

High-Dose Therapy and Autologous Transplantation for POEMS Syndrome: Effective, But How to Optimise?

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LETTER TO THE EDITOR

POEMS syndrome is a rare paraneoplastic phenomenon secondary to plasma cell dyscrasia. Treatment is aimed at the underlying plasma cell clone and its survival factors. Autologous stem cell transplantation (ASCT) is selected for patients who have multifocal skeletal disease and/or bone marrow involvement with adequate performance status (Dispenzieri et al, 2017) (Humeniuk et al, 2013). Because of the rarity of the disease, there are relatively few papers describing outcomes following ASCT. This analysis seeks to add further to the emerging evidence and elucidate prognostic factors.

All patients attending the UCLH Centre for POEMS who had previously undergone ASCT were reviewed. Forty-two patients had undergone ASCT between 1998 and July 2018. Details are shown in Table 1. Disease status on admission for ASCT was used as the baseline. Response assessment was carried out at three, six and 12 months, with a tailored frequency thereafter. The time to maximal VEGF, haematological, radiological and clinical responses were calculated, using previously published definitions (D'Souza et al, 2012). Anonymised data collection was covered by local policies.

Median follow up time was 62.2 months, range 6 to 226 months. Clinical response was observed in 38 patients. Three patients died and one patient did not have a discernible clinical response within the follow up period. Haematological response was evaluable in 33 patients: 14 (33.3%) patients achieved complete response (HR_{CR}), seven (16.7%) patients achieved very good partial response (HR_{VGPR}), three of whom could not be classified as HR_{CR} because they had not undergone repeat bone marrow examination. Three (7.1%) patients achieved partial response (HR_{PR}), whereas nine patients were classified as haematological non-responders (HR_{NR}). Of the patients who were non-assessable by haematological criteria, seven had solitary plasmacytomas and hence did not have bone marrow involvement, and two died before having repeat bone marrow examination.

Regarding VEGF response, 23 of the 36 evaluable patients achieved complete response ($VEGF_{CR}$), five patients partial response ($VEGF_{PR}$) and seven patients had no response ($VEGF_{NR}$). Average pre-ASCT VEGF was 4959pg/mL, with values available for 29 patients. VEGF showed a significant reduction to means of 489.5pg/mL at 6 months and 330pg/mL at 12 months post ASCT ($p<0.001$). Of 17 patients with FDG-avid disease, ten underwent repeat scans. Seven patients achieved complete response (R_{CR}) and three patients achieved partial radiological response (R_{PR}).

Neurological and functional responses were achieved in all but two patients during follow up. Two deaths occurred before reassessment was possible. Median time to first observed clinical improvement was four months, with continued improvement sometimes seen for several years. Three patients were bed-bound prior to ASCT, all experiencing a marked improvement in their mobility following therapy. One was able to mobilise with ankle foot orthoses only. There was a significant improvement in overall neuropathy limitation scores (ONLS), with a median pre-ASCT of 6 (range 0-12) and post-ASCT score of 2 (range 0-8) ($p<0.01$).

Thirty-nine patients (92.9%) were still alive at time of review. One year survival rate was 95.4% and five year survival rate was 89.5% (figure 1). Three patients (7.1%) had died. The first patient did not survive to discharge following ASCT and died from progressive POEMS features and recurrent hospital acquired pneumonia within two months of transplantation. The second patient died of unknown cause within two months of ASCT, following discharge and a period of uneventful recovery. Transplant-related mortality was therefore calculated as 2.4% ($n=2$). The third patient developed worsening features of POEMS two years after transplantation and was treated with cyclophosphamide followed by melphalan. They subsequently developed myelodysplastic syndrome, which resulted in death at six years.

Six patients relapsed (median time 39.2 months, range 9-78 months.). Progression free survival (PFS) was 80.1%, with three deceased patients and five patients currently undergoing further systemic therapy. One-year and five-year PFS was 81.6% and 76.9% respectively (figure 1). Of the patients who had a clinical relapse, all developed worsening neuropathy with recurrence of oedema. All but two patients received lenalidomide and dexamethasone for their relapse. One patient received Carfilzomib and dexamethasone due to a myelomatous phenotype and a higher marrow burden.

Univariate analysis of relapsed versus non-relapsed patients showed absence of HR_{CR} to be significant ($p=0.027$). No patients who achieved HR_{CR} following ASCT subsequently relapsed, whereas of those with persisting monoclonal plasma cells or monoclonal protein had a 31.6% relapse rate. Age, VEGF, albumin and functional status were not statistically different between patients in remission and those who had relapsed.

To our knowledge, this is the first paper detailing the experience of autologous stem cell transplantation for POEMS syndrome at a UK centre. This analysis confirms high rates of overall- and progression-free survival following transplantation (Kourelis et al, 2016) (Karam et al, 2015) (Cook et al, 2017) (Ohwada et al, 2018) (D’Souza et al, 2012). Our experience confirms that attainment of HR_{CR} following ASCT in POEMS syndrome is associated with a significantly lower rate of relapse (Kourelis et al, 2016) (Ohwada et al, 2018) (Wang et al, 2017). The median time to confirmed HR_{CR} was 5.5 months, demonstrating that the success of ASCT can often be determined soon after therapy and allows for early relapse risk stratification. Our work carries the limitations of retrospective analysis and is susceptible to some inter-rater variation in terms of clinical response. Further work is required to ascertain whether maintenance following ASCT has a role in patients who do not achieve HR_{CR}. Prolonged disease remission and substantial recovery is possible in the majority post ASCT, but its optimisation is critical to improve outcomes for more patients. More informative, readily applicable tools are needed to guide therapeutic decision-making, specifically the optimum depth of response before and after ASCT and biomarkers that have prognostic significance. In the current era of emerging novel therapies, clinical trials of alternative or adjuvant approaches to ASCT would be of considerable benefit to patients affected by POEMS syndrome.

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Table 1. Autologous Stem Cell Transplantation (ASCT) Details	
Male	26 (61.9%)
Median Age at ASCT	52 years (range 32-73)
Median Time from Diagnosis to ASCT	5.5 months (range 1-122 months)
ASCT First Line Treatment	41 (97.6%)
ASCT As Consolidation of Prior Induction	16 (38%)
ASCT For Relapse	1 (2.4%)
Mobilisation Agent	
Cyclophosphamide + G-CSF	10
G-CSF	16
Information not available	16
Dose of Melphalan	
140mg/m ²	2 (4.8%)
200mg/m ²	40 (95.2%)
Median CD34+ Cells Infused (Range) (x10⁶/kg)	3.45 (1.1-8.7)
Median Time to Neutrophil Engraftment in Days (Range)	12 (10-26)

Median Time to Platelet Engraftment in Days (Range)	14 (7-24)
Engraftment Syndrome	3 (7.1%)
Neutropenic Fevers	14 (33.3%)

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