

## Bortezomib Therapy Followed by Autologous Stem Cell Transplantation in POEMS Syndrome

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**Background:** The acronym POEMS refers to polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes. Increased levels of cytokines, including vascular endothelial growth factor (VEGF), appear to play a pathogenic role. POEMS syndrome is progressive and eventually leads to death from neurological problem without therapy.

**Methods:** We treated 3 patients affected by POEMS syndrome with front-line bortezomib treatment and the high-dose melphalan with autologous stem cell transplantation (ASCT).

**Results:** Bortezomib reduced circulating levels of VEGF in sera. After a median follow-up of 18 months (range, 16~20), all patients are alive with progressive improvement in neurological disease, skin changes, performance status and have no evidence of clonal plasmacytosis or organomegaly.

**Conclusion:** ASCT following bortezomib treatment may be a potential treatment option for patients with POEMS syndrome. (*Korean J Hematol 2008;43:145-149.*)

**Key Words:** POEMS syndrome, Bortezomib, Vascular endothelial growth factor, Autologous stem cell transplantation, Peripheral neuropathy

### INTRODUCTION

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome -also known as osteosclerotic myeloma, Crow-Fukase syndrome, or Takasaki syndrome- is a paraneoplastic syndrome resulting from an underlying plasma-proliferative disorder.<sup>1)</sup> The pathogenesis of POEMS syndrome is not well understood, but overproduction of vascular endothelial growth factor (VEGF), presum-

ably secreted by a plasmacytoma, is considered responsible for the characteristic symptoms.<sup>2)</sup> With the exception of those patients who have a solitary osteosclerotic lesion, the conventional treatment with cytotoxic agents, corticosteroids, intravenous immunoglobulin, and total plasma exchange produces disappointing results. In appropriate candidates, after peripheral blood stem cells collection, high-dose chemotherapy with autologous stem cell transplantation (ASCT) can be considered.

Bortezomib is a first-in-class proteasome in-

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hibitor that induces apoptosis and growth arrest and reverses chemoresistance in multiple myeloma (MM) cells.<sup>3)</sup> In addition, bortezomib offers a novel approach to the treatment of MM in phase II and III clinical trials and produces rapid control of the disease.<sup>4,5)</sup> Encouraging data from MM and AL amyloidosis,<sup>6)</sup> a plasma cell disorder, suggested that bortezomib might also be a useful agent in POEMS syndrome. The use of novel agents can increase the response rate of POEMS syndrome before ASCT, which may therefore improve post-transplantation response and survival.<sup>7,8)</sup>

There is minimal experience using the newer agents to treat POEMS syndrome, though there are anecdotal reports related to the beneficial application of thalidomide.<sup>9)</sup> Exacerbation of neuropathy is also a legitimate concern when contemplating bortezomib as a therapeutic option in patients with POEMS. We report three patients with POEMS syndrome who achieved significant improvement after treatment with high-dose melphalan with autologous stem cell support, following bortezomib induction therapy.

## PATIENTS AND METHODS

We diagnosed three patients with POEMS syndrome, all of whom fulfilled diagnostic criteria of POEMS syndrome.<sup>1)</sup> They were 40, 55, and 56 years of age. Table 1 lists the main elements of POEMS seen in each patient. Serum protein electrophoresis revealed monoclonal IgA  $\lambda$  in one patient and IgG  $\lambda$  in two patients. In all cases, the monoclonal component was small -below 10g/L- and polyclonal immunoglobulin level was normal. All three patients had multiple bone lesions; two had purely osteosclerotic lesions, and one had

mixed osteosclerotic and osteolytic lesions. In all three patients, standard bone marrow aspirate showed less than 5% plasma cells, and the plasmacytic nature of the bone lesions was demonstrated by focal biopsy. Other manifestations of POEMS syndrome included organomegaly in two patients and skin changes in two patients. In all cases, blood cell counts were normal. All patients had distal bilateral sensory and motor disturbance, predominating in the lower limbs and associated with abolition of deep tendon reflexes. Two patients were wheelchair-dependent because they had virtually no movement in the lower extremity muscles. Electromyographic studies showed sensorimotor polyneuropathy and severe diffuse neuropathic affectation with sensory and lower limb predominance in all patients. The patients gave informed consent and received ASCT following bortezomib therapy.

Patients were treated as follows: (1) local radiation was considered in the patients who had prominent focal bone lesions and was actually performed in two patients, (2) three cycles of bortezomib (1.3mg/m<sup>2</sup> intravenously twice weekly for two weeks on a 21-day schedule), (3) autologous peripheral blood stem cell (PBSC) collection was performed after mobilization by chemotherapy (intravenous cyclophosphamide over two days, 2 g/m<sup>2</sup>/day) plus subcutaneous granulocyte colony-stimulating factor (G-CSF, 10  $\mu$ g/kg/day), (4) high-dose melphalan (200mg/m<sup>2</sup>) and ASCT were performed about one month after PBSC collection.

## RESULTS

All three patients successfully underwent high-dose melphalan therapy with ASCT without ex-

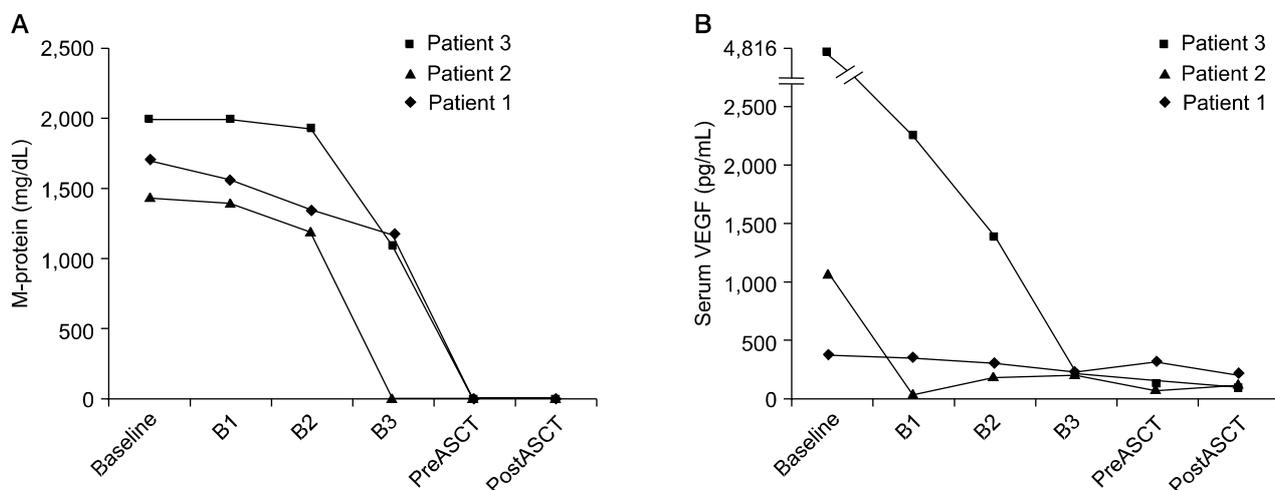
**Table 1.** Characteristics of patients with POEMS syndrome

Patient	Age (y)	Sex	Polyneuropathy	Organomegaly	Endocrinopathy	M component	Skin changes
1	40	M	Sensorimotor, 4 limbs	Spleen	(-)	IgG (lambda)	Hyperpigmentation
2	55	F	Sensorimotor, 4 limbs	Spleen	(-)	IgA (lambda)	(-)
3	56	F	Sensorimotor, 4 limbs	(-)	Diabetes mellitus	IgG (lambda)	Hyperpigmentation

cessive toxicity. During bortezomib induction therapy, there were no serious adverse events, defined as any event that was life-threatening, required hospitalization, resulted in persistent or significant disability, or had important medical consequences. A total of  $31.5$ ,  $15.5$ , and  $13.1 \times 10^6$   $CD34^+$  cells/kg were obtained for each patient by apheresis over two consecutive days. Post-transplant neutrophil and platelet recoveries ( $> 500 \times 10^6/L$  and  $> 50 \times 10^9/L$ , respectively) occurred within twelve days and were sustained in all patients. No toxic deaths occurred during PBSC mobilization or transplantation. Thus, in contrast to AL amyloidosis,<sup>1,10</sup> the unique features of POEMS syndrome, particularly bone lesions and neuropathy-related disability, may not translate into higher risk with ASCT and bortezomib treatment, as compared with classic MM.

After three cycles of bortezomib treatment, monoclonal Ig was no longer detectable by electrophoresis or immunofixation test in one patient. Criteria for defining complete response (CR), partial response, stable disease, and progressive disease were those previously reported by Bladé et al.<sup>11</sup> The other two patients did not achieve CR, and monoclonal Ig was still detectable before ASCT. In these patients, monoclonal Ig

was no longer detectable by immunofixation in the serum or urine after ASCT, suggesting that the high-dose melphalan likely played a crucial role in tumor mass reduction. In all cases, remission of plasma cell proliferation was associated with a marked improvement in performance and in neurologic symptoms. Motor deficiency significantly improved in all patients. In particular, the patients who were wheelchair dependent are now either totally independent of walking aids or using ankle/foot orthotics with or without a cane. In the ensuing months, an improvement in the patients' clinical condition was observed together with disappearance of monoclonal Ig. The patient who had distal motor deficits and inability to walk normally recovered completely, except for minimal residual motor dysfunction. Similarly, sensory disturbances improved in two of the three patients. Fig. 1A shows serial changes in serum monoclonal Ig levels before and after ASCT. In addition to neurologic symptoms, other manifestations of POEMS syndrome improved, especially skin color changes and organomegaly, which were no longer detectable after transplantation in any patient. After a median follow-up of 18 months (16~20 months) since ASCT, no patient has experienced a relapse



**Fig. 1.** Serial changes in serum levels of M-protein (A) and vascular endothelial growth factor (B) following bortezomib treatment and autologous stem cell transplantation (ASCT). Abbreviations: B1 after 1<sup>st</sup> chemotherapy, B2 after 2<sup>nd</sup> chemotherapy and B3 after 3<sup>rd</sup> chemotherapy, prior to ASCT (preASCT), and after ASCT (postASCT).

either of plasma cell dyscrasia or of related POEMS manifestations.

We studied circulating VEGF concentrations in the three patients as time went on (Fig. 1B). Pretreatment circulating VEGF levels (360, 4,816, and 1,057pg/mL) in each patient were elevated compared with the median level from five normal, healthy persons ( $207 \pm 28.5$ pg/mL). Post-bortezomib treatment VEGF levels were reduced (233, 204, and 206pg/mL, respectively), and the circulating VEGF concentrations were further reduced (215, 98, and 128pg/mL, respectively) one month after ASCT.

## DISCUSSION

This is the first report of bortezomib therapy prior to ASCT in patients with POEMS syndrome. Although still poorly understood, the pathogenesis of POEMS syndrome may be related to clonal plasma cell production of a combination of soluble factors.<sup>12,13</sup> Among various cytokines, VEGF has been shown to play a pivotal role in this process.<sup>14,15</sup> VEGF contributes to symptoms by increasing microvascular permeability, which leads to edema, increased endoneural pressure, and exposure to serum cytokines and complement, causing demyelination.<sup>16</sup> Interventions that specifically decrease VEGF levels have been successful in improving symptoms. Bortezomib was well tolerated and induced rapid reduction in circulating VEGF concentrations in our patients. All three patients had dramatic improvement in all disease features following ASCT, most remarkably the sensory-motor neuropathy, organomegaly, and skin changes. While concerns about exacerbating neuropathy are legitimate, bortezomib may do more good than harm. Although this retrospective study involved a small number of patients, it shows the feasibility of bortezomib induction treatment with ASCT in patients with POEMS syndrome.

## 요 약

**배경:** 포우임스증후군은 단클론항체와 말초신경염이 주된 임상양상으로 적절한 치료가 이루어지지 않으면 심장, 폐 등 주요 장기의 기능부전으로 사망할 수 있는 질환이다. 병적 기전에 중요한 인자로 혈관내피성장인자(vascular endothelial growth factor, VEGF)가 알려져 있다. 최근 다발성골수종에서 bortezomib은 재발, 불응성 환자뿐 아니라 초기에 투여하여도 효과적으로 종양세포를 제거하여 반응률이 향상되었다는 보고가 있다.

**방법:** 3예의 환자에서 bortezomib을 초기치료로 투여하고 이어서 고용량 멜팔란 투여와 자가 조혈모세포 이식(autologous stem cell transplantation, ASCT)을 시행하였다. 치료 전·후에 주기적으로 혈청 VEGF 농도를 측정하였다.

**결과:** 3예 모두 치료 전 혈청 VEGF 값이 상승하였고 bortezomib 투여 후 혈청 VEGF는 감소하였으며 ASCT 후 더욱 감소되었다. ASCT 후 3예 모두에서 임상 증상이 호전되었으며 단클론항체가 소실되었다. 중증의 부작용은 관찰되지 않았으며 중양값 18개월(16~20개월)의 추적관찰 후에 재발이 발생하지 않았다.

**결론:** 치료받은 환자의 수가 많지 않지만 포우임스증후군 환자에서 초기에 bortezomib 치료 후에 ASCT는 효과적인 것으로 생각한다.

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