What is the best treatment strategy before autologous peripheral blood stem cell transplantation in POEMS syndrome?

Francesco Autore,[1*] Stefania Bramanti,[2*] Federica Lessi,[3] Idanna Innocenti,[1] Eugenio Galli,[1] Serena Rocchi,[4,5] Rossella Ribolla,[6] Daniele Derudas,[7] Stefania Oliva,[8] Paola Stefanoni,[9] Magda Marcatti,[10] Angelo Schenone,[11,12] Giorgio La Nasa,[7] Claudia Crippa,[6] Elena Zamagni,[4,5] Marcello Riva,[3] Rita Mazza,[2] Daniele Mannina,[2] Simona Sica,[1,13] Andrea Bacigalupo[1,13] and Luca Laurenti[1,13]

[1]Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Roma; [2]Istituto Clinico Humanitas IRCCS, Rozzano; [3]Azienda Ospedale Università Padova, Padova; [4]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna; [5]Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna; [6]Spedali Civili, Brescia; [7]SC di Ematologia e CTMO - Ospedale Oncologico di Riferimento Regionale "A. Businco", ARNAS "G. Brotzu", Cagliari; [8]S. Giovanni Battista Hospital, Torino; [9]ASST Papa Giovanni XXIII Hospital, Bergamo; [10]San Raffaele Hospital, Milano; [11]Department of Neurosciences, Rehabilitation, Ophthalmology, Genetic and Maternal and Infantile Sciences (DINOGMI), University of Genoa, Genova; [12]IRCCS San Martino Hospital, Genova and [13]Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy

**FA and SB contributed equally as first authors.*

Correspondence: F. Autore
francesco.autore@policlinicogemelli.it

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Abstract

Autologous peripheral blood stem cell transplantation (aPBSCT) provides optimal outcomes in POEMS syndrome but the definition of the best treatment before aPBSCT remains to be defined because of the rarity of the disease and the heterogeneity of published case series. We collected clinical and laboratory data of patients with POEMS syndrome undergoing aPBSCT from 1998 to 2020 in ten Italian centers. The primary endpoint of the study was to evaluate the impact of prior therapies and mobilization regimen on outcome. We divided the patients into three groups: patients who did not receive any treatment before transplant (15 patients, group A: front-line), patients pre-treated with other agents (14 patients, group B) and patients treated with cyclophosphamide as their mobilizing regimen (16 patients, group C). The three groups did not show differences in terms of demographic and clinical characteristics. All 45 patients underwent aPBSCT after a high-dose melphalan conditioning regimen, with a median follow-up of 77 months (range, 37-169 months). The responses were not statistically different between the three groups (*P*=0.38). Progression-free and overall survival rates at 6 years were: 70% (95% confidence interval: 55-85%) and 91% (95% confidence interval: 82-99) 65%, respectively, and did not differ between the three groups. The cumulative incidence of transplant-related mortality and relapse was 4% and 36%, respectively. In conclusion, in a relatively large number of patients with POEMS syndrome, undergoing an autologous transplant, pre-treatment and disease status at transplant did not appear to have an impact on major transplant outcomes.

Introduction

POEMS syndrome is a rare paraneoplastic condition associated with an underlying plasma cell disorder. The acronym POEMS refers to the main features of this syndrome: polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes.[1-3] Treatment recommendations are based on limited trial data: the disease is so rare that literature consists mainly of small retrospectives studies or case series.

The main experience in the treatment has been with alkylating-based therapy with autologous peripheral blood stem cell transplantation (aPBSCT). Reports on the use of cyclophosphamide-based therapies are interesting with excellent

hematologic and clinical responses, good achievement of neurological improvement and also vascular endothelial growth factor (VEGF) reduction, allowing optimal progression-free survival (PFS) and overall survival (OS).[4-16]

For patients fit to undergo a transplant, in the absence of organ dysfunction, high-dose chemotherapy and aPBSCT appear to be the best strategy. The dose of melphalan in the conditioning has ranged from 140 to 200 mg/m^2, with very high response rates; the responses are long-lasting, although relapses have been reported.[10,11,15,17-21] Tandem transplantation has been applied anecdotally, but little information is available regarding any added value of the second transplant.[22,23]

For unfit patients, for whom high-dose chemotherapy is not recommended, many therapeutic approaches have been suggested, including steroids and low-dose alkylating agents associated with steroids or radiotherapy.[3]

Other promising treatments are lenalidomide,[19,24-29] thalidomide,[30,31] bortezomib,[32-37] and drugs with anti-VEGF and anti-tumor necrosis factor effects.[38] Single-agent intravenous immunoglobulin and plasmapheresis are not helpful to cure patients with POEMS syndrome.[3]

A recent retrospective study on the best first-line treatment in POEMS, conducted on 347 patients, focused attention on three options: melphalan plus dexamethasone, aPBSCT, or lenalidomide plus dexamethasone. The highest response rates were seen with aPBSCT, followed by lenalidomide plus dexamethasone, and melphalan plus dexamethasone. Although all these three treatments produced reasonable responses and survival outcomes, patients at higher risk may benefit more from aPBSCT.[21] In the setting of aPBSCT, reports on the clinical outcomes of patients with advanced disease and poor performance status are few and appropriate patient selection remains an important issue regarding the risk-benefit ratio associated with the procedure.[18,21,39]

The best protocol to collect PBSC in patients with POEMS syndrome remains to be defined because the efficacy of different treatments has not been previously compared in large cohorts of patients, and the rarity of the disease makes it difficult to conduct randomized controlled trials. Cyclophosphamide plus granulocyte colony-stimulating factor (G-CSF) mobilizes more CD34$^+$ cells and reduces the incidence of engraftment syndrome in patients with POEMS syndrome, although the combination potentially increases the risks related to the procedure, without a significant tumor mass reduction. Several published series document successful mobilization and collection through chemo-mobilization, as well as with the use of G-CSF alone.[8,10,13,15,17,40-45]

Because of the rarity of POEMS syndrome and the heterogeneity of published case series, the best treatment before aPBSCT remains to be defined. Therefore, we decided to collect data on patients with POEMS syndrome who underwent aPBSCT in different Italian centers to evaluate response to and survival after the treatment prior to transplantation as well as the response to and survival after the transplant itself.

Methods

We collected clinical and laboratory data of patients with POEMS syndrome from ten Italian centers, including all consecutive patients who underwent aPBSCT from January 1998 to December 2020. We divided our population into three different groups: patients who did not receive any treatment before transplantation (group A, front-line), patients pre-treated with other agents (group B) and patients treated with cyclophosphamide as their mobilizing regimen (group C). Before transplantation, patients in group A received G-CSF 10 mg/kg/day alone for 5 consecutive days as their mobilizing regimen. Patients in group C were given cyclophosphamide 2-4 g/m^2 followed by G-CSF 5 mg/kg/day. Group B included patients treated with Len-Dex (lenalidomide 10-25 mg on days 1-21, dexamethasone 40 mg on days 1, 8, 15, and 22), Vel-Dex (bortezomib 1 mg/m^2 on days 1, 4, 8, and 11, plus dexamethasone 20 mg on days 1-4 and 8-11) or radiotherapy; all these patients were mobilized with G-CSF 5-10 mg/kg/day for 5 consecutive days.

Patients in all the groups were treated with melphalan, at the dose of 140 or 200 mg/m^2 (Mel140 and Mel200, respectively), as the conditioning regimen. G-CSF was given after the transplant from day +6 until engraftment of neutrophils, defined as >1,000/mm^3. No patient received maintenance therapy after aPBSCT. All patients provided informed consent. The study was approved by the Institutional Review Board and conducted following the ethical guidelines of the Declaration of Helsinki.

Patients were evaluated for responses (clinical, hematologic, and radiological), toxicity, PFS and OS. Hematologic response was defined by the response criteria for POEMS syndrome.[3,46] Complete remission (CR) was determined by negative bone marrow, negative immunofixation of the serum and urine, and a normalized VEGF level. Very good partial remission (VGPR) was defined by a 90% reduction in M-protein or immunofixation positivity only as long as the M-protein was at least 0.5 g/dL at baseline, and the VEGF level improved by at least 50%. Partial remission (PR) was defined by a 50% reduction in M-protein or immunofixation positivity as long as the baseline M-protein was at least 1.0 g/dL. Progressive disease (PD) was assessed by a more than 50% increase in these proteins or the reappearance of the proteins after CR; stable disease (SD) was considered as all the statuses other than CR, VGPR, PR, and PD.

A first evaluation of the response was made before transplantation for patients in groups B and C. After the transplant we evaluated the best response for patients in all the groups using clinical, serological and radiological examinations. We also determined toxicities, defined as per the Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0).

Statistical analysis

PFS was the time from treatment to recurrence, the reappearance of clinical symptoms, or death. OS was defined

as the time from treatment to death. Patients lost to follow-up were censored on the day of the last follow-up visit. The χ^2 test or Fisher exact test, when appropriate, was used to determine the statistical significance of differences in the values of categorical variables. Continuous variables were compared by discrete categorization variables (e.g., groups) using the equal-variances *t* test or with the Mann-Whitney test if the distribution was not normal. *P* values <0.05 were considered statistically significant. Cut-off determination for a continuous variable to predict an event was explored with receiver operating characteristic curve analysis. PFS and OS were calculated with the Kaplan-Meier log-rank test. Tests were performed with NCSS 2020 Statistical Software (2020) (NCSS, LLC. Kaysville, UT, USA; *ncss.com/software/ncss*).

Table 1. Patients' characteristics.

Characteristic	All patients, N=45
Age in years, median	53
Male, N (%)	32 (71)
Polyneuropathy, N (%)	45 (100)
Endocrinopathy, N (%)	34 (76)
Organomegaly, N (%)	38 (84)
Gammopathy, N (%)	43 (95)
Monoclonal IgA, N (%)	29 (64)
Monoclonal others, N (%)	14 (31)
Skin lesions, N (%)	31 (69)
Fluid overload, N (%)	19 (42)
Hemoglobin, g/dL, median	14.1
Platelet count, x10^9/L, median	476
Platelet count >500x10^9/L, N (%)	17 (38)
WBC count, x10^9/L, median	7.6

WBC: white blood cell.

Results

Our dataset was derived from 45 patients with POEMS syndrome who underwent aPBSCT. The patients' baseline characteristics are shown in Table 1. Their median age at the time of the diagnosis was 53 years (range, 38-71) and 71% were men. Polyneuropathy was present in all the patients and gammopathy was found in 95% of them (monoclonal IgA in 64%). We conducted the analysis dividing the cohort in three different groups: 15 patients in group A, 14 patients into group B and 16 patients in group C. No differences were shown between these three groups in terms of demographic and clinical characteristics, except for the level of hemoglobin (lower in group A) and white blood cell count (higher in group C), as shown in Table 2.

Data on stem cell mobilization showed that the median number of $CD34^+$ cells collected was 5.98x10^6/kg overall (6.4x10^6/kg in group A patients, 6.2x10^6/kg in group B patients, and 5.3x10^6/kg in group C patients; *P*=0.11) with a median of one single procedure per mobilization (range, 1-3). Use of plerixafor was allowed but it was necessary in only seven patients (3 in group A and 4 in group B). The procedure was generally good in terms of effectiveness and safety in all the groups.

Evaluation of response before transplantation documented that the patients in groups B and C achieved VGPR in 14% and 13% of cases and PR in 29% and 25% of cases, respectively, such that the response rate to the treatment before aPBSCT was good. Data on conditioning and transplantation are presented in Table 3. Mel200 was the choice of conditioning regimen for 87% of the patients; the other six patients were conditioned with Mel140, with this dose being chosen by physicians based on their patients' fitness status.

aPBSCT was complicated by febrile neutropenia in 62% of all the patients, gastrointestinal toxicity in 47% and infections in 42%; a median of two red blood cell units/patient (range, 0-13) and three platelet units/patient (range, 0-10) was the transfusion need during hospitalization. Polymorphonuclear cell counts >500 x10^6/L were reached at a median of 14 days, and platelet counts >25x10^9/L also at a median of 14 days. The median time spent in hospital after transplantation was 22 days (range, 13-69). No significant differences were noted between the three groups in terms of complications, toxicity, blood support, engraftment and hospitalization.

The best response rates after aPBSCT were as follows: CR in 46%, VGPR in 23%, PR in 18%, SD in 8% and PD in 5%, evaluated at a median time of 5.5 months (95% confidence interval: 5.3-19). When comparing the response rate (CR *vs*. VGPR/PR *vs*. SD/PD) between the three groups, no difference was found (*P*=0.38). Considering that patients in group A were not treated before transplantation and that the outcomes in the three groups of patients were similar, we did not find significant differences also when comparing patients with some type of response *versus* PD at transplantation. In ten cases, a re-admission to hospital was necessary: in five cases for relapse and in five cases for infectious complications.

The median follow-up was 77 months (range, 37-169): 17 patients (37.8%) experienced disease progression without a statistical difference between the three groups. The overall 6-year PFS rate was 70% (95% confidence interval: 55-85). The three groups did not show significant differences; there was a tendency to a unfavorable PFS for patients in group C (6-year PFS of 63% for group C *vs*. 78% for group A and 68% for group B; *P*=0.3), but no variable was found to negatively affect PFS. Likewise, the treatment chosen before transplantation had no effect on PFS (Figure 1A).

The overall 6-year rate of requiring retreatment was 27% and did not differ among the treatment groups (*P*=0.29) (Figure 1B). The retreatment choice was lenalidomide plus dexamethasone in most cases (12 out of 17 patients); other choices were cyclophosphamide, radiotherapy, daratumum-

Table 2. Characteristics of the whole cohort of patients and of those in groups A, B, and C.

Characteristics	All patients N=45	Group A No treatment N=15	Group B Other treatments N=14	Group C Cyclophosphamide N=16	*P*
Age at diagnosis in years, median	53	51	53	53	0.5
Male gender, N (%)	32 (71)	12 (80)	11 (79)	9 (56)	0.26
Median year of diagnosis	2013	2011	2014	2012	-
Median year of transplant	2013	2012	2017	2012	-
Gammopathy, N (%)	43 (96)	14 (93)	13 (93)	16 (100)	0.56
Gammopathy IgA, N (%)	29 (64)	8 (53)	8 (57)	13 (81)	0.48
Gammopathy others, N (%)	14 (31)	6 (40)	5 (34)	3 (19)	-
Polyneuropathy, N (%)	45 (100)	15 (100)	14 (100)	16 (100)	NA
Bone lesions, N (%)	27 (60)	7 (47)	10 (71)	10 (62)	0.38
Endocrinopathy, N (%)	34 (76)	11 (73)	9 (64)	14 (87)	0.33
Skin lesions, N (%)	31 (69)	9 (60)	10 (71)	12 (75)	0.65
Fluid overload, N (%)	19 (42)	6 (40)	6 (43)	7 (44)	0.98
Organomegaly, N (%)	38 (84)	14 (93)	10 (71)	14 (87)	0.24
Hemoglobin, g/dL, median	14.1	11.5	14.4	14.4	0.01
Platelet count, x10^9/L, median	476	358	401	508	0.16
Platelet count >500x10^9/L, N (%)	17 (38)	3 (20)	4 (28)	10 (62)	0.035
WBC count, x10^9/L, median	7.6	5.7	4.7	15.5	0.01

NA: not applicable; WBC: white blood cell.

Table 3. Conditioning and transplant details.

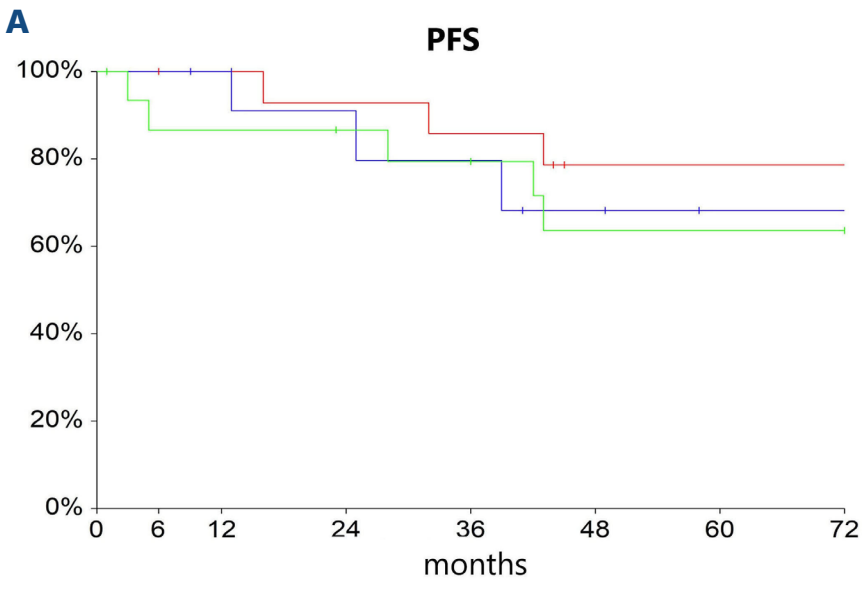
Characteristics	All patients N=45	Group A No treatment N=15	Group B Other treatments N=14	Group C Cyclophosphamide N=16	*P*
Age at transplant in years, median	53	51	54	54	0.5
Conditioning with Mel140, N (%)	6 (13)	3 (20)	1 (7)	2 (12)	0.59
Conditioning with Mel200, N (%)	39 (87)	12 (80)	13 (93)	14 (88)	0.59
$CD34^+$ cells, infused x10^6/kg, median	4.01	3.95	4.22	3.91	0.52
G-CSF, days, median	8	8	10	8	0.23
GI toxicity, N (%)	21 (47)	7 (50)	9 (64)	5 (31)	0.19
Febrile neutropenia, N (%)	28 (62)	9 (64)	8 (57)	11 (69)	0.80
Infections, N (%)	19 (42)	7 (50)	5 (36)	7 (44)	0.75
RBC unit transfusions, median	2	4	2	2	0.15
Platelet unit transfusions, median	3	3.5	2	3	0.43
Time to PMN count >500x10^6/L in days, median	14	13	14	14	0.47
Time to platelet count >25x10^9/L in days, median	14	14	14.5	14	0.29
Duration of hospitalization in days, median	27	29.5	27	23.5	0.33

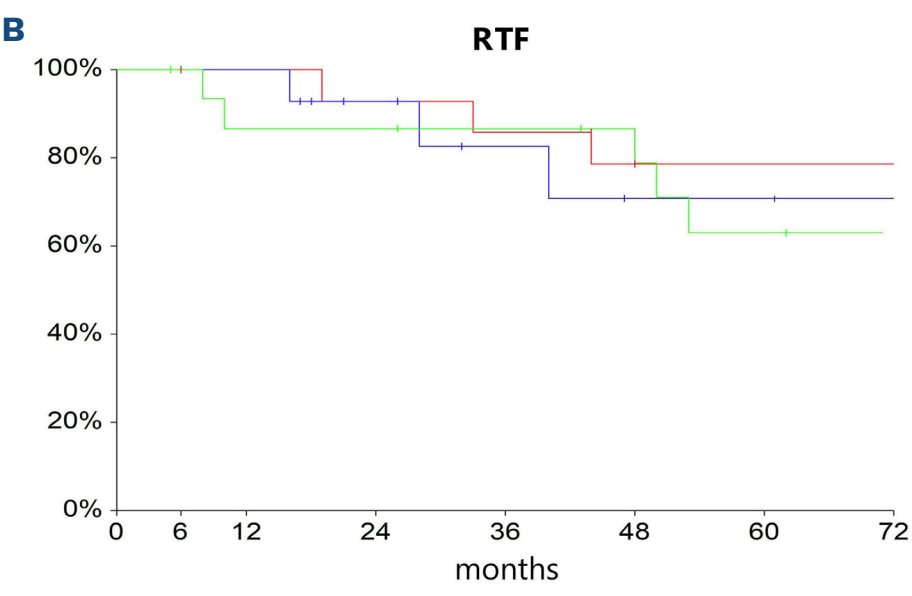
Mel140: melphalan 140 mg/m^2; Mel200: 200 mg/m^2; G-CSF: granulocyte colony-stimulating factor; GI: gastrointestinal; RBC: red blood cell; PMN: polymorphonuclear cell.

ab added to lenalidomide and steroids or rituximab.
The overall 6-year OS was 91% (95% confidence interval: 82-99) and did not differ among the treatment groups (*P*=0.35) (Figure 1C). Seven out of 45 patients (15.6%) died, four of PD and three of transplant-related infectious complications.

Discussion

Our data show that pre-transplant therapy, whether cyclophosphamide or other agents, did not have an impact on the outcome of the transplant. The results were in fact impressive in terms of PFS, time to retreatment and OS for patients affected by POEMS syndrome who underwent transplantation, confirming that aPBSCT is an effective and safe procedure in patients with this syndrome, independently of the mobilizing treatment. Zhao *et al*. recently concluded that aPBSCT was the best first-line treatment for POEMS syndrome, being better than lenalidomide plus dexamethasone and melphalan plus dexamethasone.[21]
The rarity of POEMS syndrome makes it difficult to conduct randomized trials. Consequently, a comparison between patients treated with different protocols evaluated in a multicenter cohort could be an option to stimulate debate about open questions in POEMS syndrome. In the literature there are many reports of favorable outcomes in patients who underwent aPBSCT with similar results from retrospective studies: a CR rate over 45%, improvement of neurological signs, as well as low rates of complications and transplant-related mortality.[11,15,17,18,21]
The best protocol to collect the peripheral blood stem cells (PBSC) for transplantation remains to be defined in patients with POEMS syndrome, even if PBSC mobilization was optimal in all our three groups. We recently published a report of a study to determine the better mobilizing regimen between G-CSF and alkylating agents: in 25 patients both strategies to mobilization of PBSC enabled the harvest of sufficient $CD34^+$ cell doses and allowed good and rapid engraftment.[45]
We noted that plerixafor was not used in patients in group C, so treatment with cyclophosphamide was able to yield a sufficient dose of PBSC only with G-CSF. Our previous study registered only a few poor mobilizers, equally distributed between the G-CSF and cyclophosphamide groups, so this finding would be better confirmed in a larger population of patients.
In the present analysis no significant differences were noted in clinical and laboratory characteristics between pre-treated patients and patients who underwent front-line aPBSCT. Sometimes the previous treatment with cyclophosphamide





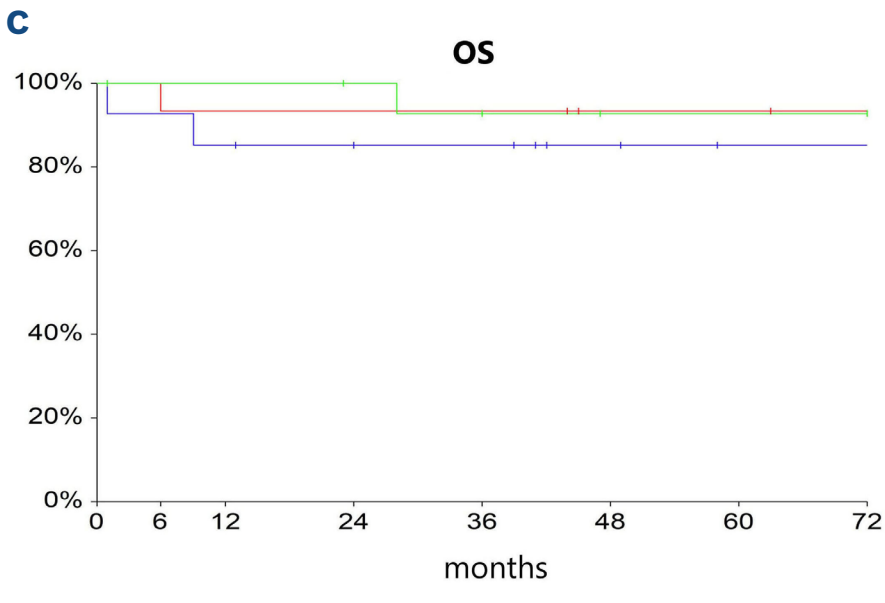


Figure 1. Outcomes of the three groups of patients with POEMS syndrome receiving different treatments prior to autologous peripheral blood stem cell transplantation. Group A (red): no treatment; group B (blue): other treatment; group C (green): cyclophosphamide). (A) Progression-free survival (PFS). (B) Percentage not requiring retreatment (retreatment-free, RTF). (C) Overall survival (OS).

served as a purging therapy to ameliorate the fitness of patients, leading them to the transplant procedure. Other studies looked at purging therapies before transplantation with cyclophosphamide as a promising approach in POEMS syndrome with disseminated bone marrow involvement.[3] In fact, we noted a role of chemotherapy in terms of eligibility to transplant for patients initially unfit for the procedure, so that patients who were not candidates for aPBSCT, after the pre-treatment achieved a better condition, becoming suitable for performance of the transplantation.

All our patients were conditioned with melphalan: Mel200 is the best option and no differences in toxicity were noted with this regimen compared to Mel140. There is a consensus in the literature about the use of melphalan, with rates of over 90-95% being registered.[11,18,21] Considering the main case series reported in literature we calculated that 460 patients were treated with Mel200/Mel140 and fewer than ten patients were treated with other conditioning regimes, mainly BEAM (carmustine, etoposide, cytarabine, and melphalan).[11,15,17,18,20,21,45,47]

Engraftment was similar in our three groups of patients and no differences between the three groups were seen in transplant complications, such as infections, hospitalization and transfusion requirements.

In conclusion, there were reasonable responses to all three schemes of treatment examined (front-line without pre-treatment, cyclophosphamide or other agents) with significant improvement in symptoms, durable PFS and impressive OS in newly diagnosed patients with POEMS syndrome who underwent aPBSCT. It should be noted that our study is one of the largest national series of patients with POEMS syndrome treated with aPBSCT in Europe. Patients unsuitable to undergo front-line aPBSCT because of comorbidity could be rescued with cyclophosphamide as a therapeutic and mobilizing agent.

Disclosures

No conflicts of interest to disclose.

Contributions

FA and LL performed research. SB, FL, II, SR, RR, DD, SO, PS, MM, AS, GLN, CC, EZ, MR, and DM collected data. EG analyzed the data. FA, EG, AB, and LL wrote the manuscript. SB, SS, and AB supervised the study.

Data-sharing statement

Data are available upon reasonable request.

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