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Low-Dose Thalidomide Ameliorates Cytopenias and Splenomegaly in Myelofibrosis With Myeloid Metaplasia: A Phase II Trial

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A B S T R A C T

Purpose

A phase II dose-escalation trial was conducted to ascertain low-dose thalidomide safety and response in patients with advanced myelofibrosis with myeloid metaplasia (MMM).

Patients and Methods

Thalidomide was administered together with current therapy to 63 patients, starting at 50 mg daily and increasing to 400 mg as tolerated.

Results

Half of the patients sustained daily doses more than 100 mg and the drop-out rate was 51% at 6 months: the drop-out rate was lower in patients with high baseline fatigue score. At efficacy analysis, anemia was ameliorated in 22% of the patients and transfusions were eliminated in 39% of transfusion-dependent patients. Platelet count increased by $50 \times 10^9/L$ or more in 22% of patients with an initial count lower than $100 \times 10^9/L$. Splenomegaly decreased by more than 50% of the initial size in 19% of patients. Reduction of an overall disease severity score occurred in 31% of patients and was associated with a significant reduction of fatigue. Disease severity amelioration was independently predicted by a high baseline myeloproliferative index (ie, large splenomegaly, thrombocytosis, or leukocytosis).

Conclusion

Low-dose thalidomide displays an acceptable toxicity profile and provides an objective and subjective advantage to a relevant portion of MMM patients.

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INTRODUCTION

Myelofibrosis with myeloid metaplasia (MMM) is the most severe among chronic Philadelphia-negative myeloproliferative disorders [1,2]. Potentially curative therapies, such as stem-cell transplantation, are reserved for a minority of patients [3] and standard treatment generally consists of supportive therapies or cytoreductive approaches aimed at reducing the tumor burden, especially in the spleen. However, prognosis remains poor because median survival is shorter than 4 years [4,5]; thus, improvement of quality of life is a major end point of novel treatment strategies.

Recently, thalidomide was advocated as means for controlling angiogenesis in several neoplastic and inflammatory diseases. In MMM, six small studies and a pooled analysis documented that thalidomide ameliorated anemia, thrombocytopenia, and splenomegaly [6-12]. Nevertheless, most of the patients treated with standard doses (200 to 800 mg/d) reported adverse effects that led to an adverse drop-out rate of nearly 50% at the third month [6]. Recently, a small prospective study reported that combining low-dose thalidomide with prednisone augmented drug's tolerability and clinical efficacy [13]. However, a large part of the clinical response vanished after dis-

continuation of prednisone, and it was thus difficult to ascertain the efficacy attributable to thalidomide rather than to prednisone.

In early 2000, we planned a phase II trial of low-dose thalidomide as a single agent in patients with advanced MMM. Dose escalation was allowed to assess tolerability threshold [14] and quality of life was monitored to quantify the palliative effect of the drug. We report the analysis of the 63 enrolled patients.

PATIENTS AND METHODS

Study Design

After obtaining approval by the Ethical Committee of the Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo and the Centre Hospitalier Régional Universitaire de Lille, a 6-month dose-escalating, multi-institutional phase II trial of thalidomide was initiated. Criteria for registered patients were a definite diagnosis of MMM [15], age between 18 and 80 years, and a poor prognosis (ie, Dupriez risk score intermediate to high [4]) or a low risk with at least one of the following: spleen size more than 10 cm from costal arc, platelet count less than $150 \times 10^9/L$, systemic symptoms, or more than 2% myeloid blast cells in peripheral blood. Patients receiving therapy at enrollment had to have been receiving therapy for at least 6 months before enrollment, with stable doses in the last month; patients could not have achieved any amelioration in their severity score in the last month. Eligibility criteria also were stringent to limit the drug toxicity: patients needed to have normal or minimally impaired neurologic function; that is, peripheral neuropathy National Cancer Institute Common Toxicity Criteria grade 0 to 1 and an Eastern Cooperative Oncology Group performance status ≤ 2 . Females had to be more than 50 years old and had to have follicle-stimulating hormone serum levels greater than 45 mU/mL in Italy or more than 55 mU/mL in France before enrollment.

Patients signed an informed consent and received the experimental drug, provided without charge by Laphal Laboratories (Paris, France). Monthly doubling of thalidomide dosage was allowed, starting from 50 mg to a maximum dose of 400 mg a day, administered orally at bedtime. Patients already receiving other treatments were allowed to continue their therapy along with thalidomide. After the first month, the concomitant drug dosage could be tapered down.

Pretreatment evaluation included physical examination, spleen ultrasonography, CBC, leukocyte differential, reticulocyte count, renal and hepatic function studies, erythrocyte sedimentation rate, serum lactate dehydrogenase (LDH), serum albumin, C-reactive protein, and routine urinalysis.

Adverse events were recorded according to the CTC coding and four symptom-specific questionnaires were also variably administered by four Italian participating centers: the Epworth Sleepiness Questionnaire (admissible values, 0 to 24), the Constipation Assessment Scale (admissible values, 0 to 16), and two subscales of the Functional Assessment Cancer Toxicity (FACT), namely the fatigue subscale (FACIT-F; admissible values, 0 to 54) and the neurotoxicity subscale (admissible values, 0 to 44) [16-20]. Response to the treatment was evaluated by assessing relevant changes in the main hematologic parameters: an increase in hemoglobin value by more than 2 g/dL or a complete elimination of transfusion requirement, a persistent reduction in spleen size by

more than 50%, and an increase in platelet count by more than $50 \times 10^9/L$. However, we also calculated the global effectiveness of thalidomide on the severity of the disease. We thus assessed any variation in a severity score, which summed to a myeloproliferation index and a myelodepletion index [6]: the former scored leukocytosis (corrected for the circulating erythroblasts), thrombocytosis, and splenomegaly (or hepatomegaly in splenectomized patients), whereas the latter scored anemia, leukopenia, and thrombocytopenia. The following parameters were scored according to three grades: splenomegaly (0 is nonpalpable or removed; 1 is ≤ 10 cm below the costal margin; and 2 is > 10 cm below the costal margin) and anemia (0 is hemoglobin concentration ≥ 12 g/dL; 1 is hemoglobin concentration from 10 to 12 g/dL; and 2 is hemoglobin concentration < 10 g/dL or transfusion dependency). Two grades were considered for leukocytosis (0 is leukocyte count $< 15 \times 10^9/L$; 1 is leukocyte count $\geq 15 \times 10^9/L$), thrombocytosis (0 is platelet count $< 500 \times 10^9/L$; 1 is platelet count $\geq 500 \times 10^9/L$), thrombocytopenia (0 is platelet count $> 150 \times 10^9/L$; 1 is platelet count $\leq 150 \times 10^9/L$), and leukopenia (0 is leukocyte count $\geq 4 \times 10^9/L$; 1 is leukocyte count $\leq 4 \times 10^9/L$). Myelodepletion and myeloproliferation indexes ranged from 0 to 4, whereas the overall severity score ranged from 0 to 6.

Statistical Analysis

Efficacy analysis that evaluated patients with a treatment duration of at least 4 weeks was conducted [6]. Continuous variables were described as medians, whereas categoric variables were described as frequencies. The Wilcoxon rank sum test or the Kruskal-Wallis test was used to assess whether continuous variables differed significantly between categories. Comparisons between categoric variables were performed using a continuity-corrected χ^2 test or Fisher's exact test. Independent predictors of response were assessed through logistic regression, whereas predictors of continuous end points were assessed through multivariate linear analysis. All tests were two sided, and *P* values of less than 5% were considered statistically significant. All data were analyzed using Statistica software version 6.0 (Statsoft, 1995; Tulsa, OK).

We planned to enroll at least 60 patients to ensure a power of 95% in detecting a 20% rate of reduction in the severity score and a power of 80% in detecting a 15% rate of reduction.

RESULTS

Pretreatment Data

Sixty-three patients were enrolled onto the trial (Table 1). Sixty-five percent of the patients had a hemoglobin value less than 10 g/dL, 41% were transfusion dependent, 55% had a baseline platelet count less than $150 \times 10^9/L$, and 21% had a leukocyte count less than $4.0 \times 10^9/L$. Spleen size was larger than 10 cm from the costal arc in 80% of the nonsplenectomized patients. Both myeloproliferative and myelodepletive features were concurrently present in a large portion of the enrolled population; thus, 38% of the patients had a baseline severity score higher than 4 (admissible values, 0 to 6).

Safety and Tolerability

During the treatment, the most frequently reported adverse effects were constipation and fatigue (Table 2). An

Table 1. Baseline Characteristics of the Study Population (63 patients)

Characteristic	No. of Patients	%	Median	Range
Male patients	37	59		
Age, years			68	43–80
Duration of the disease, months			51	3–263
Patients with a previous myeloproliferative disease	14	22		
Transfusion-dependent patients	26	41		
Transfusion-independent patients with initial hemoglobin <10 g/dL	15	24		
White blood cell count ($\times 10^9/L$)			7.5	2–74
Initial white blood cell count				
< $4 \times 10^9/L$	13	21		
$\geq 15 \times 10^9/L$	17	27		
Platelet count ($\times 10^9/L$)			140	19–747
Initial platelet count				
< $150 \times 10^9/L$	35	55		
> $400 \times 10^9/L$	6	9		
Spleen size below left costal margin, cm			13	0–25
Splenectomized patients	3	5		
Dupriez prognostic score*				
0	18	29		
1	33	52		
2	12	19		
Myelodepletive index				
> 2	26	41		
Myeloproliferative index†				
> 2	12	19		
Severity score ≥ 4	50	79		
Serum lactate dehydrogenase, mU/mL			1,179	141–5,025
Myeloblasts in peripheral blood, %			1	0–16
Immature myeloid cells (nonblasts) in peripheral blood, %			8	0–37
Erythroblasts (% leukocytes) in peripheral blood			2	0–28
Taking cytostatics	19	30		
Taking oral corticosteroids	14	22		
ECOG performance status is 2	9	14		
Constipation Assessment Scale, score			2	0–12
Epworth Sleepiness Questionnaire, score			7	0–14
FACT-neurotoxicity subscale, score			4.5	0–21
FACT-fatigue subscale, score			24.5	8–42

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FACT, Functional Assessment Cancer Toxicity.

*Dupriez score is 0 (low risk) if leukocytes are between 4 and $30 \times 10^9/L$ and hemoglobin is more than 10 g/dL. Dupriez score is 1 (intermediate risk) if either hemoglobin is less than 10 g/dL or leukocytes are more than $30 \times 10^9/L$ or less than $4 \times 10^9/L$. Dupriez score is 2 (high risk) if hemoglobin is less than 10 g/dL and leukocytes are more than $30 \times 10^9/L$ or less than $4 \times 10^9/L$.

†The myeloproliferative index sums three grades of splenomegaly (0, non palpable or removed; 1, 10 cm or less below the costal margin; 2, more than 10 cm below the costal margin), two grades of leukocytosis (0, leukocyte count < $15 \times 10^9/L$; 1, leukocyte count $\geq 15 \times 10^9/L$), and two grades of thrombocytosis (0, platelet count < $500 \times 10^9/L$; 1, platelet count $\geq 500 \times 10^9/L$). The myelodepletive index sums three grades of anemia (0, hemoglobin concentration ≥ 12 g/dL; 1, hemoglobin concentration from 10 to 12 g/dL; 2, hemoglobin concentration < 10 g/dL or transfusion dependent), two grades of thrombocytopenia (0, platelet count > $150 \times 10^9/L$; 1, platelet count $\leq 150 \times 10^9/L$), and two grades of leukopenia (0, leukocyte count $\geq 4 \times 10^9/L$, 1, leukocyte count < $4 \times 10^9/L$). The severity score sums the myeloproliferative and myelodepletive index and ranges from 0 to 6.

increase in the Constipation Assessment Scale during the treatment period was observed in 18 (64%) of 28 patients who completed the questionnaire, whereas constipation was reported to the investigating physician by 49% of the enrolled patients. Constipation limited dose escalation in eight patients. Twelve (50%) of 24 patients who completed the FACIT-F at baseline and during the treatment period reported an increased score at the end of the treatment, whereas fatigue was reported to physicians by 38% of the overall patients. Fatigue limited dose escalation in only two patients.

Sedation was reported by 17 patients (27%) and an increase above 15 points of the Epworth Sleepiness Questionnaire occurred in these patients. We did not find a significant correlation between the Epworth and the FACIT-F scores, thus we could not attribute the perceived fatigue to thalidomide-induced sedation.

Neurologic symptoms (paresthesia, tremor, altered hearing, seizure, depression, or extrapyramidal symptoms) occurred in 38 patients (60.3%); however, only four patients (6%) had neurologic toxicity of grade 3 or more, and three patients (4.8%) had electromyography-documented

Table 2. Toxicity

Adverse Event	No. of Patients	%	No. of Dose-Limiting Events	No. of Events \geq Grade 3	No. of Events Causing Discontinuation of Study Treatment
Probably related to thalidomide					
Constipation	31	49	8	3	0
Paresthesia	21	33	3	2	2
Sedation	17	27	4	4	0
Neutropenia ($< 1.5 \times 10^9/L$)	16	25	7	10	2
Tremor	9	14	2	0	0
Edema	8	13	1	1	1
Rash	7	11	3	0	3
Dizziness or vertigo	7	11	1	1	1
Decreased or altered hearing	5	8	2	0	0
Orthostatic symptoms	5	8	2	0	2
Minor venous complications*	3	5	3	0	2
Deep venous thrombosis	2	3	2	2	2
Oral aphthoid lesions	2	3	1	0	0
Cholestasis	2	3	2	0	2
Seizure	1	1.6	1	1	1
Possibly related to thalidomide					
Fatigue	24	38	6	9	2
Cramps	12	19	0	1	0
Infections†	8	12	4	5	4
Headache	5	8	0	1	0
Abdominal pain	2	3.2	0	1	0
Depression	1	1.6	0	1	1
Extra pyramidal symptoms	1	1.6	0	1	1
Not related to thalidomide					
Skin or mucosal bleeding	5	8	0	0	0
Early leukemic transformation	3	5	3	3	3
Cerebral bleeding	1	1.6	1	1	1

*Superficial thrombophlebitis and venous ulcer.

†Interstitial pneumonia occurred in three patients: in one patient, *Nocardia* was isolated and the patient recovered fully after appropriate antibiotic treatment.

peripheral neuropathy. Seven (19%) of 36 patients who completed the FACT-neurotoxicity subscale had an increase in the score by more than 6 points during the treatment period.

Undesirable thrombocytosis occurred in a few patients: transient increase of platelet count more than $500 \times 10^9/L$ was reported during the treatment period in 10 patients (16%), four of whom had a baseline count higher than $400 \times 10^9/L$. However, only in five patients (8%) was the platelet count at the end of the treatment still more than $500 \times 10^9/L$. Thrombocytosis was associated with seizure in one patient and with deep vein thrombosis in another patient. Only six patients (9%) experienced an increase of leukocyte count by more than $2 \times 10^9/L$: five of six patients had baseline leukocyte counts more than $15 \times 10^9/L$ and discontinued thalidomide treatment because of rapid leukemic evolution.

The median of maximum-tolerated doses was 100 mg daily: only eight patients (12.7%) tolerated daily doses ≥ 300 mg, whereas 16 patients (25%) discontinued the drug at a daily dose of 50 mg and four patients (6%) continued on that dose until the end of the treatment period. The

cumulative drop-out rate was 22% at 4 weeks, 24% at 3 months, and 51% at 6 months of therapy. All of the drop-outs were due to occurrence of adverse events (Table 2) and there was no patient in which thalidomide administration was stopped before the 6-month period uniquely for inefficacy. The reasons for discontinuing study treatment were, in decreasing frequency order: pneumonia, neutropenia, rash, leukemic transformation, neuropathy, venous thromboembolism, thrombocytosis, cholestasis, orthostatic symptoms, seizures, depression, Parkinsonism, fatigue, cerebral bleeding, ascites, and thyroid nodule. Overall, four patients died soon after discontinuing study treatment: one patient died as a result of cerebral bleeding, two patients died as a result of pneumonia, and one patient died as a result of sepsis. Of the 31 patients who completed the treatment period, 10 continued taking thalidomide for compassionate use at a dose of 50 to 100 mg/d. Completion rate was higher in patients with a FACIT-F subscale score higher than 19 points (84% v 52%; $P = .04$).

The median cumulative dose of thalidomide was 9.8 g. Forty percent of the patients with an Epworth sleepiness

Table 3. Response Rates in Patients Treated for Longer Than 4 Weeks

Evaluated Response	Response Rate	%
Anemia		
Hemoglobin increase > 2 g/dL in transfusion-independent patients	4 of 31	13
Transfusion interruption rate in transfusion-dependent patients	7 of 18	39
Hemoglobin increase > 2 g/dL or transfusion interruption	11 of 49	22
Thrombocytopenia		
Increase of platelet count by > 50 × 10 ⁹ /L in all patients	20 of 49	41
Increase of platelet count by > 50 × 10 ⁹ /L in patients with initial platelet count < 100 × 10 ⁹ /L	4 of 14	22
Splenomegaly		
Spleen reduction by ≥ 2 cm	20 of 47	42
Spleen reduction by ≥ 50%	9 of 47	19
Severity score		
Reduction by ≥ 1 point	15 of 49	31
Reduction of the myeloproliferative index	14 of 49	28
Reduction of the myelodepletive index	4 of 49	8
Dupriez risk score		
Reduction by ≥ 1 point	7 of 49	14

score higher than 7 before treatment did not achieve the median thalidomide cumulative dose, whereas 74% of those with a lower Epworth sleepiness score did achieve the median dose ($P = .06$).

Clinical Response to Treatment

Detailed response to treatment is listed in Table 3. Twenty-six percent of the patients who sustained the treatment for at least 4 weeks had an increase in hemoglobin value and/or a reduction of transfusion requirement. Out of 18 transfusion-dependent patients, nine (50%) had a 50% reduction of transfusion requirement and seven (39%) had a complete elimination of transfusion requirement. Conversely, only 13% of those patients who were not transfusion dependent at enrollment and sustained at least 4 weeks of treatment had an increase of more than 2 g/dL in hemoglobin value. Amelioration of anemia was predicted at univariate analysis by transfusion dependence ($P = .017$).

During treatment, the median platelet count increased from $140 \times 10^9/L$ to a maximum count of $265 \times 10^9/L$ at the fourth week of treatment ($P < .001$), and to $184 \times 10^9/L$ at the end of the treatment ($P = .035$). Overall, an increase in platelet count greater than $50 \times 10^9/L$ was achieved in 41% of the whole patient population and in 22% of the patients with a baseline platelet count less than $100 \times 10^9/L$. No statistically significant predictor of platelet response could be found at univariate analysis.

The median value of spleen sizes, as measured by physical examination, was reduced by treatment from 13 to 10 cm from the costal margin ($P = .002$). A persistent spleen reduction by more than 50% was achieved in 19% of patients being treated for more than 4 weeks. Spleen reduction by more than 50% was predicted by a higher baseline spleen size ($P = .03$) and was independent of treatment duration.

Spleen ultrasound follow-up was performed in 16 patients: longitudinal spleen diameter was decreased by more than 50% in all four patients who proved to have such a reduction at physical examination.

In contrast to anemia and thrombocytopenia, leukopenia became worse in all of the patients with initial counts below $4 \times 10^9/L$, and leukocyte count decreased below $4 \times 10^9/L$ in 12 (36%) of 33 patients with a baseline count between 4 and $15 \times 10^9/L$. A decrease of neutrophil absolute count below $1.5 \times 10^9/L$ was reported during the treatment period in 16% of the patients.

Overall, a relevant amelioration of anemia, thrombocytopenia, or splenomegaly was achieved by 40% of the patients. Clinical response rate was not significantly different in patients receiving other treatments together with thalidomide; rather, clinical response was predicted by both a high myeloproliferative index ($P = .044$) and a large spleen size ($P = .023$). Spleen size also predicted clinical response rate independently from treatment duration and cumulative thalidomide dose.

Other disease features with negative prognostic value were ameliorated by thalidomide therapy. LDH values decreased from 1,159 U/L to 1,094 U/L ($P = .048$) and 20 (47%) and nine (21%) of the 42 assessable patients had a decrease of LDH greater than 100 and 500 mU/mL, respectively. By limiting this analysis to patients who had a high level of LDH at the start of treatment ($> 1,000$ mU/mL), eight (40%) of 20 patients had a decrease greater than 500 mU/mL.

An overall decrease in the severity score was observed in 31% of the patients but no patient achieved a zero final score. The reduction in the severity score was associated with a reduction in the Dupriez risk score ($P = .028$) and

with a reduction in the FACIT-F score ($P = .017$). Indeed, the FACIT-F score decreased in 55% of the patients who also achieved a reduction in the severity score, corresponding to an average score reduction of 4.6 points, versus an increase of 4.4 points in those patients with no reduction in the severity score ($P = .01$). The minimal clinically important difference in the FACIT-F score was reached by 29% of the assessable patients.

There was no evidence that thalidomide was differentially effective in any group of patients defined by age, sex, length of time with disease, type of disease (idiopathic or secondary MMM), transfusion dependence, or degree of anemia. However, there was a significant difference in the rate of response according to the severity of the disease at the start of the treatment: 36% of the patients with a severity score ≥ 4 had a reduction in the score, versus 7% in patients with lower baseline scores ($P = .047$). This difference was greater in patients with a high myeloproliferative index (> 2), who had a higher probability to achieve a reduction in the severity score (50% *v* 21%; $P = .04$). Finally, the degree of splenomegaly and LDH values at baseline also predicted the decrease in the severity score. In fact, patients with a baseline spleen size smaller than 10 cm from the costal arc did not achieve any reduction in the severity score, whereas more than one third of the patients with larger spleens did achieve a reduction in the severity score ($P = .019$). Patients achieved a reduction in the severity score twice more often if their initial LDH values were more than 1,500 mU/mL (54% *v* 19%; $P = .025$).

Baseline values of spleen size, LDH (ranked $>$ or $<$ 1,500 mU/mL), and myeloproliferative index were entered into a multivariate logistic model aimed at predicting a reduction in the disease severity score. A high myeloproliferative index (OR, 3.10; $P = .018$) was an independent predictor of a successful reduction in the severity score.

DISCUSSION

We investigated the feasibility and efficacy of low-dose thalidomide in a cohort of 63 patients with advanced MMM. Starting from 50 mg/d up to 400 mg/d by monthly escalation of the dose and with a median tolerated dose of 100 mg, 76% of the patients could be treated for more than 3 months and 49% were able to continue for the duration of the trial. This result confirms the better tolerability of low doses of thalidomide (less than 200 mg/d) reported both in patients with multiple myeloma and myelodysplastic syndromes [14,21]. Combining thalidomide with prednisone improves tolerability, as reported by Mesa et al [13] in a study in which only one of 21 patients discontinued the treatment, when compared with this study in which 25% of the patients did not tolerate 50 mg/d dose of thalidomide. This study also provides evidence of the safety of treatment with low doses of thalidomide in patients with MMM: in

234 patient treatment-months we reported two thrombotic events, no relevant neurologic toxicity, and no signs or symptoms of extrasplenic or extrahepatic myeloid metaplasia.

Regarding efficacy, a substantial proportion of patients achieved a clinical and hematologic response: amelioration of anemia, thrombocytopenia, or splenomegaly was achieved by 40% of the patients receiving at least 3 months of therapy. The most beneficial effect was exerted on patients with transfusion-dependent anemia, 39% of whom required no further transfusions. Clinically meaningful efficacy also was provided to patients with a platelet count less than $100 \times 10^9/L$, 22% of whom achieved a platelet count increase of more than $50 \times 10^9/L$. Forty-six percent of patients reduced spleen volume by 2 cm or more and 19% reduced spleen volume by 50% or more of the initial value. Overall, these results are not at great variance with those obtained with standard-dose thalidomide, as reported in a pooled-analysis of five small trials [6] (Table 4). When the response rates of this dose-escalating regimen were compared with that of a fixed low-dose (50 mg/d) of thalidomide combined with prednisone, the latter schedule achieved a higher response rate for non-transfusion-dependent anemia and thrombocytopenia [13] (54% and 50%, respectively; Table 4). However, after discontinuation of prednisone, hemoglobin and platelet response vanished in 38% and 34% of the patients, respectively [13]. It is conceivable that prednisone contributed to the response because corticosteroids alone, as well as other immunosuppressive treatments, have an effect on anemia and thrombocytopenia in MMM [22,23].

For ethical reasons, the design of this study allowed patients to continue previously started therapies, provided that the response had already been stabilized. This could produce a synergic effect of ongoing therapies with thalidomide. However, we explored this issue with a multivariate analysis and did not find any significant association between response and the associated treatment.

Considering that in MMM no standardized response criteria exist, and that during thalidomide therapy, untoward neutropenia, thrombocytosis, and leukocytosis could mitigate the overall utility of the treatment [6], we also used a composite response assessment tool capable of measuring both amelioration and worsening of the major hematologic and clinical parameters of MMM. We adopted a severity score (not yet validated) that summed myelodepletive and myeloproliferative features of the disease. We could observe a severity score reduction in 31% of the patients who sustained thalidomide treatment for more than 4 weeks. The reduction rate in the severity score was independently predicted by an elevated baseline myeloproliferation index, which confirmed the results of a previous analysis conducted in 62 patients treated with standard-dose thalidomide [6]. An improvement of the severity score was also

Table 4. Published Trials of Thalidomide in MMM Patients

Studies	Barosi et al [6]	Merup et al [11]	Mesa et al [13]	Present Study
No. of patients	62*	15	21	63
Median age, years	65	68	63	68
Previous myeloproliferative disease	26%	40%	28%	22%
Thalidomide dose				
Minimum, mg/d	100	200	50	50
Maximum, mg/d	800	800	50	400
Associated treatments	Various	Various	Prednisone	Various
Transfusion-dependent patients	37%	46%	48%	41%
Median hemoglobin, g/dL	9.46†	10.1	9.0	9.2
Median WBC, 10 ⁹ /L	7.9	12.6	7.7§	7.5
Median platelet count, 10 ⁹ /L	150	235	154	140
Spleen size, median below costal arc, cm	13	NA	14	13
Dupriez score of 2	25%	6%	28%	19%
Severity score ≥ 4	63%	NA	NA	79%
Drop-out rate at 3 months	45%	36%	5%	24%
Response at efficacy analysis‡				
Increase by 2 g/dL of hemoglobin value in all patients	14%	0%	45%§	13%
Increase by 2 g/dL of hemoglobin value in transfusion-independent patients	NA	0%	54%§	13%
Transfusion interruption in transfusion-dependent patients	30%	0%	40%§	39%
Increase by > 50 × 10 ⁹ /L of platelet count in all patients	45%	0%	76%§	41%
Increase by > 50 × 10 ⁹ /L of platelet count in patients with a platelet count < 100 × 10 ⁹ /L	NA	0%	50%§	22%
Decrease of spleen size by > 2 cm from costal arc	37%	0%	43%§	42%
Decrease of spleen size by > 50%	NA	NA	19%§	19%

Abbreviations: MMM, myelofibrosis with myeloid metaplasia; NA, not available.

*Pooled data from studies in.

†Means.

‡Efficacy analysis includes only patients who received at least 4 weeks of therapy.

§Response rates reported after 3 months of therapy.

associated with a relevant improvement in fatigue, a major aspect of the quality of life in cancer patients [24].

Thalidomide also was successful in reducing disease features that indicate disease severity, namely serum LDH level. However, controlled studies with long follow-up are necessary to ascertain the impact of thalidomide on long-term disease progression.

The mechanism of action of thalidomide in MMM has to be clarified. In this study we reported neither evaluations of bone marrow fibrosis nor direct or indirect measurements of neoangiogenesis. However, in a previous study [13], neither intramedullary fibrosis nor angiogenesis, as measured by bone marrow section immunostaining, predicted clinical response to thalidomide or changed during therapy.

On the basis of the results of this study, we conclude that low-dose thalidomide is a useful therapy for MMM patients, in particular for transfusion-dependent and/or thrombocytopenic patients, but also for those who need a

control of a progressive splenomegaly. This is of particular relevance considering that the drugs currently used in MMM, such as danazol, 1,25-dihydroxy vitamin D3, corticosteroids, hydroxyurea, interferon, or melphalan [1], do not improve the concurrent myeloproliferative characteristics and cytopenias, and they often need to be administered in combination. We also conclude that optimization of tolerability is fundamental to achieve the potential benefits of thalidomide: a slow dose escalation is a necessary strategy in administering this drug.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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