Brief report

High-dose therapy and autologous blood stem cell transplantation in POEMS syndrome

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We treated 5 patients with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome and multifocal bone lesions or diffuse bone marrow plasmacytic infiltration with high-dose therapy (HDT) and autologous blood stem cell transplantation. In all cases, the treatment produced remission of plasma cell proliferation associated with marked improvement in the patients' performance status, neurologic symptoms, and other manifestations of the syndrome. HDT with stem cell support should be investigated further as a therapeutic option in patients with POEMS syndrome and disseminated plasma cell dyscrasia. (Blood. 2002;99: 3057-3059)

Introduction

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a multisystem disorder initially described by Japanese authors[1] and then reported in Europe and North America.[2-4] It is characterized by the combination of conditions that make up its abbreviation and may also include systemic symptoms, edema and anasarca, thrombocytosis, and various other manifestations.[1-4]

This syndrome is associated with a plasma cell dyscrasia having some unique features such as osteosclerotic bone lesions and λ-light chain isotype of secreted monoclonal immunoglobulin (MIg).[1-4] The pathogenesis of POEMS syndrome is still unknown, but all symptoms are likely secondary to the plasma cell proliferation as supported by the dramatic improvement that may be obtained by radiotherapy and/or surgical excision in patients with solitary plasmocytoma and by the reappearance of POEMS symptoms when bone lesions recur.[5,6]

In patients with diffuse bone marrow infiltration or multifocal lesions, conventional chemotherapy is usually proposed, but patient's quality of life most often deteriorates because of progressive neuropathy.[7,8] Because of the well-established dose-response effect of melphalan in myeloma patients,[9] we explored high-dose therapy (HDT) and stem cell rescue as an alternative approach in 5 patients.

Study design

Diagnosis of POEMS syndrome was considered in patients who presented with plasma cell proliferation associated with peripheral neuropathy, in the absence of any known cause of nerve involvement. All patients with multifocal bone lesions or diffuse bone marrow plasmatic infiltration were offered the option of HDT followed by autologous transplantation.

Since 1996, 5 patients (of 9 patients with POEMS) fulfilled these criteria. All gave informed consent and received HDT. They were between 44 and 62 years of age. Table 1 lists the main elements of POEMS in each patient. Monoclonal IgAλ and IgGλ were detected in the serum of 3 and 1 patients, respectively. The last patient had a biclonal IgMλ and IgGκ gammopathy. In all cases, the monoclonal component was small, below 10 g/L, and polyclonal immunoglobulin level was normal. One patient (case 3) had nephrotic syndrome, and renal biopsy showed glomerular alterations, including cellular proliferation and mesangiolysis that suggested POEMS nephropathy[10,11]; congo red staining was negative.

Three patients had multiple bone lesions that were purely osteosclerotic and mixed, osteosclerotic and osteolytic, in 1 and 2 cases, respectively. In these patients, standard bone marrow examinations were normal, and the plasmacytic nature of the bone lesions was proven by a focal biopsy. One patient (case 5) presented with solitary mixed iliac plasmocytoma and has diffuse bone marrow infiltration by monotypic plasma cells bearing λ light chains. Patient 3 had no detectable bone lesion but diffuse bone marrow lymphoplasmacytic infiltration. Appropriate staining of biopsies did not detect AL amyloidosis in any case.

All patients had distal bilateral sensory disturbance predominating in the lower limbs, associated with abolition of deep tendon reflexes. Two patients also presented with motor deficiency, including one who was bedridden because of tetraparesia. Isolated increase in protein level (above 1 g/L) was detected in the cerebrospinal fluid of the 4 studied patients. Electromyographic studies provided evidence for demyelinating lesions in all patients either isolated ($n = 2$) or associated with axonal degeneration ($n = 3$).

Other manifestations of POEMS syndrome (Table 1) included organomegaly in 3 patients; impotence, diabetes mellitus, adrenal insufficiency, and/or hypothyroidism in 4 patients; skin changes in 4 patients (hyperpigmentation in 3, telangiectasia in 1); and peripheral edema in 3 patients, associated with papilledema in 2 cases. In all cases, blood cell counts were normal.

As indicated in Table 2, patient 1 was initially considered to have Guillain-Barré syndrome and progressively became bedridden despite various therapeutic attempts. Other patients had been briefly or not previously treated.

Patients were treated as follows: (1) Local radiation was considered in the patients who had a prominent focal bone lesion and was actually performed in 3 patients. (2) Autologous peripheral blood stem cell (PBSC) collection was performed after mobilization by chemotherapy (intravenous cyclophosphamide over 2 days, 60 mg/kg/d) plus subcutaneous granulocyte colony-stimulating factor (G-CSF, 5 μg/kg/d). (3) HDT and PBSC transplantations were performed about 1 month after PBSC collection according to the regimens listed in Table 2.

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Table 1. Main characteristics of patients with POEMS syndrome

Patient no.	Age (y)	Sex	Polyneuropathy	Organomegaly	Endocrinopathy	M component	Skin changes*
1	44	F	Tetraplegia	Spleen	—	IgGλ	—
2	52	M	Sensory, 4 limbs	—	Impotence	IgGκ+ IgMλ†	Melanodermy
3‡	50	M	Sensory, predominating in lower limbs with disabling ataxia	Liver, spleen, adenopathy	Adrenal insufficiency	IgAλ	Melanodermy
4	62	M	Sensory 4 limbs, distal motor deficit of lower limbs	—	Diabetes mellitus	IgAλ	Melanodermy
5	54	M	Sensory, lower limbs	Liver	Diabetes mellitus, hypothyroidism	IgAλ	Telangiectasia

POEMS indicates polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; Ig, immunoglobulin.
*Associated with peripheral edema in patients 2, 3, and 4.
†Associated with monotypic plasma cells bearing λ light chains in the biopsied osteosclerotic bone lesion.
‡Patient of Asiatic origin presenting with, in addition, POEMS nephropathy.

Results and discussion

All 5 patients in whom we planned to perform HDT actually received this treatment. No toxic deaths occurred during PBSC mobilization or transplantation. Posttransplant neutrophil and platelet recoveries ($> 500 \times 10^6$/L and $> 50 \times 10^9$/L, respectively) occurred within 15 days and were sustained in all cases. The morbidity of the procedure, including mucositis and culture-negative neutropenic fever for 2 to 6 days, was not unexpected in any case, including in the patient who received sequential HDT and tandem transplantation while bedridden. Thus, in contrast to AL amyloidosis,[12,13] the unique features of POEMS syndrome, particularly osteosclerosis and neuropathy-related disability, may not translate into higher risk of HDT as compared with classic multiple myeloma.

After HDT, MIg was no longer detectable by immunofixation in the serum or urine of 4 patients. The other patient (case 3) achieved a very good response with disappearance of abnormal bone marrow infiltration and with normal serum electrophoresis, whereas the MIg was still detectable by serum immunofixation. In all patients, MIg was easily detectable before transplantation, and HDT likely played a crucial role in tumor mass reduction. The small number of patients precludes any definitive conclusion about the best high-dose therapeutic strategy (one or 2 HDT, with or without total body irradiation) to propose to patients with POEMS. In contrast, mobilizing PBSCs by growth factor alone might be more convenient than using high-dose cyclophosphamide, which potentially increases the risks of the procedure, whereas it did not produce significant tumor mass reduction in any of our patients, as assessed by follow-up of MIg level.

In all cases, remission of plasma cell proliferation was associated with a marked improvement in performance and in neurologic symptoms (Table 2). Motor deficiency significantly improved, particularly in the tetraplegic patient who could walk again about 4 months after transplantation. Similarly, sensory disturbance improved in all cases, allowing, for instance, patient 3 to jog a few kilometers, whereas ataxia precluded running even a few meters before HDT. In all cases but one (case 2), initially abolished deep tendon reflexes reappeared. Electromyographic studies were repeated only in patient 5, who initially had isolated demyelinating lesions, and showed posttransplantation normalization of nerve conduction speeds.

In addition to neurologic symptoms, other manifestations of the POEMS syndrome improved, especially skin changes, edema, papilledema, and organomegaly that was no longer detectable after transplantation in any case. Serum thyroid-stimulating hormone levels returned to normal value in the 2 patients with hypothyroidism, whereas the patient with adrenal insufficiency still needed low-dose hydrocortisone after transplantation. In the same patient,

Table 2. Therapy and patients' outcome

Patient no.	Previous treatment	Prior local irradiation	HDT regimen*	MIg response	Follow-up, mo (since PBSC collection)	Clinical response
1	Cs, Imurel, plasma exchange, intravenous IgG	Left iliac wing (40 Gy)	HDM 140, HDM 140 + TBI 12 Gy	CR	58	Recovered walking and returned to normal life; residual distal motor after effects in lower limbs
2	None	None	HDM 200, HDM 140 + VP16 3 g + TBI 10 Gy	CR	49	Slight persistent distal hypoesthesia in lower limbs; cycling 15 km daily
3	Cytoxan (3 courses)	None	HDM 140 + oral busulfan 12 mg/kg	> 90%	32	Complete, except persistent arterial hypertension and need for cortisone supplementation
4	Plasma exchange	Left iliopubic area (40 Gy)	HDM 200	CR	25	Residual distal motor after effects in lower limbs
5	None	Right iliac wing (40 Gy)	HDM 200	CR	12	Complete (including normalization of nerve conduction studies)

HDT indicates high-dose therapy; MIg, monoclonal immunoglobulin; PBSC, peripheral blood stem cell; Cs, corticosteroids. Ig, immunoglobulin; TBI, total body irradiation; VP16, vepeside; CR, complete remission.
*In all cases, supported with PBSC (collected as described in "Study design"), and granulocyte colony-stimulating factor (5 μg/kg/d) that was started on day 6 after transplantation and maintained until the neutrophil count was greater than 10^9/L. High-dose melphalan, either 140 mg/m^2 (HDM 140) or 200 mg/m^2 (HDM 200) intravenously.

all symptoms related to POEMS nephropathy disappeared except hypertension. Within a median follow-up of 36 months since HDT, no patient experienced a relapse either of plasma cell dyscrasia or of related POEMS manifestations.

Although still poorly understood, the pathogenesis of the POEMS syndrome may be related to production by the clonal plasma cells (or their environment) of a combination of soluble factors, resulting in increased vascular permeability and neoangiogenesis.[14,15] Among various cytokines, vascular endothelial growth factor may have a pivotal role.[16,17] We studied vascular endothelial growth factor serum levels in 2 patients (cases 1 and 2) by using an enzyme-linked immunosorbent assay adapted from Fixe et al.[18] In both, pretreatment level was high (3684 and 2644 pg/mL, respectively, as compared with 471 (± 86) pg/mL in 37 healthy blood donors), and posttransplantation levels returned to normal (240 and 394 pg/mL 1 month after HDT, respectively).

Although involving a small number of patients, this retrospective study shows the interest of HDT with stem cell support in patients with POEMS syndrome who present with multifocal bone lesions and/or diffuse plasmacytic bone marrow infiltration. In patients with a limited number of solitary plasmocytomas, radiation therapy probably remains the treatment of choice, but HDT should be studied in larger studies as an alternative, particularly when complete remission, including disappearance of the MIg, is not achieved or when relapse occurs.

References

1. Nakanishi T, Sobue I, Toyokura Y, et al. The Crow-Fukase syndrome: a study of 102 cases in Japan. Neurology. 1984;34:712-720.
2. Bardwick PA, Zvaifler NJ, Gill GN, Newman D, Greenway GD, Resnick DL. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M-protein and skin changes: the POEMS syndrome: report on two cases and a review of the literature. Medicine. 1980;59:311-322.
3. Driedger H, Pruzanski W. Plasma cell neoplasia with peripheral polyneuropathy: a study of five cases and a review of the literature. Medicine. 1980;59:301-310.
4. Soubrier M, Dubost JJ, Sauvezie B, and the French Study Group on POEMS Syndrome. POEMS syndrome: a study of 25 cases and a review of the literature. Am J Med. 1994;97:543-553.
5. Miralles GD, O'Fallon JR, Talley NJ. Plasma-cell dyscrasia with polyneuropathy. The spectrum of POEMS syndrome. N Engl J Med. 1992;327:1919-1923.
6. Schey S. Osteosclerotic myeloma and POEMS syndrome. Blood Rev. 1996;10:75-80.
7. Delauche MC, Clauvel JP, Seligmann M. Peripheral neuropathy and plasma cell neoplasias. Br J Haemat. 1981;48:383-392.
8. Kelly JJ, Kyle RA, Miles JM, Dick PJ. Osteosclerotic myeloma and peripheral neuropathy. Neurology. 1983;33:202-210.
9. Selby P, McElwain T, Nandi AC, et al. Multiple myeloma treated with high dose intravenous melphalan. Br J Haematol. 1987;66:55-62.
10. Modesto-Segonds A, Rey JP, Orfila C, Huchard G, Suc JM. Renal involvement in POEMS syndrome. Clin Nephrol. 1995;43:342-345.
11. Nakamoto Y, Imai H, Yasuda T. A spectrum of clinicopathological features of nephropathy associated with POEMS syndrome. Nephrol Dial Transplant. 1999;14:2370-2378.
12. Moreau P, Leblond V, Bourquelot P, et al. Prognostic factors for survival and response after high-dose therapy and autologous stem cell transplantation in systemic AL amyloidosis: a report on 21 patients. Br J Haematol. 1998;101:766-769.
13. Gertz MA, Lacy MQ, Gastineau DA, et al. Blood stem cell transplantation as therapy for primary systemic amyloidosis (AL). Bone Marrow Transplant. 2000;26:963-969.
14. Gherardi RK, Belec L, Fromont G, et al. Elevated levels of interleukin-1β (IL-1β) and IL-6 in serum and increased production of IL-1β mRNA in lymph nodes of patients with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes (POEMS) syndrome. Blood. 1994;83:2587-2593.
15. Gherardi RK, Belec L, Soubrier M, et al. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. Blood. 1996;87:1458-1465.
16. Watanabe O, Arimura K, Kitajima I, Osame M, Maruyama I. Greatly raised vascular endothelial growth factor (VEGF) in POEMS syndrome. Lancet. 1996;347:702.
17. Soubrier M, Dubost JJ, Serre AF, et al. Growth factors in POEMS syndrome: evidence for a marked increase in circulating vascular endothelial growth factor. Arthritis Rheum. 1997;40:786-787.
18. Fixe P, Lorgeot V, Meur YL, et al. Development of enzymo-immunoassays (EIA) for macrophage colony-stimulating factor (M-CSF) and leukaemia inhibitory factor (LIF) by using the same capture and signal generating polyclonal antibody. Cytokine. 1996;8:586-591.