SHORT REPORT

Long term melphalan-prednisolone chemotherapy for POEMS syndrome

Satoshi Kuwabara, Takamichi Hattori, Yutaka Shimoe, Ikuro Kamitsukasa

Abstract

The effects of long term melphalan-prednisolone (MP) therapy was studied on 12 patients with POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome. Six were treated with MP every six weeks for 16 to 52 months; three also with cyclophosphamide, and three with localised irradiation for osteoclastic lesions. Five of the six survived during the follow up period and showed various degrees of lessening of their neuropathy and other symptoms. There were no serious side effects. The other six patients received treatments that included corticosteroids, short term chemotherapy, or irradiation, but not long term chemotherapy. Five showed transient lessening of their non-neurological symptoms, and one, obvious neurological improvement. Five of these six patients died from nine to 70 months after POEMS onset. The findings suggest that long term MP therapy may be an effective treatment for the POEMS syndrome.

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Keywords: POEMS syndrome; melphalan; prednisolone; chemotherapy

POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome is an unusual multisystem disorder and the rare cause of demyelinating and axonal polyneuropathy.¹⁻³ The polyneuropathy is symmetric, with predominant motor involvement, and is progressive.⁴ Most patients are treated with corticosteroids, immunosuppressive agents, or localised irradiation for a solitary osteosclerotic lesion, but the long term prognosis is unclear because of the rarity of the disorder. Radiotherapy may be effective for some patients who have solitary osteosclerotic lesions,⁴⁻⁹ but not for all.¹⁰ Patients who have multiple bone lesions have been treated with chemotherapeutic agents, but with mixed results.^{4 10-15} Furthermore, little is known about treatment for patients without bone lesions.

We studied the effect of long term melphalan-prednisolone (MP) therapy on six patients with POEMS syndrome, and compared the results with those for another six patients who did not receive this long term chemotherapy.

Patients and methods

Twelve patients with POEMS syndrome (four women, eight men) were studied (table). All except patient 1, who had no M protein, had the five features of "POEMS". Six patients had osteosclerotic lesions; solitary in five and multiple in one. Bone surveys by roentgenography and radioisotope bone scans were negative in the other six. Peripheral oedema, pleural effusion, ascites, papilloedema, and increased CSF protein concentrations were present in all the patients.

Six patients (1-6) were treated with MP long term (20 to 56 months). For three patients (1-3), cyclophosphamide initially was combined with MP for two to 12 months. Patients 2-4, who had single osteosclerotic lesions, received localised irradiation. The MP therapy was a six week regimen that consisted of melphalan (0.24 mg/kg for four days during the first week) and prednisolone (50 mg/day during the first week, 25 mg/day during the second week, 25 mg on alternate days during the third and fourth weeks). Hematology and biochemical profiles were monitored every four weeks.

The other six patients (7-12) received various treatments, including prednisolone with or without a short course of a chemotherapeutic agent. Two (7 and 8) were treated initially with three series of MP or MP plus cyclophosphamide, then with prednisolone alone. Patient 9 received radiotherapy.

The disabilities of the patients were evaluated by the modified Hughes functional grading scale¹⁶ as 0, healthy; 1, minor symptoms and signs, but capable of running; 2, able to walk 5 m without assistance but unable to run; 3, able to walk 5 m with the help of one person and a waist level walking frame; 4, confined to a wheelchair, unable to walk as in 3; 5, tetraplegic and confined to bed; 6, death. The nerve conduction study was done by a routine procedure.

Department of
Neurology, School of
Medicine, Chiba
University, Chiba,
Japan

S Kuwabara
T Hattori

Department of
Neurology, Chiba
Rosai Hospital, Chiba,
Japan

Y Shimoe
I Kamitsukasa

Correspondence to:
Dr Satoshi Kuwabara,
Department of Neurology,
School of Medicine, Chiba
University, 1-8-1 Inohana
Chuo-ku, Chiba 260 Japan.

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Clinical features and prognoses of patients with POEMS syndrome

				Clinical disability*			
Patient No	Age and sex	Duration before treatment (months)	Bone lesion	Before treatment	Best during course	At the end of follow up	Survival time (months)
Treated long term with melphalan and prednisolone:							
1	61M	5	None	4	2	2	> 44
2	40F	12	Solitary	4	3	3	> 55
3	47F	5	Solitary	2	1	1	> 49
4	50M	10	Solitary	2	1	1	> 64
5	32F	16	None	2	1	1	> 29
6	62F	15	None	4	3	6	50
Mean (SD)		10.5 (4.3)		3.0 (1.0)	1.8 (0.9)	2.3 (1.8)	
Treated without long term chemotherapy:							
7	44M	5	None	3	3	6	9
8	63M	7	None	4	3	6	17
9	60M	9	Solitary	4	4	6	11
10	56M	12	Multiple	4	4	6	15
11	69M	11	None	4	4	6	61
12	69M	12	Solitary	2	2	3	> 74
Mean (SD)		9.3 (2.6)		3.5 (0.8)	3.3 (0.7)	5.5 (1.1)	

* On the functional grading scale¹⁶; MP = melphalan-prednisolone; CP = cyclophosphamide; P = prednisolone.

The conditions of the patients were followed up until October 1996 or death.

Results

Before treatment, no significant differences in age, disease duration, clinical disability, type of M protein, CSF protein concentration, or nerve conduction indices (terminal motor latency, conduction velocity, amplitude of compound muscle action potential, and F wave latency) were found between the patient groups with and without long term MP therapy.

PATIENTS (1–6) TREATED WITH LONG TERM MP (TABLE)

MP therapy was continued for 20 to 56 (mean 42) months. The non-neurological symptoms of peripheral oedema, pleural effusion, and ascites began to improve within a month after initiation of treatment. Improvement of neuropathy was slow, beginning three to 14 months later. Five patients (1–5) showed slow, continued improvement for the next 10 to 48 months. At the end of the follow up period, their mean functional grades had improved from 2.8 to 1.6, and four of them were able to walk without assistance. Immunoelectrophoresis showed no M protein in two patients (3 and 4) 22 and 26 months after the initiation of therapy, whereas it persisted in the others. Sequential nerve conduction studies done on four patients showed gradual increases in the conduction velocities and amplitudes of the compound muscle action potentials which paralleled their clinical responses (figure). Patient 6 showed slight improvement but remained confined to a wheelchair until his death from pneumonia 54 months after the onset of POEMS.

There were no serious side effects of the long term chemotherapy. Leucocytopenia ranging from 2500 to 3600/mm³ was found in two patients. Minor side effects included nausea, transient headache, slight fever, facial oedema, and general malaise.

PATIENTS (7–12) TREATED WITHOUT LONG TERM MP (TABLE)

Five patients had lessened peripheral oedema, pleural effusion, and ascites after being given

prednisolone. Transient improvement of the neuropathy occurred in three patients but did not reach one functional grade change in two of the three, their courses being progressive. Five patients died four to 50 months after the initiation of treatment. The causes of death for four of them were cardiac and renal failure due to intractable pleural effusion and ascites and for one pulmonary embolism. Patient 12, who was treated only with prednisolone, improved slightly with subsequent deterioration but was capable of walking with a stick 74 months after the onset of POEMS.

Discussion

Our findings suggest that long term MP therapy may be an effective treatment for the POEMS syndrome. This therapy enhanced survival and lessened the neuropathy and other symptoms, whereas most patients treated without long term chemotherapy died within a few years. It is notable that, unlike multiple myeloma, most of the deaths were due to intractable pleural effusion and ascites that resulted in multiorgan failure, rather than to tumour expansion or metastasis, bone marrow suppression, or amyloidosis. Although the causes of the features of this syndrome are unknown, a humoral substance, probably secreted by plasma cells, is considered responsible for multisystem dysfunction,^{4 15 17} which may bring on a fatal endocrinological crisis in

Conduction velocity of the median nerve before and after melphalan-prednisolone therapy in patients 1–4.

the course of the POEMS syndrome. This is consistent with the report of Nakanishi *et al*² that 34 of 58 Japanese patients with POEMS syndrome died within a mean survival period of 33 months and that most died of heart failure. We consider that the POEMS syndrome is a potentially fatal disorder that should be treated aggressively.

Treatment of the POEMS syndrome depends on whether osteosclerotic lesion or extramedullary plasmocytoma is present and whether such lesions are solitary or multiple. For some patients, who have a single plasmocytoma mass, surgical removal or tumoricidal radiation therapy may give long lasting improvement,⁴⁻⁹ but this does not work for all such patients.² In our series, patient 9 who received radiotherapy for a solitary lesion died 11 months after the onset.

Chemotherapy with MP has been used with patients who have multiple lesions, but the results are inconclusive.^{4 10-15} Kelly *et al*⁴ treated seven patients with MP at six week intervals, but the results were not satisfactory; slight improvement in three, stabilisation in two, and no response in two. The duration of treatment was not given. In our study, the lessening of neuropathy was very slow after treatment was initiated but improvement was substantial and long lasting in five of the six patients treated with long term MP for a mean period of 42 months, whereas two patients given only three series of MP showed less clinical improvement and eventually died. The two treatment groups in our study were not randomly selected with respect to irradiation, cyclophosphamide administration, and sex. However, improvement of the neuropathy seemed more evident in long term MP group patients (table).

Many patients with clinically apparent POEMS syndrome do not have osteosclerotic lesions. Six of the 12 patients in our study, and 46 of the 102 in the report by Nakanishi *et al*² did not have bone lesions or extramedullary plasmocytoma. Our findings show that even in the absence of osteoclastic lesions, patients

with POEMS syndrome respond to long term chemotherapy, as shown in patients 1 and 5.

In conclusion, long term MP therapy may be beneficial for patients with POEMS syndrome. There is risk of myelodysplasia or acute leukaemia with long term chemotherapy, but we think that the benefits exceed the risk.

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