

Original Articles

Fluid Retention During Thalidomide Therapy for Refractory Multiple Myelomas

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Fluid retention of more than 2 kg, with no sign of pitting edema, was observed in 5 of 15 patients with refractory multiple myelomas treated by thalidomide. Cardiac function in all except one patient, who developed overt heart failure, were controlled well by diuretics. Median time from starting thalidomide to developing fluid retention was ten days (range 6 to 41 d). The fluid retention was transient in most patients, allowing thalidomide therapy to continue. However, when fluid retention could not be controlled by diuretics, thalidomide had to be discontinued. It is important that fluid retention is a significant adverse reaction to thalidomide therapy and that even overt heart failure can be obvious.

Key words Thalidomide ; Fluid retention ; Multiple myeloma

INTRODUCTION

Singhal and colleagues¹ demonstrated a response rate of 32% in thalidomide treatment of patients with resistant myeloma. Although its mechanism of action remains unclear², thalidomide is effective for patients who are resistant to multiple standard therapeutic regimens, including alkylating agents, anthracyclines, glucocorticoids, and intensive therapy with stem cell support³⁻⁶.

Adverse reactions to thalidomide include fatigue, constipation, skin rash and peripheral neuropathy, although they are reported to be tolerable^{1,3,4}. Edema, which is a sign of extravascular fluid retention, is induced by thalidomide, and has been described in earlier reports^{1,3,4,6}. We found evidence that fluid retention may occur in an intravascular space, rather than in extravascular space.

PATIENTS AND METHODS

During the period from August 2001 to August 2003, 15 patients with multiple myeloma resistant to standard treatment, including MP (melphalan, prednisolone) and VAD (vincristine, doxorubicin, dexamethasone) combination chemotherapy, were referred to us for thalidomide therapy. Characteristics of patients are shown in Table 1. Their median age was 64 years (range: 48-73 y), with 7 males and 8 females. There were 11 patients with immunoglobulin (Ig)G, 2 IgA, and each one of IgD and Bence - Jones protein types. The initial dose of thalidomide was 200 mg p.o. daily at bedtime. Then the dose was adjusted depending on disease activity and severity of toxic side effects to a maximum dose of 600 mg. All patients were treated only by thalidomide. Written, informed consent was obtained from all patients. This study was reviewed extensively before being approved by the institutional review board of Fukuoka University Hospital.

The grade of adverse events were classified according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC). Response criteria were used according to the guidelines of the European/International Bone Marrow Transplantation Registry (EBMT/IBMTR)⁷.

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Table 1. Characteristics of patients with thalidomide therapy

Response	Age, Gender	PS	Myeloma Stage	Previous treatment	Maximum dose (mg/day)	Treatment duration(day)	Adverse events
a) Responsive group							
PR1	50M	4	IgG κ/λA	MP, VAD	200	2184	Fever G2, Rash G2
PR2	72F	2	IgG λ/λIIA	MP, Rx	200	187	Depression G3
PR3	53F	3	IgG κ/λIIA	MP, VAD	600	234	Fluid retention G1, Hearing G4
MR1	66M	2	IgG κ/λIA	MP, VAD	200	106	Rash G2
b) Unresponsive group							
NC1	48F	1	IgG κ/λIIA	VAD, VAD, PRSCT	200	45	Fever G2, Rash G3 Liver dysfunction G3
NC2	58M	3	IgG κ/λIIA	MP	200	185+	Depressed level of consciousness G2
NC3	61F	1	IgG κ/λIIA	MP, VAD	200	196+	Fluid retention G0, Neutropenia G3
NC4	71M	0	IgG κ/λIIA	MCNU-VAD, IFN	200	135	Fatigue G2
NC5	70F	1	IgA κ/λIA	MP, VAD	300	53	Neutropenia G3
NC6	66F	3	IgG κ/λIIA	VAD	600	665+	-
PD1	72M	3	IgG κ/λIIA	VAD, Ara-C	200	36	Congestive heart failure, Depressed level of consciousness G3
PD2	55F	4	IgG κ/λIIB	MP, VAD, Rx	200	73	Fluid retention G2, Neutropenia G4
PD3	75M	2	IgA κ/λIIA	VAD, II, N, Rx	200	96	-
PD4	62F	2	IgG κ/λIIA	MP, VAD	300	296	Fluid retention G1, Rash G3

PR, partial response; MR, minor response; NC, no change; PD, progressive disease
 MP, melphalan, prednisolone; VAD, vincristine, doxorubicin, dexamethasone; Rx, radiotherapy; VAD, vincristine, melphalan, prednisolone; decamethasone;
 auto PRSCT autologous peripheral blood stem cell transplantation; MCNU-VAD, melphalan, vincristine, melphalan, prednisolone;
 IFN, interferon; Ara-C, cytarabine

RESULTS

The responses to thalidomide in the 14 patients who completed the study are summarized in Table 1. One patient was excluded because he completed only one day of treatment due to pneumonia and heart failure. Four patients showed an objective response; a partial response occurred in 3 and a minor response in 1 patient.

One patient (PD1) was complicated with pneumonia on the fifth day after starting thalidomide (Fig. 1). By the tenth day, he gained 2 kg in weight, and congestive heart failure was obvious with distended jugular veins, hepatomegaly and cardiomegaly. His echocardiogram before starting thalidomide showed normal cardiac function with a 75% ejection fraction. An echocardiogram taken after starting thalidomide showed normal cardiac function with a 67% ejection fraction, with dilatation of the left atrium, left ventricle and inferior vena cava. He recovered from pneumonia, but his heart failure did not respond to diuretic therapy. Reducing his dose of thalidomide to 100 mg/day did not improve his condition. Subsequently, thalidomide was discontinued on the 26th day. Notably, he quickly recovered from heart failure after thalidomide was removed. The patient and his family were eager to restart thalidomide

therapy because his myeloma progressed during the cessation of thalidomide. After thalidomide therapy at 100 mg/day was restarted he redeveloped signs and symptoms of heart failure on the fourth day. Diuretics and vasodilator produced no improvement. Therefore, the patient decided to stop taking thalidomide. At the same time, peripheral plasma cells increased rapidly and dyspnea recurred. He became oliguric and his blood pressure decreased. He died of rapid progression of myeloma 2 days after thalidomide was discontinued. An autopsy showed bilateral pulmonary edema, pleural effusion and ascites but no amyloidosis of the heart nor pulmonary emboli with deep vein thrombosis. Furthermore, there were no findings that pointed to the cause of heart failure, such as myocardial infarction. Based on these autopsy findings fluid retention on this patient appeared to be related closely to thalidomide therapy.

Five patients experienced fluid retention of more than 2 kg with no evidence of edema (Table 1). All of them had the IgG type of myeloma; one patient was in clinical stage IIA, 3 in IIIA and 1 in IIIB. Fluid retention was graded according to the NCI-CTC classification system: grade 0 (less than 5.0% weight gain) occurred in 2 patients, of whom one developed heart failure; grade 1 (5.0 to 9.9%) occurred in 2; and grade 2 (10.0 to 19.9%) occurred in 1 patient. All but one

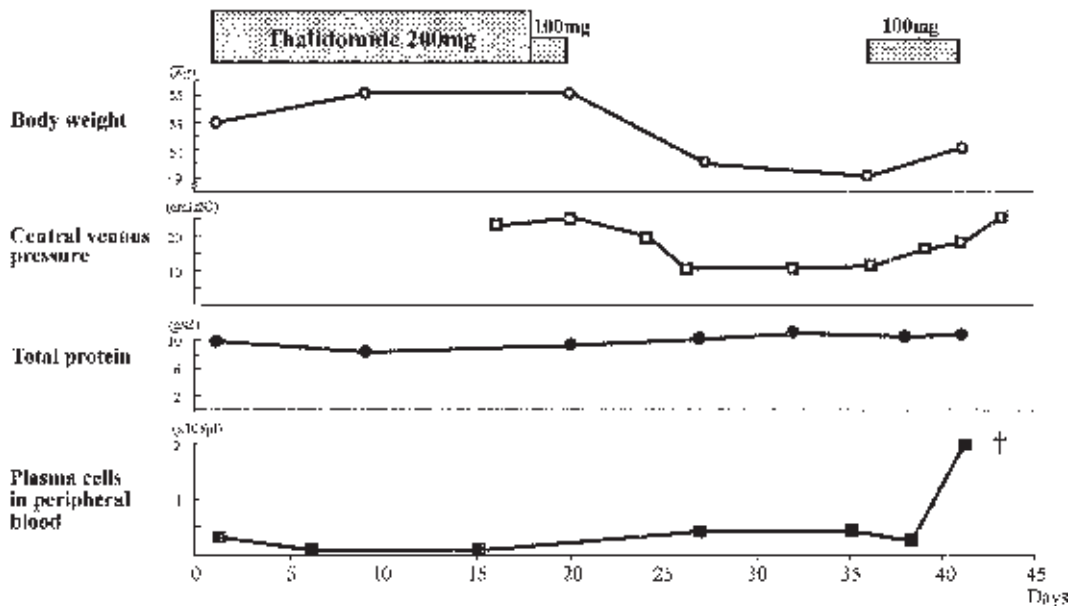


Fig. 1. Clinical course of patient PD1
 Patient PD1 gained 2 kg by the 10th day after starting thalidomide and developed heart failure. He quickly recovered from heart failure after cessation of thalidomide. After thalidomide therapy at 100 mg/day restarted, he redeveloped heart failure again.

of the patients with heart failure (case PD1) were controlled well by diuretics. The median time from starting thalidomide to the appearance of fluid retention of more than 2 kg was ten days, ranging from 6 to 41 days. All five patients with weight gains had normal renal function and their electrolytes were within the normal range.

DISCUSSION

Haslett, et al⁸ demonstrated that thalidomide therapy induced weight gain in patients infected with human immunodeficiency virus (HIV). Biometric impedance data from that study suggested that a significant proportion of the early (first week) weight gain was due to extracellular fluid retention, although there were no clinical signs of pitting edema. Thalidomide has been shown to inhibit angiogenesis induced by fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) in a rabbit-cornea micropocket assay⁹ and in a murine model of corneal vascularization¹⁰. VEGF is also called vascular permeability factor¹¹. There is speculation that thalidomide plays a role in inhibiting the activity of VEGF and decreases vascular permeability. In turn, intravascular fluid can not move to the interstitial space and is retained in the intravascular space, leading to excessive

intravascular fluid.

One third of patients in our study retained fluid. Therefore, patients should be weighed every day during thalidomide therapy. If they gain more than 2 kg, then diuretics should be considered. Because fluid retention usually was transient in most of the patients, it may be possible to continue thalidomide. When a patient does not respond to diuretics, thalidomide may have to be discontinued. It is especially important to recognize that some patients may develop full-blown heart failure associated with thalidomide and that careful observation is warranted.

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