Thalidomide Treatment for Immunoglobulin D Multiple Myeloma in a Patient on Chronic Hemodialysis

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Abstract

A 64-year-old Japanese man suffering from IgD λ myeloma and renal failure requiring chronic hemodialysis was treated with thalidomide. Serum IgD concentration was 4,050 mg/dl and myeloma cells constituted 95.6% of nucleated cells in bone marrow at the start of treatment. These parameters improved markedly to 1,590 mg/dl and 22.0%, respectively, in the 4 months immediately prior to his death due to pneumonia. Thalidomide caused peripheral neuropathy and constipation at a dose of 100 mg daily in the first week of treatment, but adverse effects resolved upon dose reduction. Thalidomide represents a valid therapeutic option for some myeloma patients receiving hemodialysis. (Internal Medicine 42: 605–608, 2003)

Key words: IgD myeloma, renal failure, hemodialysis, thalidomide, optional treatment, adverse effect

Introduction

Immunoglobulin (Ig) D multiple myeloma is rare, comprising only 2% of all myelomas (1, 2). The condition typically develops in male patients, is often accompanied by hepatosplenomegaly, lymphadenopathy, extraosseous lesions, λ -type monoclonal component, renal failure and hypercalcemia, and displays a poor prognosis (1–3).

Thalidomide was initially used as a sedative and hypnotic in the late 1950s, but was found to cause birth defects such as phocomelia when taken during the first trimester of pregnancy, and was withdrawn from the global market in 1961 (4). Thalidomide is currently available in Europe and the United States, but sale of this drug has not been approved in Japan. In recent years, thalidomide has re-entered the lime-

light as a therapeutic agent against myelomas refractory to chemotherapy (5–7).

We describe herein a patient with IgD myeloma and renal failure requiring chronic hemodialysis who responded to thalidomide treatment.

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Case Report

A 64-year-old Japanese man was diagnosed with IgD λ type myeloma with Bence Jones proteinuria in April 2001. He was 156 cm tall and weighed 60.5 kg. Laboratory examinations demonstrated acute renal failure with elevated serum β_2 -microglobulin levels of 21.6 mg/dl and hypercalcemia. Blood counts revealed anemia and leukocytosis, and bone marrow aspiration identified diffuse infiltration of myeloma cells (Table 1). Extraosseous lesions, lymphadenopathy and hepatosplenomegaly were not detected. He had diabetes mellitus and a duodenal ulcer.

After six courses of combination chemotherapy comprising melphalan, vincristine and prednisolone, and occasional bisphosphonate (pamidronate disodium) injections, serum IgD dropped to 2,060 mg/dl (Fig. 1) and hypercalcemia disappeared in October 2001. However, since anemia progressed and serum creatinine reached 8.7 mg/dl, chronic hemodialysis was performed twice a week with erythropoietin injections and occasional blood transfusions.

In January 2002, serum IgD again increased (Fig. 1) and marked infiltration of myeloma cells into the marrow was observed (Table 1). The patient and his wife then agreed to try thalidomide treatment against relapsed myeloma. Thalidomide treatment was administered after obtaining written informed consent from both individuals and approval from the Human Investigation Committee of our hospital under the protocols of the Helsinki Declaration. Oral thalido-

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Table 1. Laboratory Findings

	At diagnosis (Apr. 17, 2001)	Start of thalidomide (Jan. 29, 2002)	Follow-up (May 29, 2002)
Blood count			
White blood cells ($\times 10^9/l$)	10.7	4.3	2.1
Neutrophils (%)	52.5	62.0	55.0
Basophils (%)	0	0.5	0.5
Eosinophils (%)	1.5	0	0.2
Monocytes (%)	10.0	7.0	5.4
Lymphocytes (%)	31.0	30.0	38.9
Hemoglobin (g/dl)	7.7	10.5*	10.2*
Platelets ($\times 10^9/l$)	194	144	33
Serum immunoglobulins			
IgG (mg/dl)	722	519	412
IgA (mg/dl)	25	10	8
IgM (mg/dl)	22	11	15
IgD (mg/dl)	4,670	4,050	1,590
IgE (IU/ml)(RIST)	12	Not tested	Not tested
Blood chemistry			
Urea nitrogen (mg/dl)	62.8	21.0	40.2
Creatinine (mg/dl)	6.4	6.1	6.9
Serum calcium (mg/dl)	11.5	10.0	11.2
Bone marrow			
Myeloma cells (%)	94.4	95.6	22.0

*under blood transfusions.

midate tablets were imported from Penn Pharmaceuticals Co. Ltd. (London, UK) with the permission of the Japanese Ministry of Health, Welfare and Labour.

In January 2002, administration of thalidomide was initiated at 100 mg once a day. The patient was emaciated (weight, 43 kg) by this time. However, the patient complained of generalized sensory disturbance and numbness (grade 2 according to World Health Organization classifications) and constipation (grade 1) in the first week of therapy. Dosage was therefore reduced to 100 mg every 3 days and the adverse effects disappeared. Once on chronic hemodialysis, the patient tolerated thalidomide well at a dose of 100 mg every other day. By the end of May 2002, serum IgD was decreasing (Fig. 1) and myeloma cells had diminished in the marrow (Table 1), although hematopoiesis did not recover. The patient died of pneumonia in early June 2002.

Discussion

The prognosis of our patient was considered very poor at the diagnosis of IgD myeloma. In IgD myeloma patients, median survival time is reportedly 9–21 months (1–3). Furthermore, reference to a multivariate analysis of 165 Japanese IgD myeloma patients indicated that our patient, with leukocytosis and λ type paraproteinemia at diagnosis, belonged to a high risk group with a median survival time of

only 8 months (3). In addition, our patient displayed irreversible renal dysfunction that was resistant to chemotherapy and required chronic hemodialysis. Mean survival time of myeloma patients who develop acute renal failure that is refractory to chemotherapy is reportedly 7.8 months, which is significantly shorter than that of myeloma patients with reversible renal failure (8). Furthermore, in one series of myeloma patients, the survival rate at 1 year was 45% after initiation of chronic dialysis (9).

The present patient initially displayed a favorable response to chemotherapy, but relapse occurred after the development of renal failure requiring chronic hemodialysis. Administration of aggressive chemotherapy was difficult due to poor general condition and renal failure. Thalidomide treatment was therefore considered. Oral thalidomide has been administered for myeloma refractory to chemotherapy with a reported response rate of 32–43% (5–7), and event-free survival and overall survival after 1 year of follow-up of 22% and 58%, respectively (5). The antitumor activity of thalidomide is thought to involve inhibition of angiogenesis, alteration of the expression of adhesion molecules, suppression of the production of tumor necrosis factor α , increased production of interleukin 10, enhancement of cell-mediated immunity, and complex effects by cytokines (5).

When our patient and his wife requested thalidomide treatment against the relapsed myeloma, we faced the prob-

Figure 1. Serum IgD M-protein levels in the patient. Bisphosphonate: pamidronate disodium 30 mg/day, MVP: melphalan 8 mg/m² for 4 days, vincristine 1.5 mg/m² for 1 day, and prednisolone 30 mg/m² for 4 days.

lem of the lack of previous reports of thalidomide treatment against myeloma in chronic hemodialysis. Moreover, serum concentrations of thalidomide could not be measured at our laboratory, or at any other commercial laboratories in Japan, complicating the determination of a maintenance dose. The dosage of thalidomide against myeloma has ranged from 100 mg to 800 mg daily (5–7). Thalidomide is predominantly excreted by nonrenal routes, and is detected in plasma up to 24 hours after a single oral dose of 200 mg in healthy volunteers (4). A daily dose of 100 mg of thalidomide is reportedly effective for uremic pruritus without any adverse effects in uremic patients requiring hemodialysis (10). In addition, our patient was of small stature, and was also emaciated. An initial dose of thalidomide of 100 mg daily was therefore selected for our patient.

The patient then complained of peripheral neuropathy and constipation. Constipation, weakness or fatigue, and somnolence are the principal adverse effects of thalidomide treatment, occurring in one-third or more of myeloma patients (5, 6). Peripheral nerve palsy caused by thalidomide is less common among myeloma patients (5–7), and is more often observed among patients with dermatologic conditions, suggesting a dose-dependent effect (4). Adverse effects in

the present case improved upon dose reduction of thalidomide from 100 mg daily to 100 mg on alternative days.

Over 50% reduction in IgD was attained within 2 months in our patient, not by chemotherapy but by thalidomide treatment, and notably, using a smaller dose than previously reported (5–7). One reason for this is presumably the short stature and emaciation of our patient. However, some uncertainty remains as to whether lower doses of thalidomide may be effective in myeloma patients receiving dialysis. In another study, dialysis patients with myeloma who attained a more than 50% reduction in paraprotein in response to chemotherapy survived significantly longer than those who did not (9). Unfortunately, the present patient died of pneumonia, and the survival time from diagnosis of myeloma was 14 months. Reductions of IgD in serum and plasmacytosis in marrow indicated that our patient was a responder to thalidomide treatment (5–7) before the fatal lung infection. The duration of partial response in our patient was 4 months, which was shorter than that of a previous report (6).

Conversely, the present patient demonstrated cytopenia, hypercalcemia and suppression of serum immunoglobulins, suggesting the progression of myeloma just before death. The existence of extraosseous lesions could not be excluded,

as general examinations were not performed on our patient at that time, and extraosseous lesions do not seem to respond to thalidomide, even if reduction of serum paraprotein is achieved (6). Worthy of note is the fact that cytopenia is one of the known adverse effects of thalidomide (5), and some patients develop pneumonia during thalidomide treatment (6). The possible contribution of thalidomide to the death of our patient therefore could not be excluded, although treatment-related mortality was not observed in another report (7).

In conclusion, thalidomide treatment is recommended for patients with IgD myeloma, in addition to those with other types of myelomas that are refractory to or display contraindications for chemotherapy. Thalidomide can be administered to myeloma patients on chronic hemodialysis, although careful consideration of the dose and potential adverse effects must be made.

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