

Efficacy of Long-Term Treatment with Low-Dose Thalidomide for Patients with Relapsed/Refractory Multiple Myeloma

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ABSTRACT

Introduction: We report the results of a prospective study of long-term treatment with single-agent thalidomide in patients who had responded in a preceding trial of the use of thalidomide for relapsed/refractory myeloma. **Patients and Methods:** Nineteen patients were enrolled: 11 patients (57.9%) treated at a dosage of 100 mg/day; 2 patients (10.5%) at a dosage of 200 mg/day; 2 patients (10.5%) at a dosage of 300 mg/day; and 4 patients (21.1%) at a dosage of 400 mg/day. The median follow-up from the start of the preceding study was 3.0 years. At the time of entry to this study, 5 patients (26.3%) had partial response (PR), another 5 patients (26.3%) had a minimal response (MR), and the remaining 9 patients (47.4%) had shown no change (NC). **Results:** The cumulative MR rate was 78.9% (at the 32nd week) and the cumulative PR rate was 47.4% (at the 112th week). The median progression-free survival was 104 weeks and the median time to next treatment was 144 weeks. No patients experienced grade 4 or greater hematologic toxicity or grade 3 or greater non-hematologic toxicity. **Conclusion:** Long-term thalidomide maintenance therapy induced an increase in response rate, suppressed the progression to active myeloma without severe adverse events, and contributed to long survival with good activities of daily living.

Keywords: Maintenance Therapy, Progression-Free Survival, Time to Next Treatment, Efficacy, Safety

1. Introduction

Whereas the positive role of thalidomide as a consolidation treatment after high-dose therapy with autologous stem cell transplantation (HDT-ASCT), in the context of newly diagnosed myeloma, has been clarified in the patients without high-risk cytogenetics who have obtained less than a very good partial response [1,2], its role as a maintenance therapy remains controversial because of its toxicity and the concern of potential induction of resistance to subsequent treatment [3-5]. In addition, we cur-

rently have much less information on the role of thalidomide as maintenance therapy, in the context of cases of relapsed/refractory multiple myeloma, after successful salvage treatment. Based on the results of phase II trials in which the cumulative dose of thalidomide did not have an impact on the efficacy of maintenance therapy and toxicity increased above a dosage of 200 mg/d [6,7], treatment with low-dose thalidomide is now the preferred option.

We have conducted a prospective study to evaluate the efficacy and safety of thalidomide given as a single-agent maintenance therapy to patients with relapsed and/or re-

fractory multiple myeloma who had been enrolled in a previous phase II study [8] and who achieved at least no change (NC) with thalidomide treatment as per the study protocol.

2. Patients and Methods

2.1. Eligibility

Patients were deemed eligible for enrollment in this study if they had responded and maintained at least NC assessed at the 16th week of the phase II study period with single-agent thalidomide treatment given for at least 4 weeks [8]. According to the phase II study protocol, patients who achieved at least a minimal response (MR) continued on thalidomide treatment at the dosage with which the response had been obtained until the cutoff of the study. Otherwise, the dose of thalidomide was escalated by 100 mg every 4 weeks until the cutoff of the study (16th week) to a maximum of 400 mg/d. In total, 19 patients had achieved and maintained a response of at least NC according to the European Group for Blood and Marrow Transplantation response criteria [9] by the cutoff of the phase II study and were studied.

All patients gave written informed consent and agreed to abide by strict contraception. The study and the written informed consent form were approved by the institutional review board of each participating hospital. The study was conducted in accordance with the Good Clinical Practice for Trials of Drugs and the Declaration of Helsinki.

2.2. Treatment Schedule

Single-agent thalidomide treatment was continued in the 19 patients at their individual final doses of the phase II study until disease progression or intolerance occurred, for a maximum of 3 years. Patients were evaluated every 4 weeks for response and drug toxicity. Thalidomide was supplied by the Fujimoto Pharmaceutical Corporation (Osaka, Japan) and was given orally before sleep. No anti-thrombotic prophylaxis was instituted because no patients experienced thromboembolic events during the phase II study.

2.3. Response, Progression-Free Survival, Time to Next Treatment, and Toxicity Criteria

Responses were assessed by the decrease in the monoclonal protein measured at the time of entry into the phase II study using the European Group for Blood and Marrow Transplantation response criteria [9]. Progression-free survival (PFS) was measured from the date of initiation of thalidomide treatment in the phase II study until death or disease progression, whichever was earlier. Time to next treatment (TTNT) was measured from the date of initia-

tion of thalidomide treatment until death or the date of initiation of the next treatment. The PFS and TTNT curves were constructed according to the Kaplan-Meier method. Toxicities were graded using the National Cancer Institute Common Toxicity criteria (version 3).

3. Results

3.1. Patient Characteristics

A total of 19 patients were enrolled between December 2005 and April 2006. Patients were followed until March 2009 and the median follow-up from the start of the phase II study was 3 years (156 weeks; range, 28 - 180 weeks). The characteristics of the 19 patients are shown in **Table 1**. The mean age was 60 years (range, 42 - 81 years). More than half of the patients had relapsed after HDT-ASCT.

Eleven patients (57.9%) were treated with thalidomide at a dosage of 100 mg/day, 2 patients (10.5%) were treated at a dosage of 200 mg/day, 2 patients (10.5%) were treated at a dosage of 300 mg/day, and 4 patients (21.1%) were treated at a dosage of 400 mg/day.

3.2. Response

At the time of entry to this study, 5 patients (26.3%) had partial response (PR), another 5 patients (26.3%) had MR,

Table 1. Patients characteristics.

Variables	Total
Number of cases	19
Mean age (yr)	60.0
Range (yr)	42 - 81
Time sinceDx(yr)	5.03
Range (yr)	0.17 - 17
Sex (male/female)	8/11
M protein type	
IgG	12
IgA	6
Light chain	1
PS (0/1/2)	15/3/1
ISS stage (I/II/III)	11/3/5
Prior therapy	
Chemotherapy	8
Lines (median, range)	1.5, 1 - 3
ASCT	11
β 2M (mg/L) median, range	2.50, 1.0 - 10.24
LDH (IU/L) median, range	162.5, 105 - 346

Dx; diagnosis, PS; performance status, β2M; β2 microglobulin.

and the remaining 9 patients (47.4%) had shown NC to the latest thalidomide therapy.

The cumulative response rate is shown in **Figure 1**. The reduction of M-protein was continued at the 112th week. MR was obtained in 73.7% at the 24th week and in 78.9% at the 32nd week. PR was obtained 31.6% at the 24th week, 31.6% at the 32nd week, 42.1% at the 48th week, and 47.4% at the 112th week.

3.3. Progression-Free Survival

Figure 2 shows the PFS curve of the 19 patients studied; the median PFS was 104 weeks (1.99 years). The PFS rates were 73.0% at 1 year, 55.1% at 2 years, and 28.0% at 3 years. Only 1 patient has died on the 31st week.

3.4. Time to Next Treatment

Figure 3 shows the TTNT curve of the 19 patients. The median TTNT was 144 weeks (2.76 years). The TTNT rate was 73.7% at 1 year, 63.2% at 2 years, and 47.4% at 3 years. Thalidomide/high-dose dexamethasone treatment was conducted in 6 patients and melphalan/prednisolone/thalidomide treatment was conducted in 3 patients after the discontinuance of single-agent thalidomide maintenance therapy. Eight patients continued single-dose thalidomide treatment over 40 months after progressive disease. Thalidomide was discontinued in only 2 patients.

3.5. Toxicities

All 19 patients experienced at least Grade 1 toxicity; however, no patient experienced Grade 4 or greater hema-

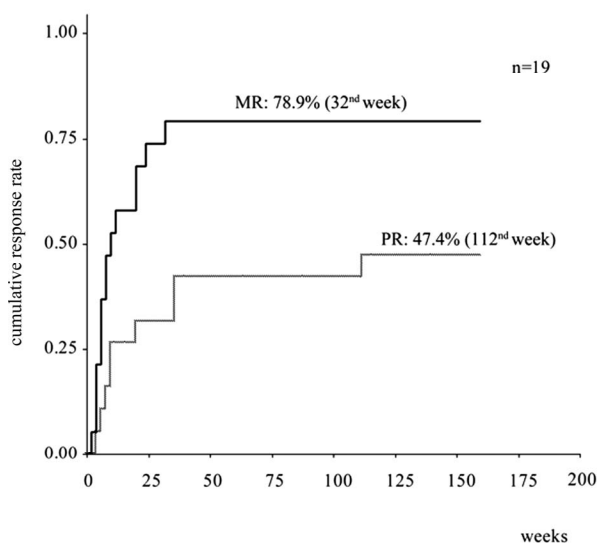


Figure 1. The cumulative response rate in patients treated with long-term thalidomide maintenance. The black line shows minimal response rate and the gray line shows partial response rate.

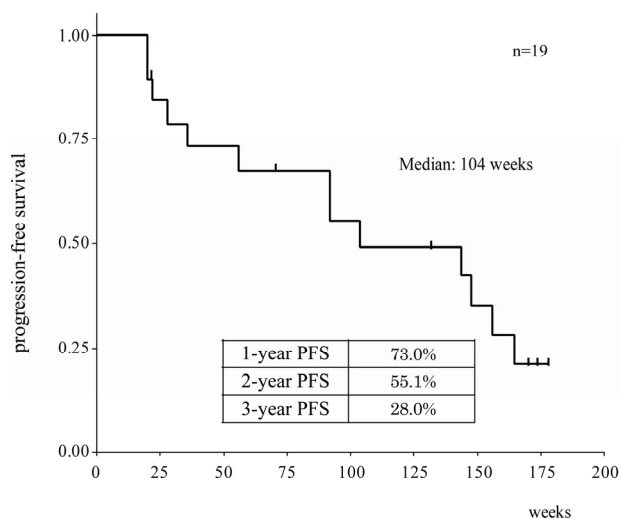


Figure 2. Progression-free survival in patients treated with long-term thalidomide maintenance. The curve was constructed according to the Kaplan-Meier method.

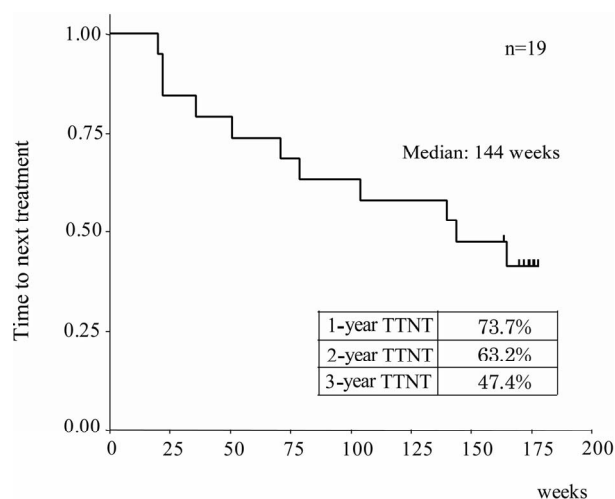


Figure 3. Time to next treatment in patients treated with long-term thalidomide maintenance. The curve was constructed according to the Kaplan-Meier method.

toxicity or Grade 3 or greater non-hematologic toxicity. The toxicity profile observed in at least 10 patients is shown in **Table 2**. The most common Grade 3 hematologic toxicities were neutropenia in 9 patients (47.4%), lymphopenia in 5 (26.3%), and leucopenia in 4 (21.1%). The most common Grade 2 non-hematologic toxicities were peripheral neuropathy in 3 patients (15.8%), constipation in 2 (10.5%), and skin rash in 2 (10.5%). One patient receiving 200 mg/d thalidomide but no thromboprophylaxis experienced deep vein thrombosis on the 71st week.

Toxicity or intolerance that resulted in the discontinuation or dose reduction of thalidomide occurred in 4 of

Table 2. Toxicity profile.

Toxicity	n (%)			
	Total	Grade 1	Grade 2	Grade 3
Hematological				
Neutropeni	14 (73.7)	1 (5.3)	4 (21.1)	9 (47.4)
Lymphopenia	10 (52.6)	1 (5.3)	4 (21.1)	5 (26.3)
Leucopenia	10 (52.6)	2 (10.5)	4 (21.1)	4 (21.1)
Basophilia	11 (57.9)	11 (57.9)	0	0
Non-hematological				
Constipation	16 (84.2)	14 (73.7)	2 (10.5)	0
Peripheral neuropathy	15 (78.9)	12 (63.2)	3 (15.8)	0
Somnolence	14 (73.7)	13 (68.4)	1 (5.3)	0
Dry mouth	11 (57.9)	11 (57.9)	0	0
Edema	10 (52.6)	10 (52.6)	0	0
Tremor	10 (52.6)	10 (52.6)	0	0
Skin rash	10 (52.6)	8 (42.1)	2 (10.5)	0

the 19 patients (21.1%). These 4 patients were treated with thalidomide at a dosage of over 200 mg/day. Thalidomide treatment was discontinued in 2 patients: deep vein thrombosis occurred in 1 patient treated with 200 mg/d on the 71st week, and nephrotic syndrome occurred in 1 patient on the 132nd week. Thalidomide dosage was reduced in another 2 patients because of peripheral neuropathy and neutropenia. No patients treated with 100 mg/d thalidomide discontinued treatment due to toxicity.

4. Discussion

This study was conducted prospectively to evaluate the efficacy and safety of long-term treatment with single-agent thalidomide in patients who had been enrolled and obtained at least NC in a phase II trial of the use of thalidomide in patients with relapsed/refractory multiple myeloma [8]. The dosage of thalidomide in this continuous treatment study was determined by the one with which each patient had responded by achieving at least NC in the preceding phase II trial.

Nineteen patients were enrolled. Eleven patients (57.9%) were treated with continuous thalidomide treatment at a dosage of 100 mg/day, 2 patients (10.5%) were treated at a dosage of 200 mg/day, 2 patients (10.5%) were treated at a dosage of 300 mg/day, and 4 patients (21.1%) were treated at a dosage of 400 mg/day. The discontinuation or dose reduction of thalidomide occurred in 4 patients

(21.1%). These 4 patients were treated with thalidomide at a dosage of over 200 mg/day. In contrast, no patients treated with 100 mg/d discontinued thalidomide due to toxicity. According to these findings, low-dose thalidomide might be adequate for the maintenance treatment for multiple myeloma.

The beneficial effect of long-term treatment with thalidomide was observed at least until week 112 (2.15 years). The PR rate was 26.3% at the time of initiation of maintenance treatment (16th week) and continuously increased up to 47.4% at the 112th week. The MR rate also increased from 26.3% at the initiation of maintenance treatment to 78.9% at the 32nd week. Singhal *et al.* reported that the response of thalidomide treatment was obtained within 4 months in patients with refractory myeloma [10]; however, our study revealed the response of long-term thalidomide maintenance treatment gradually increased over 4 months after initiation of thalidomide.

The PFS was fairly long in this study. It is difficult to compare this result with those in the published reports on single-agent thalidomide treatment in cases of relapsed/refractory multiple myeloma, because most trials used a starting thalidomide dose of 200 mg/d and utilized a dose escalation up to 800 mg/d, and also because the follow-up period is not as long as that in our study [6,11]. The case series studied may be mostly composed of low-risk patients in terms of age, International Staging System stages,

β 2-microglobulin levels, and lactate dehydrogenase levels. Recent studies have shown the importance of obtaining complete response (CR) not only in patients with newly diagnosed multiple myeloma but also relapsed/refractory multiple myeloma [12,13]. However, in patients in the low-risk category, survival is not significantly different between patients with CR and those with PR [14]. Another recent study has disclosed that maintaining CR is more important than obtaining CR in terms of longer survival duration [15]. It is also noted that patients with low-risk disease can survive longer with PR status [14]. In our patients, long-term maintenance treatment with thalidomide upgraded the initial response status and sustained the upgraded response status, which resulted in prolonged PFS.

The TTNT was extremely long compared with the PFS. Eight patients continued single-dose thalidomide treatment after progressive disease because of the absence of progression to active myeloma, namely clinical relapse [16]. According to this finding, one of the reasons for the long TTNT might depend on the slow progression to active myeloma during thalidomide maintenance treatment. Our results are in agreement with the comment of Stewart [17] that, in a slower-tempo relapse, sequencing of drugs may offer superior overall survival results.

With regard to a long-term treatment with thalidomide, there has been a concern of the late development of neuropathy if given sufficient length of time with low-dose thalidomide [18]. However, long-term treatment with low-dose thalidomide for as long as 3 years in the present study did not result in delayed development of adverse events. Furthermore, because of the lower toxicity of low-dose thalidomide, the patients could stay on the treatment and enjoyed a long-term survival with good activities of daily living.

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