

Clinical, electrophysiological and VEGF two-year response after Lenalidomide or Stem Cell Transplantation in patients with POEMS

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INTRODUCTION

POEMS syndrome is a rare multisystem disease characterized by polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal gammopathy (M) and skin changes (S)[1]. A usually severe demyelinating and axonal neuropathy is often the most prominent and disabling clinical manifestation [2]. The pathogenesis of POEMS syndrome is unclear even if overproduction of vascular endothelial growth factor (VEGF) seems to play a major role.[1,2] Autologous haematopoietic stem cell transplantation (HSCT) is now considered the most effective therapy in patients with disseminated disease.[1] This therapy is however not feasible in all patients because of their advanced age or the presence of severe concomitant conditions. A number of immune or cytostatic agents have been also used with variable efficacy in POEMS,[1] including lenalidomide whose efficacy we recently reported in 13 of the 18 treated patients.[3] Little is known however on the degree of response to lenalidomide in comparison to HSCT.

SUBJECTS

We retrospectively reviewed the clinical, biological and electrophysiological data from 15 patients with POEMS syndrome diagnosed according the criteria proposed by Dispenzieri[1] who neurologically improved after therapy with lenalidomide or HSCT. All the patients had been treated and followed at our Institution for at least two-years. The study was approved by the IRB of our Institute and all the patients signed an informed consent for the review of their data.

Six patients (4 males, 2 females; mean age at disease onset 48 years, range 41-53; mean disease duration 23 months, range 5-76) received high-dose melphalan chemotherapy followed by HSCT. Nine patients (7 males, 2 females; mean age at disease onset 54 years, range 44-65; mean disease duration 48 months, range 9-226) were treated with lenalidomide (25 mg/day for 21 days every month for 10-58 cycles) and oral dexamethasone (40 mg weekly)[3]. These patients did not undergo HSCT because of advanced age (2), severe concomitant conditions (3), patient preference (2), or relapse after a previous HSCT (2). Five of them had not previously improved after therapy with intravenous immunoglobulins (IVIg) alone (1) or with corticosteroids (1) or cyclophosphamide (1), corticosteroids (1) or cyclophosphamide (1). Three patients treated with HSCT did not respond to previous therapy with IVIg (2) or local radiotherapy (1). In all the patients the clinical, electrophysiological parameters and VEGF levels were assessed,[3] before therapy (T0)

and one (T1) and two years (T2) after starting the therapy. Clinical response was measured with the modified Medical Research Council (MRC) sumscore for muscle strength, range 0 (no contraction) to 80 (normal in 16 muscles), and the Overall Neuropathy Limitation Scale (ONLS), range 0 (normal) to 12 (unable to do any purposeful movement with arms and legs). Motor conduction studies were performed on the ulnar, tibial and peroneal nerves, and included the measurement of distal and proximal compound motor action potential (CMAP) amplitudes, distal motor latency (DML) and motor nerve conduction velocity (MCV). Sensory conduction velocities (SCV) and sensory action potentials (SNAP) were measured in the ulnar and sural nerves. VEGF levels were measured by enzyme-linked immuno sorbent assay (ELISA)(normal: < 1000 pmol/L)[3]. In each group, the difference in the clinical, electrophysiological and biological parameters between baseline (T0), and one (T1) and two years (T2) after therapy was assessed by analysis of variance (ANOVA). A probability (p) value of < 0.05 was considered statistically significant.

RESULTS

We found a significant improvement in the MRC sumscore and in the ONLS score after one and two years both in patients treated HSCT (p=0.001) and in patients treated with lenalidomide (p=0.002)(Table). The number of patients was too small for a statistical comparison of the improvement between the two groups, but the mean improvement was similar in the two groups.

The frequency of nerves with no potential was higher in lower than in upper limbs with no CMAP response in 67% peroneal nerves, 73% tibial nerves and 73% sural nerves before and after treatment. Similarly infrequent was the response in the sensory ulnar nerve. We focused our study on the ulnar motor nerve. The mean DML of this nerve was reduced in patients treated with HSCT or lenalidomide, but the difference was significant only for HSCT (p=0.009; lenalidomide p=0.08). MCV significantly improved in patients treated with HSCT (p=0.03) and lenalidomide (p=0.0004) as did distal CMAP amplitude (HSCT p=0.009; lenalidomide p=0.003). We did not compare the improvement between two groups, but the mean improvement was similar in the two groups (Table).

Serum VEGF levels were reduced after treatment in patients treated with HSCT or lenalidomide, but the difference was significant for lenalidomide (T0 vs T1: p=0.027; T0 vs T2: p=0.046) but not for HSCT (T0 vs T1: p = 0.156; T0 vs T2: p=0.112);

CONCLUSIONS

POEMS syndrome is a chronic progressive and often disabling disorder with estimated median survivals of nearly 14 years. In patients with disseminated disease, HSCT is considered the preferred treatment. Of the 59 patients receiving HSCT at the Mayo Clinic in Rochester, progression-free survival (PFS) after a median follow-up of 45 months was 98% and 75% after one and 5 years respectively [4]. Lenalidomide has been recently reported to be effective in patients with POEMS and was not associated with neurotoxicity.[3,5] A recent analysis of 51 patients with POEMS syndrome showed hematologic response in 95% of the patients, a neurological response in 92% with a PFS at one year of 94% [5]. In our study HSCT and lenalidomide resulted in a significant improvement over two years in the MRC sumscore, ONLS score, and in the ulnar CMAP and MCV while serum VEGF levels were significantly reduced only in the lenalidomide group. Even if the number of treated patients was too small to compare statistically the difference in the improvement between the two groups, we observed a comparable degree of response in the two groups by the end of the first and second year. Since HSCT may not be suitable for all patients or may be refused by others for its potential risks, lenalidomide may represent a valuable alternative for at least two years in these patients or in those relapsing after HSCT.

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Authors' contributions

Study design: MB, ENO

Experiments and procedures: FT, FG, AN, AS, MZF, CG

Data analysis and interpretation: MB, ENO

Manuscript drafting: MB, ENO

Manuscript editing: All

Approval of final draft: All

Conflicts of interest

ENO: personal fees for lecturing or Advisory/Scientific/Safety Board Membership not related to this study from Baxter, Italy; CSL Behring, Switzerland; Kedrion Biopharma, Italy; LFB, France; Novartis, Switzerland; UCB, UK; Astellas Biopharma, the Netherlands.

The other Authors have no conflicts of interests.

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Table

Clinical and electrophysiological findings in patients with POEMS syndrome treated with HSCT and lenalidomide

| | HSCT (n=6) | Lenalidomide (n=9) |
|--|--------------------|---------------------------|
| MRC (mean \pm SD; median) | | |
| Time 0 | 65 \pm 13; 74 | 64 \pm 19; 70 |
| Time 1 | 71 \pm 11; 70 | 67 \pm 13; 77 |
| Time 2 | 71 \pm 7; 75 | 71 \pm 10; 73 |
| p | 0.001 | 0.001 |
| ONLS (mean \pm SD; median) | | |
| Time 0 | 5.8 \pm 3.2; 5 | 5.4 \pm 2.3; 6 |
| Time 1 | 3.5 \pm 2.5; 3 | 3.7 \pm 1.5; 3.5 |
| Time 2 | 3.0 \pm 2.2; 2.5 | 4 \pm 1.8; 3.5 |
| p | 0.0001 | 0.002 |
| Ulnar DML (msec) (mean \pm SD; median) | | |
| Time 0 | 3.2 \pm 0.6; 3.4 | 4.2 \pm 1.4; 3.8 |
| Time 1 | 3.3 \pm 0.4; 3.3 | 3.3 \pm 0.5; 3.1 |
| Time 2 | 3 \pm 0.5; 2.8 | 3.2 \pm 0.4; 3.1 |
| p | 0.009 | 0.08 |
| Ulnar MCV (m/sec) (mean, median, range) | | |
| Time 0 | 41.3 \pm 9.4; 38 | 34.7 \pm 11.3; 33 |
| Time 1 | 39.7 \pm 6.7; 38 | 45.2 \pm 9.9; 47 |
| Time 2 | 47.1 \pm 11; 47 | 48.6 \pm 8.7; 46 |
| p | 0.03 | 0.0004 |
| Ulnar CMAP (mV) (mean, median, range) | | |
| Time 0 | 8.6 \pm 2.1; 8.5 | 5.6 \pm 2.4; 6.1 |
| Time 1 | 8.7 \pm 2.6; 9.3 | 6.3 \pm 3.3; 6.7 |
| Time 2 | 9.7 \pm 1.4; 9.4 | 5.8 \pm 2.2; 6.3 |
| p | 0.009 | 0.003 |

MRC: Medical Research Council; ONLS: Overall Neuropathy Limitation Scale; DML: Distal Motor Latency; MCV: motor nerve conduction velocity; CMAP: compound muscle action potential; SD: standard deviation