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Case Report

Successful Second Autologous Stem Cell Transplantation for Late Disease Progression after the First Procedure in POEMS Syndrome

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Abstract: Autologous stem cell transplantation (ASCT) is a good option in fit young patients affected by POEMS syndrome. Few data are published on how to treat these patients in case of relapse. In this paper we described our two patients who underwent a second ASCT. From our experience, we can confirm that a second transplant is a real treatment option with good results and limited side effects. It provided excellent response and long-term disease-free survival in POEMS patients who relapsed after a first transplant, including late relapses.

Keywords: POEMS; ASCT; relapse

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Citation: Autore, F.; Innocenti, I.; Sora, F.; Chiusolo, P.; Piccirillo, N.; Bacigalupo, A.; Sica, S.; Laurenti, L. Successful Second Autologous Stem Cell Transplantation for Late Disease Progression after the First Procedure in POEMS Syndrome. *Appl. Sci.* **2022**, *12*, 2577. https://doi.org/10.3390/app12052577

Academic Editor: Oleh Andrukhov

Received: 22 December 2021
Accepted: 23 February 2022
Published: 2 March 2022

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1. Introduction

POEMS syndrome is a rare plasmacellular disorder characterized by polyradiculoneuropathy, organomegaly, endocrinopathy, monoclonal plasma-cell disorder and skin changes. Other findings, not included in the acronym are papilledema, extravascular overload, sclerotic bone lesions, thrombocytosis/erythrocytosis and elevated VEGF levels [1].

The pathogenesis is poorly understood, but a role of VEGF(Vascular-Endothelial Growth Factor), probably over-secreted by clonal plasma cells, is recognized both in diagnosis and in assessment of the response to therapy [2].

For fit patients, high-dose chemotherapy and/or autologous stem cell transplantation (ASCT) appear to be the best strategies [3–6].

For unfit patients, for whom high-dose chemotherapy is not recommended, many therapeutic approaches have been suggested, including steroids, low-dose alkylating agents and/or radiotherapy. Novel agents proposed are thalidomide, lenalidomide and bortezomib [7–9].

Relapsed POEMS syndrome is difficult to treat; a possible option in fit patients is a second ASCT.

We want to describe our experience with two patients who underwent a second ASCT for late disease progression after the first ASCT in comparison to a previous published case series of four patients successfully treated with ASCT after a brief progression [10].

2. Case Series

The main characteristics of our patients are summarized in Table 1.

The study was conducted in accordance with the and the patients signed informed consent.

Table 1. Patients characteristics.

	Patient 1	Patient 2
Age/sex	44/M	37/F
Induction therapy	CY-steroids	CY-steroids
Time from diagnosis to 1st ASCT (months)	4	3
Response prior to 1st ASCT	PR	PR
Conditioning regimen of 1st ASCT	Mel 200	Mel 200
Infused CD34+ cells (×106/kg)	5.43	2.99
Response after 1st ASCT	VGPR	VGPR
Time from 1st ASCT to relapse or progression (months)	73	43
Salvage therapy	Rd plus radiotherapy and CyBorD	Rd
Age at the 2nd ASCT	54	45
Time from 1st to 2nd ASCT (months)	115	68
Response prior to 2nd ASCT	CR	Clinical PD
Conditioning regimen	Mel 140	Mel 200
Infused CD34+ cells (×106/kg)	1.85	2.89
Response after 2nd ASCT	CR	CR
Relapse or progression	No	No
Follow up from 2nd ASCT (months)	86	11
Outcome	Alive	Alive

CR, complete response; PR, partial response; VGPR, very good partial response; PD, progressive disease; CY, cyclophosphamide; Rd, lenalidomide and dexamethasone; CyBorD, cyclophosphamide, bortezomib, and dexamethasone; Mel 140, melphalan 140 mg/m^2; Mel 200, melphalan 200 mg/m^2.

Both the patients were initially treated with steroids for their neurological symptoms; when referred to our hematologic Centre, they were diagnosed as POEMS syndromes and received an induction treatment with cyclophosphamide 4 g/m^2 and methyprednisolone for two courses. Peripheral blood stem cells (PBSCs) were harvested in the second course, with high-dose cyclophosphamide (CY) and granulocyte-colony stimulating factor (G-CSF). No toxicities were registered during the mobilization.

At the time of the first ASCT, both patients showed a positive serum immune-fixation and neurological signs. The conditioning regimen was high-dose melphalan 200 mg/m^2. The hospitalization was complicated by febrile neutropenia, successfully treated with antibiotics. Engraftment was prompt, both patients achieved a very good partial response (VGPR), with persistence of a positive serum immune-fixation, but showed an improvement in POEMS neurological and cutaneous signs.

The patients relapsed, 73 and 43 months respectively, after the first ASCT, and we decided to treat them with the Rd regimen (lenalidomide 25 mg/die d1-21 and dexamethasone).

Patient 1 received 21 courses of Rd and then radiotherapy of femur and pelvis; he was then treated with CyBorD (cyclophosphamide, bortezomib, and dexamethasone, 6 courses) for persistent disease before organizing a second PBSCs mobilization. In Patient 2 PBSCs were mobilized before 12 courses of Rd. In both patients a second ASCT was performed after a period of 115 and 68 months, respectively, from the first ASCT.

A second PBSC collection was successfully performed by G-CSF alone in Patient 1 and G-CSF plus plerixafor in Patient 2. There were no adverse events related to the second mobilization and harvesting procedure.

Both patients were conditioned with melphalan for the second ASCT: the dose was 140 mg/m^2 in Patient 1, due to toxicity from previous treatments and a suboptimal

CD34 + collection, and 200 mg/m^2 in Patient 2. The infused cell dose was 1.85 and 2.89 $\times$ 10^6 CD34 + cell/kg body weight, respectively.

Both patients achieved a successful engraftment: the median time to 500 polymorphonuclear (PMN)/µL was 12 and 11 days, respectively and to 1000 PMN/µL 13 days for both patients. The median time to 25 $\times$ 10^9 platelets/L was 17 and 13 days; the median time to 50 $\times$ 10^9 platelets/L was 25 and 17 days.

Patient 2 experienced a grade 2 febrile neutropenia, but no other adverse events including engraftment syndrome were registered.

After the second ASCT, both patients achieved a complete response with immunefixation negativity, an improvement in POEMS syndrome features, and VEGF dosages were negative in both patients.

The two patients are alive, treatment- and progression-free, at 91 and 17 months, respectively from the second ASCT. No secondary malignancy or myelodysplastic syndrome has occurred.

The two subjects signed the informed consent and the study was conducted in accordance with the Declaration of Helsinki and the Institutional Review Board (IRB).

3. Discussion

We confirm results reported by Shibamiya and colleagues [10]: a second ASCT is an effective treatment option for POEMS patients relapsing after a first ASCT. A second exposure to high-dose melphalan seems to be well-tolerated and produces a good response, without more neurotoxic drugs, in patients with significant neurological impairment [11]. We have observed some differences between our cases and other published papers.

The Shibamiya study [10] described relapses within one year from a first ASCT; in our cases relapses were late, and in keeping with previous studies [6,12,13]. The median interval from the first ASCT to the second was 40 months (range, 21–125 months) in Shibamiya [10] and 91 months in ours.

In previous studies the incidence of complications associated with ASCT in patients with POEMS syndrome was found to be associated with age and comorbidities [13–15]; therefore, a correct re-evaluation of relapsed patients in terms of fitness for ASCT needs to be done. The median age at second ASCT was comparable in Shabamiya's study [10] and in our two patients, as well as our data in terms of low rates of toxicity. We decided to perform a second ASCT in patients with an aggressive, but melphalan chemosensitive, POEMS. We also agree with the findings of aberrant cytokines, which could correlate with the risk of peri-transplant complications; if reduced with a good control of the disease progression due to an optimal induction therapy, it could explain the low rates of complications and toxicities in these studies.

Both our patients required a second PBSC collection, pointing out the issue of a reduced stem cells pool, and one patient required the combination of G-CSF and plerixafor [16,17].

Patient 1 was previously treated with lenalidomide, which is generally considered to hamper PBSC collection, so treatment with lenalidomide does not seem to reduce the possibility of mobilization. However, in young and fit patients affected by an aggressive POEMS syndrome we are considering harvesting a greater number of PBSCs up front, and cryopreserving a suitable CD34+ cell dose for a second ASCT, to be used in the case of a relapse. In addition, the Rd combination produced a deep response in both patients and it can be therefore used as a purging therapy or as a bridge to transplant, in late relapses after a first ASCT.

From our experience, we are considering harvesting a greater number of stem cells up front, to be used in the case of a relapse in patients affected by an aggressive POEMS syndrome. Following the success of our two patients, we modified our clinical practise starting with the stem cells harvest procedure.

4. Conclusions

We confirm that a second ASCT is a real treatment option, providing excellent response and long-term disease-free survival in POEMS patients who relapsed after a first ASCT.

Author Contributions: Conceptualization and methodology, F.A. and L.L.; validation, resources, and data curation, I.I., F.S., P.C. and N.P.; writing original draft preparation, F.A.; writing review and editing, supervision, A.B., S.S. and L.L. All authors have read and agreed to the published version of the manuscript.

Funding: No funding was received for this study.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Hematology JACIE date 02/03/2020.

Data Availability Statement: Data is contained within the article.

Conflicts of Interest: The authors declare that they have no conflict of interest.

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