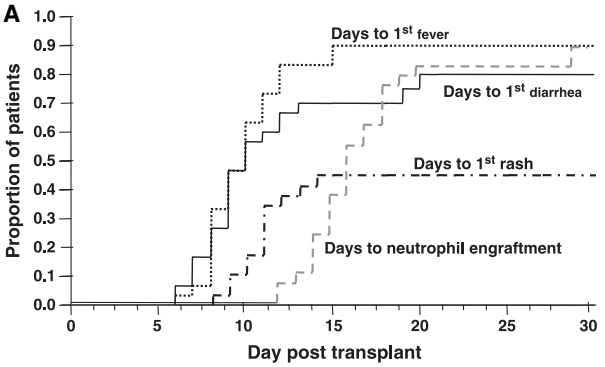
Engraftment syndrome

As shown in Fig. 1A, the classic symptoms of ES – fever, rash, diarrhea, non-cardiogenic pulmonary edema, weight gain – were prevalent in these patients, but the majority did not satisfy the time criteria tied to neutrophil recovery as proposed by Spitzer (10) or Maiolino *et al.* (11) (Fig. 1B). The time to the first complication consistent with ES was day +9 (IQR 8–11), whereas, the median time to neutrophil engraftment was day +16 (IQR 14.5–18).

Prospectively, rash was attributed to drugs, with a resultant change in antibiotic regimen from cefepime to meropenem. Sixty-three percent of patients had infiltrates and/or effusions on CXR at a median of day +12. Of the 14 patients who initially had a normal CXR with their first fever, six patients went on to have a second CXR that was abnormal – most commonly with infiltrates, effusions or both. The findings may be subtle or dramatic (Fig. 2).

Depending on the published definition of ES employed, 27–47% of patients had the syndrome. If allowance was made for the delayed neutrophil engraftment, rates exceeded 50% (Fig. 1B). Only five patients were prospectively identified as having ES (patient no. 22, 19, 17, 24 and 25), and they were treated at 10, 11, 12, 13 and 15 d post-transplant with doses of corticosteroids from 620 to 1200 prednisone equivalents. Of the five patients requiring endotracheal intubation, three satisfied Maiolino's criteria for ES. Although these three received bolus corticosteroids during their course, administration was delayed at 18, 14 and 18 d. The patient whose corticosteroids bolus antedated intubation received only prednisone 30 mg/d. The same held true for the PERDS. Although seven patients required oxygen supplementation at the anticipated time of engraftment, i.e. at a median of 12 d (IQR 7–17), the time requirement of 5 d between the need for oxygen and engraftment was satisfied in for only two patients.

Risk factors for ES depended on which definition of ES was used. No factors other than the defining



B

SPITZER, BMT 2001
96 h w/in ANC 0.5 x 10^9/L
•Temp >38.3, and
•Rash >25% body, and
•Non-card. pulm. edema
•Bili 2X normal, transaminases 2x normal, creatinine 2x normal, weight gain 2.5% baseline, or encephalopathy

MAIOLINO BMT, 2003
24 h w/in 1st neutrophils
Fever and….
•Skin rash, or
•Pulmonary infiltrates, or
•Diarrhea

Engraftment syndrome **No engraftment syndrome**

Maiolino	47 %																											
M-Maiolino	57 %																											
Spitzer	27 %																											
M-Spitzer	50 %																											
SCT #	8	10	14	20	22	23	25	29	4	7	16	17	11	27	19	21	24	1	2	3	5	6	9	12	13	15	18	26	28	30
CTX			C	C														M	M	M		M		M	C			C		
CS day	11	12		18	12	11	15		18		14	13			11	13	10			9						59				
CS dose	0.02	0.04		1.2	1.2	0.02	0.62		0.5		0.03	1.2			1.2	0.02	1.2			0.12						0.03				

Figure 1 Engraftment syndrome (ES): signs and definitions. (A) Timing of neutrophil engraftment relative to other ES entities. (B) ES definitions and rates. M-, 'modified' Spitzer and Maiolino engraftment definitions relax the 96 and 24 h neutrophil requirements; CS, corticosteroid; CTX, cyclophosphamide; M, cyclophosphamide mobilization; C, cyclophosphamide used for 2–3 cycles prior to coming to transplant; SCT, stem cell transplant patient number. Patients no. 1–11 are those previously reported.

elements predicted for ES when definition tied tightly to the neutrophil count. In contrast, three features stood out as risk factors for the modified Spitzer and modified Maiolino definitions (Fig. 1B): baseline splenomegaly, baseline lymphadenopathy and mobilization with growth factor alone (Table 3). In a multiple logistic model, type of mobilization ($P = 0.02$) and either lymphadenopathy ($P = 0.03$) or splenomegaly ($P = 0.004$) retained significance for the modified Spitzer, but for modified Maiolino, only type of mobilization ($P = 0.02$) and lymphadenopathy ($P = 0.002$) were significant. Surprisingly, scheduled sargramostim after transplant did not affect risk of ES.

The role of corticosteroids in POEMS patients undergoing PBSCT

As mentioned, 13 patients began their transplant on maintenance corticosteroids. Their post-transplant course differed slightly from those who were not on chronic corticosteroids: later time to first fever and rash (day +10.5 vs. +8.0, $P = 0.002$; and day +12 vs. +10, $P = 0.01$, respectively); and later time to corticosteroid bolus (day +12 vs. day +11, $P = 0.03$). The number of patients who received corticosteroid bolus was comparable in the maintenance vs. no maintenance group. There was no difference in the number of transfusions they required, their time to neutrophil or platelet engraftment or their risk of bacteremia or of developing ES.

We postulated that patients with ES, who received corticosteroids in a timely manner, would fare better than those who did not. Fourteen patients received corticosteroid boluses (range 20–1200 mg/d prednisone equivalents) during the course of their transplant from day +9 to day +57, median 12.5 (Fig. 1B). Indications were ES in five, diffuse alveolar hemorrhage in one (patient no. 20), drug rash in two (patient no. 8 and 10), stress dose for adrenal insufficiency in four (patient no. 15, 16, 21 and 23) and acute respiratory distress syndrome in two (patient no. 3 and 4). Patients receiving corticosteroids for the indications of drug rash or adrenal insufficiency received lower doses (20–40 mg/d). The prednisone dose used for the indication of acute respiratory distress syndrome was 120 mg/d in one patient and 500 mg/d in the other.

Ninety-three percent of patients receiving bolus corticosteroids had baseline organomegaly as compared with an incidence of organomegaly of 50% in patients who did not require bolus corticosteroids, $P = 0.01$, or stated slightly differently, 79% of patients with baseline splenomegaly received bolus corticosteroids; whereas only 18% of those without were given bolus corticosteroid, $P = 0.001$. A similar relationship existed for

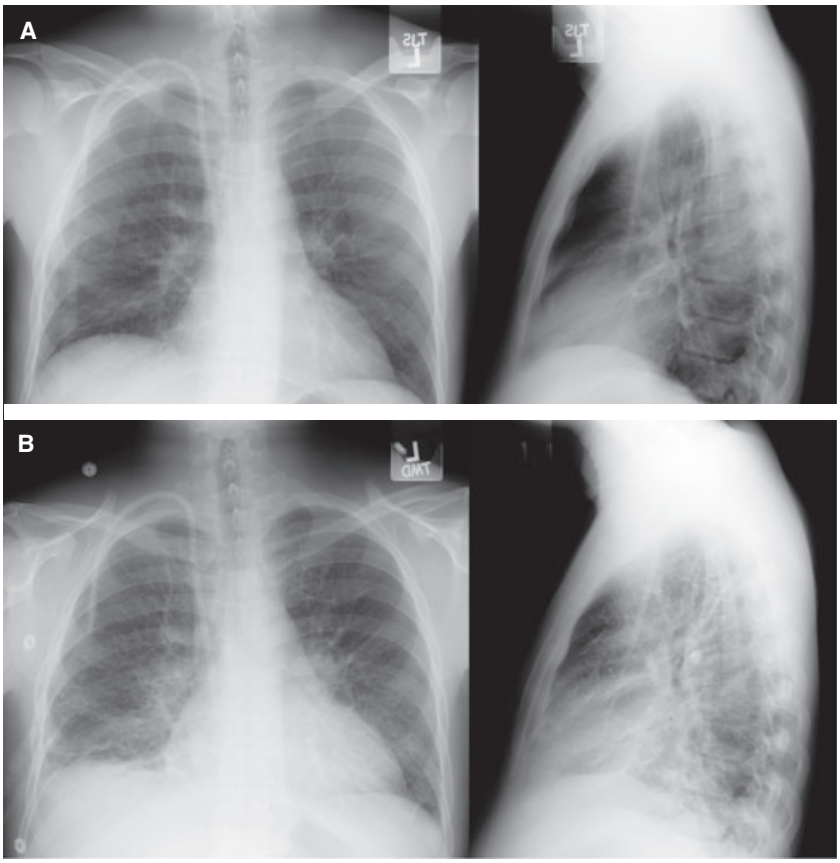


Figure 2 Engraftment syndrome (ES) radiograph findings. (A) Day +8 PBSCT demonstrating relatively normal CXR despite fever and diarrhea. (B) Day +11 PBSCT (same patient) demonstrating increased heart size, diffuse interstitial infiltrates throughout both lungs with alveolar infiltrates in the lower lungs.

lymphadenopathy with the respective numbers at 78% and 33%, $P = 0.05$. There was also a higher percentage of patients with a baseline pericardial effusion (89% vs. 44%, $P < 0.05$) receiving bolus corticosteroids. In contrast, there was no difference in their baseline fluid retention, their DLCO, conditioning regimens, their scheduled use of post-transplant growth factors.

Patients receiving bolus corticosteroids were more likely to meet criteria for ES (Maiolino, $P = 0.07$; Spitzer $P = 0.06$; modified Maiolino, $P = 0.003$ and modified Spitzer, $P = 0.0003$). They were more likely to have had weight gain due to fluid retention (0.005), rash ($P = 0.04$), delayed neutrophil and platelet engraftment ($P = 0.04$ and 0.02, respectively), higher platelet and erythrocyte transfusion needs ($P = 0.0004$ and < 0.0001, respectively), have spent time in the ICU ($P = 0.0005$) and had longer times to hospital dismissal ($P = 0.0005$). All but one patient who received a corticosteroid bolus had an abnormal CXR, $P = 0.002$. These patients were no more likely to have bacteremia than those who did not get corticosteroids, but they were more likely to require mechanical ventilation.

In an effort to separate the use of corticosteroid boluses as a reactive strategy of desperation from a proactive therapeutic strategy, we evaluated the impact of the timing of bolus corticosteroids on outcomes. There were no significant baseline differences between the early and late groups. However, those seven patients who received corticosteroids before day 13 had superior outcomes as compared with the seven who received them

Table 3 Risk of engraftment syndrome

	Modified Spitzer ES			Modified Maiolino ES		
	ES, $n = 15$	No ES, $n = 15$	*P*-value	ES, $n = 17$	No ES, $n = 13$	*P*-value
Splenomegaly, $n = 14$	10/15	4/15	0.03	11/17	3/13	0.02
Lymphadenopathy, $n = 9$	8/15	1/15	0.005	9/17	0/13	0.002
Any CTX, $n = 8$	2/15	6/15	NS	2/17	6/13	0.03
Mobilization CTX/G, $n = 5$	0/15	5/15	0.01	0/17	5/13	0.005

Any CTX, cyclophosphamide used as therapy or for mobilization.

Table 4 Patient outcomes based on bolus corticosteroid usage[1]

	No steroid (n = 16)	Steroid ≤D12 (n = 7)	Steroid >D12 (n = 7)	P	P, early vs. late CS
ES: M/S/mM/mS, n^2	5/2/5/3	4/4/6/6	5/2/6/6	NA	NA
Weight change, %	0.6 (0.42–6.7)	6.7 (3.6–27.2)	11.2 (–2.1 to–23.2)	0.005	NS
Rash, %	27	71	43	NS	NS
Diarrhea, %	73	86	86	NS	NS
T_{max}, °C	39 (37.8–41)	40.1 (39–41.1)	38.9 (38.7–40.8)	0.08	0.07
1st fever, day	10 (6–15)	8 (7–9)	12 (8–146)	0.007	0.007
Abnormal CXR1, %	13	71	71	0.03	NS
Ventilator, %	0	14	71	0.004	0.03
First WBC, day	12 (8–21)	14 (12–14)	14 (12–17)	0.03	NS
ANC500, day	15 (12–29)	16 (14–115)	18 (15–45)	0.08	NS
PLT20, day	12 (8–41)	20 (11–115)	24 (9–170)	0.05	NS
PLT50, day	15 (11–192)	32 (16–115)	56 (13–551)	0.03	NS
RBCs, units	3 (2–8)	6 (4–31)	11 (6–64)	0.0008	NS
PLTS, apheresis units	2 (1–9)	9 (4–51)	18 (4–60)	0.0004	NS
Hospital dismissal, day	15 (13–36)	21 (15–69)	41 (16–175)	0.009	0.05

[1]Except where stated otherwise, values are expressed as median (range).
[2]ES, engraftment syndrome according to definition of Maiolino (11) (M), Spitzer (10) (S), modified Mailino (mM) and modified Spitzer (mS) – see text and Fig. 1 for definitions.
ANC500, absolute neutrophil count >0.5 × 10^9/L; PLT20, platelet engraftment to 20 × 10^9/L; PLT50, platelet engraftment to 50 × 10^9/L; RBCs, red blood cell transfusion; PLTS, platelet transfusions.

day 13 or later (Table 4) with regards to earlier achievement of maximum temperature, lower likelihood of requiring mechanical ventilation and earlier hospital dismissal. There was a trend toward a lower transfusion requirement and a higher maximum temperature, but given the small sample size, these differences were not significant.

Overall survival and response

With a median follow-up of 19 months, there has been only one death at 4 months, which was previously reported (8). According to the international response criteria (13), 62% have achieved a complete hematological response, 17% a very good PR, 3% a PR and 10% had less than a PR. One patient is too early for assessment; another died prior to assessment and one had no measurable disease other than lymphadenopathy, which resolved. All evaluable patients have derived clinical benefit from the therapy, including those patients who achieved less than a PR. Of these three patients without significant hematological response, two had baseline VEGF measurements. Their respective plasma VEGF levels decreased from 331 pg/ml to undetectable and from 713 to 117 pg/ml despite the lack of hematological response. The other patient has normal VEGF levels more than 3 yr post-transplant. One patient who achieved only minimal hematological response received consolidative radiation to persistent fluorodeoxyglucose positron emission tomagram positive bone lesions, without any further reduction in his M-protein. There has been one relapse 65 months post-ASCT.

Discussion

We and others have demonstrated the value of high-dose chemotherapy with peripheral blood stem cell transplant in patients with POEMS syndrome (2–8, 17–25). This report takes these initial observations several steps further. The median overall survival for this cohort has not been reached, and the treatment-related mortality was 3%. Patients with POEMS appear to be at high risk for an engraftment-type syndrome, which is associated with considerable morbidity. In this work, we describe several novel findings including the predictive power of splenomegaly for a complicated post-transplant course. In addition, important clinical improvements and reductions in plasma VEGF levels can occur in the absence of significant drops in the monoclonal protein.

In our previous report of 16 patients with POEMS, we were impressed by excessive peritransplant complications, but with excellent long-term clinical outcomes (8). What stood out previously was a rate of ICU admission of nearly 40%. We attributed much of this to poor pulmonary reserve – both neuromuscular restriction and diffusion capacity deficits. This, however, did not explain the entire clinical course, including culture-negative fevers and excessive weight gain, observed in these patients. Over time it became increasingly evident that these patients were exhibiting signs of an engraftment-type syndrome, which in real-time was under recognized. For our last 12 transplants (Fig. 1B), there has been a heightened awareness of this complication leading to faster response with corticosteroids. Although it did not reach

statistical significance, the number of patients being dismissed from hospital after day 24 has decreased from 33% to 8%. Moreover, nearly 60% of the more recent cohort has received bolus corticosteroids as compared with fewer than 40% of the earlier cohort. Of those receiving corticosteroids, more patients have been receiving them earlier and at higher doses.

Given the delayed neutrophil engraftment seen in this patient population, we took liberties with the definition of ES by loosening the time restriction of peripheral blood neutrophil reconstitution. In the context of engraftment, the peripheral neutrophil counts are surrogates for more complex cellular, cytokine and chemokine interactions. Since there is no standard definition of ES, we used a total of four definitions of ES and one for PERDS: (i) Spitzer (10); (ii) Maiolino *et al.* (11); (iii and iv) a variant of each, which uncoupled the timing of peripheral blood neutrophil recovery and symptoms. Using these various definitions, as many as 57% of patients developed ES. The definition, which seemed to best reflect reality, was the Spitzer modification. Using this definition, 50% of our patients would be labeled as having had a type of ES.

The early identification of an ES is more than an academic exercise. Based on both our own experience and retrospective reviews of the literature (10, 26–28), corticosteroids are an important adjunctive therapy in patients with this condition and they decrease the duration of the syndrome. In the POEMS cohort, we have observed an almost instantaneous cessation of unrelenting high fevers, followed by diuresis and improvement of rash and diarrhea. One of the most common reasons for delayed institution of corticosteroids has been the concern that these patients are septic. The very high fevers, the third-spacing and the dropping blood pressures are all consistent with sepsis. Although corticosteroids are immunosuppressive, a short course should not affect the outcome even in a septic patient if they are on broad spectrum antibiotics (29). A major question in the field of ES is the dose of corticosteroids sufficient to terminate the process. Based on our experience with POEMS patients, prednisone doses of < 0.5 mg/kg are not sufficient. More recently, we have been using methylprednisolone 500–1000 mg/d for 2–3 d followed by a rapid taper, but certainly one could also consider doses of 1–2 mg/kg.

Our study provokes as many questions as answers, which will require further study. Why would patients with POEMS syndrome have rates of fever, diarrhea, weight gain of ≥3% baseline and rash of 93%, 77%, 53% and 43%, respectively? One could postulate that patients with POEMS syndrome have an aberrant cytokine milieu that is amplified and exaggerated by the process of marrow reconstitution. It is known that the vast majority of patients with POEMS have significant elevations in VEGF (22, 30–32), and many have increased levels of tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) (33). Marrow reconstitution has been shown to be associated with significant increases in the concentration of circulating macrophage colony-stimulating factor (M-CSF), erythropoietin, IL-6 and TNF-α, reaching near maximal values at around day $+12$ (34). The cytokine burst appears to predate neutrophil engraftment.

Why would splenomegaly predict for a more complicated course? The answer is unclear. Patients with POEMS syndrome are quite heterogeneous, but there is little understanding about that heterogeneity from a pathogenic standpoint. Splenomegaly in and of itself has not been shown to be an adverse prognostic finding in the retrospective reviews that have evaluated clinical outcomes of POEMS patients. One could speculate that the spleen serves as a reservoir of cells that participate in a feedback loop of cytokine/chemokine stimulation that occurs during engraftment.

The other peculiar aspect relates to their transfusion need and their delayed engraftment, even among those patients with uncomplicated courses. In a myeloma patient receiving an up-front ASCT, the median number of erythrocyte and platelet transfusions is two of each (35). Contrast those figures to those of the POEMS patients. Up to 70% required transfusion of more than 3 units of erythrocytes, and almost 60% required more than 3 units of apheresis platelets. Only 7% and 33% of patients had engrafted their neutrophils and platelets, respectively, by day 12. Once again, the only explanations that can be posited have to do with cytokine milieu. In their study of cytokine levels in the weeks following bone marrow and peripheral blood stem cell transplantation, Rabinowitz *et al.* found that M-CSF was the best predictor of platelets required, followed by IL-6 (34). High M-CSF and IL-6 both correlated with an increased demand to platelet transfusion. This needs to be studied prospectively in patients with POEMS syndrome.

The final curiosity elicited by this study was the partial disconnect between clinical response and hematological response. The majority of patients achieved either a complete response or a very good partial response, but we observed three patients with less than a PR, all of whom had improvements in their neuropathy and other clinical findings. These patients highlight the relative lack of importance of the monoclonal protein and point to other factors in the etiology of this disorder. VEGF is the extracellular signaling peptide most consistently elevated in patients with POEMS syndrome and is likely the preferred serial marker to follow a patient's status (36).

In conclusion, POEMS syndrome is a complex syndrome characterized by elevations in VEGF and other

proinflammatory cytokines. High-dose chemotherapy with peripheral blood stem cell transplantation is an effective treatment strategy for selected patients. Patients are at high risk for an engraftment-type syndrome, which may be corticosteroid responsive. Splenomegaly and lymphadenopathy appear to raise the risk for post-transplant complications.

Acknowledgements

We would like to thank other members of the Dysproteinemia and Blood and Marrow Transplant groups for their excellent care of the patients.

Contributions

AD designed research, performed research, collected data, analyzed and interpreted data, performed statistical analysis and drafted the manuscript. MQL, SRH, SKK, FB, DD, MRL, DAG, DJI, MAE, INM, SMA, WJH, LFP, PAJ, BA, AB, RAK, MAG performed research, collected data, analyzed and interpreted data and drafted the manuscript.

References

1. Dispenzieri A, Kyle RA, Lacy MQ, *et al*. POEMS syndrome: definitions and long-term outcome. *Blood* 2003;**101**:2496–506.
2. Hogan WJ, Lacy MQ, Wiseman GA, Fealey RD, Dispenzieri A, Gertz MA. Successful treatment of POEMS syndrome with autologous hematopoietic progenitor cell transplantation. *Bone Marrow Transplant* 2001;**28**:305–9.
3. Wiesmann A, Weissert R, Kanz L, Einsele H. Long-term follow-up on a patient with incomplete POEMS syndrome undergoing high-dose therapy and autologous blood stem cell transplantation. *Blood* 2002;**100**:2679–80.
4. Soubrier M, Ruivard M, Dubost JJ, Sauvezie B, Philippe P. Successful use of autologous bone marrow transplantation in treating a patient with POEMS syndrome. *Bone Marrow Transplant* 2002;**30**:61–2.
5. Peggs KS, Paneesha S, Kottaridis PD, *et al*. Peripheral blood stem cell transplantation for POEMS syndrome. *Bone Marrow Transplant* 2002;**30**:401–4.
6. Jaccard A, Royer B, Bordessoule D, Brouet JC, Fermand JP. High-dose therapy and autologous blood stem cell transplantation in POEMS syndrome. *Blood* 2002;**99**:3057–9.
7. Rovira M, Carreras E, Blade J, *et al*. Dramatic improvement of POEMS syndrome following autologous haematopoietic cell transplantation. *Br J Haematol* 2001;**115**:373–5.
8. Dispenzieri A, Moreno-Aspitia A, Suarez GA, *et al*. Peripheral blood stem cell transplantation in 16 patients with POEMS syndrome, and a review of the literature. *Blood* 2004;**104**:3400–7.
9. Dispenzieri A. POEMS syndrome. *Blood Rev* 2007;**21**:285–99.
10. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2001;**27**:893–8.
11. Maiolino A, Biasoli I, Lima J, Portugal AC, Pulcheri W, Nucci M. Engraftment syndrome following autologous hematopoietic stem cell transplantation: definition of diagnostic criteria. *Bone Marrow Transplant* 2003;**31**:393–7.
12. Capizzi SA, Kumar S, Huneke NE, *et al*. Peri-engraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2001;**27**:1299–303.
13. Durie BG, Harousseau JL, Miguel JS, *et al*. International uniform response criteria for multiple myeloma. *Leukemia* 2006;**20**:1467–73.
14. Kruskal WH, Wallis WA. Use of ranks in one-criterion variance analysis. *J Am Stat Assoc* 1952;**47**:583–621.
15. Mehta CR, Patel NR. A network algorithm for the exact treatment of Fisher's exact test in RxC contingency tables. *J Am Stat Assoc* 1983;**78**:427–34.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;**53**:457–81.
17. Wong VA, Wade NK. POEMS syndrome: an unusual cause of bilateral optic disk swelling. *Am J Ophthalmol* 1998;**126**:452–4.
18. Kamboj G, Abdel-Raheem M, Shurafa M, *et al*. Autologous hematopoietic stem cell transplantation for multicentric Castleman's/POEMS syndrome. *Blood* 2002;**100**:5457 (abstract).
19. Schliamser LM, Hardan I, Sharif D, Zukerman E, Avshovich N, Attias D. Significant improvement of POEMS syndrome with pulmonary hypertension following autologous peripheral blood stem cell transplant. *Blood* 2003;**102**:5664 (Abstract).
20. Ganti AK, Pipinos I, Culcea E, Armitage JO, Tarantolo S. Successful hematopoietic stem-cell transplantation in multicentric Castleman disease complicated by POEMS syndrome. *Am J Hematol* 2005;**79**:206–10.
21. Kojima H, Katsuoka Y, Katsura Y, *et al*. Successful treatment of a patient with POEMS syndrome by tandem high-dose chemotherapy with autologous CD34+ purged stem cell rescue. *Int J Hematol* 2006;**84**:182–5.
22. Kastritis E, Terpos E, Anagnostopoulos A, Xilouri I, Dimopoulos MA. Angiogenetic factors and biochemical markers of bone metabolism in POEMS syndrome treated with high-dose therapy and autologous stem cell support. *Clin Lymphoma Myeloma* 2006;**7**:73–6.
23. Sanada S, Ookawara S, Karube H, *et al*. Marked recovery of severe renal lesions in POEMS syndrome with high-dose melphalan therapy supported by autologous blood stem cell transplantation. *Am J Kidney Dis* 2006;**47**:672–9.
24. Kuwabara S, Misawa S, Kanai K, *et al*. Autologous peripheral blood stem cell transplantation for POEMS syndrome. *Neurology* 2006;**66**:105–7.

25. Imai N, Kitamura E, Tachibana T, *et al*. Efficacy of autologous peripheral blood stem cell transplantation in POEMS syndrome with polyneuropathy. *Intern Med* 2007;**46**:135–8.
26. Lee CK, Gingrich RD, Hohl RJ, Ajram KA. Engraftment syndrome in autologous bone marrow and peripheral stem cell transplantation. *Bone Marrow Transplant* 1995;**16**:175–82.
27. Cahill RA, Spitzer TR, Mazumder A. Marrow engraftment and clinical manifestations of capillary leak syndrome. *Bone Marrow Transplant* 1996;**18**:177–84.
28. Ravoet C, Feremans W, Husson B, *et al*. Clinical evidence for an engraftment syndrome associated with early and steep neutrophil recovery after autologous blood stem cell transplantation. *Bone Marrow Transplant* 1996;**18**:943–7.
29. Mossad S, Kalaycio M, Sobecks R, *et al*. Steroids prevent engraftment syndrome after autologous hematopoietic stem cell transplantation without increasing the risk of infection. *Bone Marrow Transplant* 2005;**35**:375–81.
30. Watanabe O, Maruyama I, Arimura K, *et al*. Overproduction of vascular endothelial growth factor/vascular permeability factor is causative in Crow–Fukase (POEMS) syndrome. *Muscle Nerve* 1998;**21**:1390–7.
31. Nishi J, Arimura K, Utsunomiya A, *et al*. Expression of vascular endothelial growth factor in sera and lymph nodes of the plasma cell type of Castleman's disease. *Br J Haematol* 1999;**104**:482–5.
32. Scarlato M, Previtali SC, Carpo M, *et al*. Polyneuropathy in POEMS syndrome: role of angiogenic factors in the pathogenesis. *Brain* 2005;**128**:1911–20.
33. Soubrier M, Sauron C, Souweine B, *et al*. Growth factors and proinflammatory cytokines in the renal involvement of POEMS syndrome. *Am J Kidney Dis* 1999;**34**:633–8.
34. Rabinowitz J, Petros WP, Stuart AR, Peters WP. Characterization of endogenous cytokine concentrations after high-dose chemotherapy with autologous bone marrow support. *Blood* 1993;**81**:2452–9.
35. Moreau P, Facon T, Attal M, *et al*. Comparison of 200 mg/m2 melphalan and 8 Gy total body irradiation plus 140 mg/m2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood* 2002;**99**:731–5.
36. Mineta M, Hatori M, Sano H, *et al*. Recurrent Crow–Fukase syndrome associated with increased serum levels of vascular endothelial growth factor: a case report and review of the literature. *Tohoku J Exp Med* 2006;**210**:269–77.