Thalidomide versus placebo in myeloid metaplasia with myelofibrosis: a prospective, randomized, double-blind, multicenter study

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Background and Objectives. In non-randomized studies, thalidomide appeared to be effective in myeloid metaplasia with myelofibrosis (MMM). We compared thalidomide to placebo for treatment of anemia in MMM.

Design and Methods. A prospective phase II B, randomized double-blind multicenter trial comparing thalidomide 400 mg/d with placebo for 180 days was conducted in 52 anemic patients (hemoglobin ≤9 g/dL or transfused). The main outcome measure was a 2 g/L increase in hemoglobin or 20% reduction in transfusions.

Results. In the thalidomide group only 10 patients completed 6 months of treatment. At 180 days, in an intention-to-treat analysis, no difference was observed between the thalidomide and placebo groups as regards improvement of hemoglobin levels (one patient in each group) or reduction of red blood cell transfusions (three vs five patients, respectively). The spleen size, determined by ultrasonography, increased significantly less in the thalidomide group than in the placebo group ($p<0.05$). Thalidomide had no apparent benefit on the Dupriez score, the severity score, survival, death, or any other clinical or biological parameter. Somnolence, gastro-intestinal signs, weight gain, and edema were significantly more frequent in the thalidomide group. Outpatient discontinuation of thalidomide was significantly correlated with a high severity score > 4 (odds ratio, OR = 16; $p<0.01$), and γ-glutamyl transferase levels > 40 IU/L (OR=12; $p<0.05$).

Interpretation and Conclusions. Thalidomide (200-400 mg/d) does not demonstrate substantial efficacy in anemic MMM patients. The natural history of disease in the placebo group revealed spontaneous periods of remission of anemia. Tolerance of thalidomide was significantly correlated wih the severity and liver involvement of the disease.

Key words: myelofibrosis, anemia, thalidomide, placebo, randomized trial.

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Myeloid metaplasia with myelofibrosis (MMM) is a chronic myeloproliferative disorder characterized by bone marrow myelofibrosis, splenomegaly, leukoerythroblastic blood smears, extramedullary hematopoiesis, and the absence of Philadelphia chromosome or previous myeloproliferation, such as essential thrombocythemia or polycythemia vera.[1-3] During the course of the disease, anemia, thrombocytopenia, enlargement of the spleen and constitutive symptoms may occur, necessitating therapeutic interventions. In the absence of evidence-based treatment, supportive (androgens, transfusions) or cytoreductive therapies (hydroxyurea, melphalan) are prescribed with some benefit.[4,5] A high degree of tumoral neoangiogenesis is observed in the majority of patients with MMM and is an independent risk factor for prognosis.[6-8] This prompted research into the effectiveness of thalidomide, a known angiogenic inhibitor,[9] in MMM.[10,11] In 14 studies, including approximately 205 patients, correction of anemia was observed in 0-62% of cases, reduction or elimination of red blood cell (RBC) transfusions in 39-75%, reduction in spleen volume in 17-71% ; and increased platelet counts in 0-100 % of cases.[12-18] The largest study, a phase II, multicenter, European trial of thalidomide in MMM, prospectively including 63 patients, indicated improvement of anemia in 22%, independence from RBC transfusion in 39%, an increase in platelet count in 22%, and reduction of splenomegaly in 19% of patients.[19] Only one study showed no effect of thalidomide in 14 patients with MMM.[20]

The use of thalidomide is limited by the adverse effects observed with standard doses, which often lead to premature discontinuation of the drug in approximately half of patients.[12,15,19,20] The combination of a lower thalidomide dose with prednisone appears to be better tolerated and more effective.[21,22]

We describe the results of the first multicenter, randomized, double-blind, placebo-controlled trial investigating the effectiveness of thalidomide at increasing hemoglobin levels and/or reducing red blood cell (RBC) transfusion requirements in patients with advanced MMM complicated by anemia.

Design and Methods

Patients

This prospective phase II B, randomized, double-blind, multicenter, placebo-controlled study enrolled patients with advanced MMM with anemia. Patients received treatment for 180 days. Between January 2001 and June 2003, 52 patients from 19 French hospitals (13 university hospitals and 6 general hospitals) were enrolled and randomized to receive either thalidomide or placebo. Patients provided written informed consent. The trial was approved by the Institutional Ethics Committee and registred by the French agency AFSSAPS (*Agence Française de Sécurité Sanitaire des Produits de Santé*) under the reference 001332. The criteria used for including patients were those defined by the Polycythemia Vera Study Group (PVSG), i.e., splenomegaly, myelofibrosis on bone marrow biopsy, a leukoerythoblastic blood smear, morphologic abnormalities in a red blood cell smear, and absence of the Philadelphia chromosome or *bcr-abl* transcript.[23] Only patients with a hemoglobin level ≤9g/dL, and/or requiring RBC transfusions were included. The V617F *JAK2* mutation was not tested in these patients. Bone marrow biopsies were obtained for each patient at the time of diagnosis and not performed again at inclusion in the trial. Females of child-bearing potential, subjects with severe neuropathy or secondary myelofibrosis related to other myeloproliferative disorders, and subjects who had already undergone splenectomy were excluded from the trial.

Treatment and outcome

Thalidomide and placebo were provided by Laphal/Pharmion LTD (Paris, France) without charge. The treatment period lasted 180 days. The primary outcome measure was either an increase in hemoglobin level in patients not requiring RBC transfusions (≥2 g/dL), or a 20% reduction in the mean number of RBC units transfused, as calculated during the last 3 months of the trial and compared to the last 3 months before treatment initiation. The secondary outcome measures, evaluated at day 180, were reduction in spleen size, liver size, change in ECOG performance status, change in platelet and leukocyte counts, modification in RBC mass and plasma volume as determined by isotopic methods, modifications in the Dupriez score[24] and in the Barosi severity score.[16] Quality of life (QOL) was assessed at inclusion and at day 180 using the EORTC QLQ-C30 questionnaire comprising 32 items. The survival rate was calculated and compared between the two groups. Based on available literature at the time of designing the protocol,[10,11] the number of patients required in each arm to obtain significant results was calculated, according to the hypothesis of a 50% positive response in the thalidomide group and 10% in the placebo group for the main outcome criteria. Randomization was done by blocks of four patients. The treatments were administered in identical capsules containing either 100 mg thalidomide or placebo. The initial thalidomide dose was 400 mg/d for 15 days, then increased (to a maximum of 800 mg/d) or decreased based on response and tolerance both evaluated at days 15, 30, 60, 90, 120, and 150. Other potentially effective treatments for MMM (including chemotherapy, androgens, interferon, steroids, or splenic irradiation) were not allowed during the study, and had to have been discontinued at least one month before study initiation.

Statistical analysis

The statistical analysis was divided into four stages: control of the initial comparability of the groups defined by the randomization, intention-to-treat analysis, *per protocol* analysis, and research of compliance criteria in the thalidomide group. The intention-to-treat analysis included all patients enrolled in the trial, regardless of treatment compliance, and compared available data between the groups defined by the randomization to thalidomide or placebo. The *per protocol* analysis was restricted to patients from both groups who completed the 180-day treatment period, without major deviation from the protocol. Major deviations included adjuvant corticosteroids, chemotherapy, or radiotherapy at the beginning or during the trial period, initial hemoglobin > 9 g/dL, and the absence of a bone marrow biopsy. The statistical analyses were performed using the EPI-INFO and SPSS statistical software. These analyses were limited to available data: missing data were due to death which was considered as failure for treatment response, and refusal to undergo clinical and biological controls at day 180. Qualitative and quantitative data were compared using χ^2, Fischer's exact test, and the non-parametric Kruskal Wallis test, respectively. The cumulative probability of survival rate and adverse effects were estimated by Kaplan Meier methods and compared using a log rank test.

Results

It took longer than expected to complete the enrollment of patients (30 months instead of the 6 months initially expected). This was due to difficulties in obtaining informed consent from these aged patients and to the frequent exclusion of potential participants due to splenectomy and/or disallowed use of corticosteroids. At study initiation, the two treatment groups were comparable except for three variables: patients in the thalidomide group were significantly older (fewer patients under 60 years old), had fewer previous treatments with interferon-α, and had higher plasma levels of gamma glutamyl transferase (γ-GT) (Tables 1 and 2). QOL questionnaires were completed by 20 patients in the thalidomide group and 22 patients in the placebo group and gave similar results in the two groups. Forty patients required RBC transfusion, and 12 patients were

Table 1. Clinical and histologic data at the onset of treatment.

	Thalidomide n=26	*Placebo n=26*	*p value*
Gender: males	18	20	ns
Age (years)	68.0±8.1	64.6±11	ns
Age < 60 years	2	10	<0.01
RBC (transfused patients)	21	19	ns
RBC units / 3 months	12.0±9.0	9.2±6.4	ns
Platelet transfusion	0	2	ns
Hemoglobin < 9 g/dL (not transfused)	5	7	ns
Hemoglobin (g/dL) (not transfused)	8.8±0.9	8.2±0.6	ns
Dupriez score			ns
Low risk	1	0	
Intermediate risk	12	16	
high risk	13	10	
Severity score			ns
Score 3	3	3	
Score 4	6	10	
Score 5	12	7	
Score 6	5	6	
Spleen, clinical size (cm)	11.1±6.7	12.0±5.9	ns
Spleen size, ultrasonography (cm)	20.3±4.1	20.4±4.1	ns
Liver, clinical size (cm)	6.1±5.7	5.7±5.7	ns
Liver size, ultrasonography (cm)	16.3±3.4	15.6±2.2	ns
Weight (kg)	69.7±11.9	69.5±12.4	ns
Height (m)	1.67±0.11	1.71±0.10	ns
Body mass index	25.0±2.7	23.8±3.0	ns
Weight loss	10	5	ns
Fever	0	1	ns
Night sweats	1	2	ns
ECOG performance status			ns
grade 0	4	4	
grade 1	15	17	
grade 2	7	5	
grade 3-4	0	0	
Bone marrow histology (known type)			ns
Type 1	8	9	
Type 2	8	7	
Type 3	7	9	
Previous treatments			
Hydroxyurea	12	15	ns
Steroids	6	6	ns
Pipobroman	3	6	ns
Interferon α	1	6	<0.05
Spleen irradiation	1	2	ns
Others	2	1	ns

Quantitative data: mean±standard error; Kruskal Wallis non-parametric test. Qualitative data: patient frequency; χ^2 or Fisher's test when appropriate. ns: not significant.

Table 2. Biological data at the onset of treatment.

	Thalidomide n=26	*Placebo n=26*	*p value*
RBC mass (mL/kg)	19.6±4.7	20.7±5.5	ns
RBC mass < 20 mL/kg (patients)	12	11	ns
Plasma volume (mL/kg)	64.2± 16.1	60.6±12.9	ns
Plasma volume > 50 mL/kg	14	18	ns
Hematocrit (%)	24.3± 3.8	23.9±5.0	ns
Platelets ($\times10^9$/L)	144.7±167.6	180.1±201.8	ns
Platelets < 100 ($\times10^9$/L)	15	10	ns
Platelets > 400 ($\times10^9$/L)	1	3	ns
WBC ($\times10^9$/L)	20.1±33.2	13.2±15.4	ns
WBC > 15 ($\times10^9$/L)	7	8	ns
WBC < 4 ($\times10^9$/L)	9	8	ns
PMN ($\times10^9$/L)	11.4±19.4	7.9±9.0	ns
Monocytes ($\times10^9$/L)	0.82±1.09	0.49±0.48	ns
Myeloblasts ($\times10^9$/L)	0.56±1.24	0.28±0.60	ns
Myelemia ($\times10^9$/L)	5.7±12.4	2.3±4.5	ns
Erythroblasts ($\times10^9$/L)	0.93±2.77	0.21±0.46	Ns
Alkaline phosphatase (IU/L)	149.3±137.4	120.3v77.6	ns
γ glutamyl transferase (IU/L)	76.4±71.8	38.6±26.4	<0.05
Lactate dehydrogenase (IU/L)	1382.3±1142.9	1297.0±800.2	ns

Quantitative data: mean±standard error; Kruskal Wallis non-parametric test. Qualitative data: patient frequency; χ^2 or Fisher's test when appropriate. ns: not significant.

Table 3. Frequency of patients in the thalidomide group according to daily dose (mg/d) and month of treatment.

	Patients at onset of month			*Daily dose (mg/d)*			
Month	*Alive and followed*	*Treated*	*600*	*400*	*300*	*200*	*100*
1st	25	25		25			
2nd	22	16		9		6	1
3rd	20	15	1	5		9	
4th	19	11		4	1	6	
5th	18	10		4		6	
6th	16	10	1	3		6	

One patient died between randomization and the start of treatment; ten patients were treated with thalidomide during the whole study period. Four patients were treated with at least 400 mg/d for the whole study period.

anemic without transfusion (Table 1). Most of the patients had a high plasma volume and 23 patients had a RBC mass under 20 mL/kg. According to the Dupriez score,[23] one patient was classified as low risk, 29 patients as intermediate risk and 22 as high risk (Table 1). Forty-five patients had a high severity score (≥4). One patient in each group did not receive treatment. However, the data available for these patients were included in the statistical analysis. In the thalidomide group, only ten patients completed the 180 days of treatment (four at 400 mg/d, six at 200 mg/d). Another four patients received thalidomide for at least for 60 days, and nine patients received the drug for less than 1 month (Table 3). No patient received 800 mg/d thalidomide. In the placebo group, 15 patients completed the 6-month period of treatment and four patients, while alive at day 180, discontinued the treatment before.

After 2 months, 40% and 20% of thalidomide and placebo patients, respectively, had discontinued study participation; after 4 months, 56% and 32%, respectively, had discontinued. At day 180, data were not available for 17 patients: 14 died during the study (eight in the thalidomide group and six in the placebo group), and three patients (all in the thalidomide group) refused to undergo the 180-day study assessment. Intention-to-treat results did not demonstrate differences between the thalidomide group and the placebo group for the

Table 4. Outcome of clinical and biological data at day 180 in an intention-to-treat analysis.

	Thalidomide		Placebo		p
	Available	Result	Available	Result	value
Main end-points					
Treatment efficacy	23	4	26	6	ns
Hb increase ≥2 g/dL	5	1	7	1	ns
Normalization of Hb (≥11 g/dL)	5	1	7	0	ns
RBC transfusion reduction (≥20 %)	18	3	19	5	ns
Elimination of transfusions	18	1	19	2	ns
Progression of anemia		7		9	ns
Secondary end-points					
RBC transfusion/month	10	+ 0.97±3.6	14	+ 1.31±2.8	ns
Liver, size (cm, clinical)	10	- 0.8±7.1	15	- 0.3±3.5	ns
Liver, size (cm, ultrasonography)	7	+ 0.7±1.4	13	+ 0.8±3.4	ns
Spleen size (cm, clinical)	14	+ 0.1±4.5	19	+ 1.1±3.5	ns
Spleen, size (cm, ultrasonography)	12	+ 0.4±2.7	17	+ 2.1±2.3	< 0.05
Plasma volume (mL/kg)	10	+ 1.6±8.4	9	+ 5.9±5.3	ns
RBC mass (mL/kg)	11	-0.29±3.8	9	-1.74±6.0	ns
Myeloblasts ($\times 10^9$/L)	14	- 0.19±0.7	19	+ 0.23±1.3	ns
Myelemia ($\times 10^9$/L)	13	- 3.3±11.6	19	+ 0.3±2.5	ns
Erythroblasts ($\times 10^9$/L)	14	+ 0.08±0.9	20	+ 0.12±0.7	ns
Lactate dehydrogenase (IU/L)	10	+ 1.4±463	14	+ 227±585	ns
GammaGT (IU/L)	11	- 10.0±38.3	13	+ 5.6±18.8	ns
Alkaline phosphatase (IU/L)	13	+ 3.1±77.1	16	+ 7.3±30.2	ns
ALT difference (IU/L)	13	- 2.3±30.4	16	+ 1.4±12.6	ns
AST difference (IU/L)	13	+ 1.4±16.9	16	+ 2.2±18.9	ns
Dupriez score: worsening	13	4	17	3	ns
Severity score: worsening	14	7	19	9	ns
ECOG performance status: aggravation	13	2	18	7	ns

ALT: alanine amino transferase; AST: aspartase amino transferase; all included patients with available data are involved in the analysis. Quantitative data: differences between day 180 and day 0; positive data correspond to increasing values ; mean ± standard error; Kruskal Wallis non parametric test. Qualitative data: status modification between day 180 and day 0; patient frequency; χ^2 or Fisher's test when appropriate. ns: not significant.

Table 5. Survival and side effects at day 180.

	Thalidomide n	Placebo n	p value
N. of deaths	8	6	ns
Gastro-intestinal disturbances	17	7	<0.001
Paresthesia	5	5	ns
Neuropathy	4	2	ns
Somnolence	19	7	<0.001
Weight gain	16	8	< 0.05
Edema	14	6	<0.01
Skin dryness	7	3	ns
Mucosal dryness	11	10	ns

n: number of events during the follow-up (6 month period or until death). p: log rank test for censored data.

Table 6. Clinical and biological data at day 180 in the per-protocol analysis.

	Thalidomide		Placebo		p
	Available	Result	Available	Result	value
Per protocol analysis					
Hb (+ 2 g/dL) or transfusion - 20 %	9	3	14	6	ns
Plasma volume difference (mL/kg)	7	2.2±6.5	8	+4.8±4.5	<0.05
γ-GT (IU/L)	9	-20.9±29.6	10	+10.4±18.6	<0.01
Dupriez score worsening	8	3	11	0	ns
Severity score worsening	9	5	14	7	ns

The analysis was restricted to patients without major deviation from the protocol who completed the treatment during the 6 month period. Quantitative data: differences between day 180 and day 0; positive data correspond to increasing values; mean±standard error; Kruskal-Wallis non- parametric test. Qualitative data: status modification between day 180 and day 0; patient frequency; χ^2 or Fisher's test when appropriate. ns: not significant.

primary outcome measure (Table 4). Normalization of hemoglobin levels occurred in one patient treated with thalidomide and in no patients receiving placebo. Elimination of RBC transfusions was observed in one patient receiving thalidomide and in two patients given placebo. A significant difference was observed in spleen size measured by ultrasound, which increased less in the thalidomide group than in the placebo group (0.4±2.7 vs 2.1±2.3 cm, $p<0.05$).

The Dupriez score, the severity score, and the ECOG performance status were not modified by thalidomide, and the median survival rate was not significantly different between the two groups (Tables 4 and 5). Liver size was not different in the two groups, and no biological parameters, such as leukocyte count, platelet count, lactate dehydrogenase concentration, circulating myeloblasts, myelemia, and erythroblasts, were significantly modified after thalidomide (Table 4). Changes in RBC mass and plasma volume were not different in the two groups, but the plasma volume increased less in the thalidomide group than in the placebo group (+1.6±8.4 vs + 5.9±5.3 mL/kg). Tolerance was poor in the thalidomide group with somnolence, gastrointestinal signs, weight gain, and edema being significantly more frequent in this group (Table 5). QOL questionnaires were available for only 11 patients in the thalidomide group and for 14 patients in the placebo group and did not reveal significant differences between the two groups. The *per protocol* analysis included 23 patients (9 in the thalidomide group and 14 in the placebo group). No statistical difference was observed between the two groups with regards to initial data. At 6 months, three positive results for anemia were observed in the thalidomide group and six in the placebo group. Plasma volume and γ-GT were significantly decreased in the thalidomide group (Table 6).

Compliance was a serious concern. In the thalidomide group, only ten patients completed the 6-month period of treatment, one of them with a major deviation from the protocol. In this study withdrawal from treatment was significantly correlated with a high severity score (>4) (odds ratio OR=16; 95% confidence interval: 1.7-208; $p<0.01$) and with a γ-GT serum level over 40 IU/L (OR=12; 95% confidence interval: 1.2-160; $p<0.05$) (Table 7).

Discussion

To our knowledge, this is the first randomized controlled trial investigating treatments for MMM. Evidence-based treatments remain unavailable at present for this disease. In this phase II B clinical trial, we included only patients with advanced disease: i.e anemic or transfused patients. Using the thalidomide dosing experience in refractory/replapsed myeloma, we started thalidomide treatment at 400 mg/d and increased or decreased the dose according to response and tolerance. An intention-to-treat analysis was done, but only nine thalidomide patients and 14 placebo patients received the complete treatment without major deviations from the protocol. In most of the cases, thalidomide was discontinued prematurely because of intolerance related to high treatment doses. In these patients, thalidomide was ineffective for reducing anemia and RBC transfusions or increasing platelet or leukocyte counts.

Our results conflict with those reported in other non-randomized studies,[10-19] but support the findings of Merup *et al.*[20] However, our results should be interpreted cautiously because only 15 patients received at least 200 mg/d thalidomide for more than 60 days, and only ten patients completed the 180-day protocol-defined treatment period (with a thalidomide dose of 200-400 mg/d). The discrepancy between our results and other studies could be due in part to the short duration of treatment with thalidomide, to lower doses used in other studies, and also to the larger proportion of high risk patients in our study. In all, 42% of our patients had a high risk Dupriez score compared to 28%, 19%, and 26% reported by Mesa *et al.*, Marchetti *et al.*,[19] and Barosi *et al.*,[16] respectively. Additionally, 86% of patients in our trial had a severity score ≥4, compared with 79% and 63% in the studies by Marchetti and Barosi. Another explanation for the inefficacy of thalidomide in our trial could be that the thalidomide was not associated with corticosteroids. Our results did not allow any conclusion to be drawn on the treatment of MMM using lower doses of thalidomide.

The *per protocol* analysis demonstrated the lack of a significant effect of thalidomide on anemia, but did show a significant reduction in isotopic plasma volume and γ-GT level. Reduction in plasma volume suggests an effect of thalidomide on the vasculature; the decrease in γ-GT levels suggests thalidomide activity on hepatic myeloid metaplasia. Among the four patients whose hemoglobin concentration rose while receiving thalidomide, three were treated for more than 4 months, which appears to indicate the importance of prolonged treatment.

In contrast to the results reported by Marchetti, thalidomide had no effect on the Dupriez score or on the severity score in our patients. The single significant positive advantage of thalidomide over placebo was observed on spleen size measured by ultrasound, which increased less with thalidomide. This finding suggests that thalidomide had a limited effect in MMM but not on the related anemia. Our study also questions the adequacy of measuring the transfusion rate in MMM as an indicator of treatment efficacy. The large hemodilution present in MMM could confound the effect of RBC transfusion. This was probably the case in two patients in the placebo group, who received two RBC units during in the 3 months before entering the trial, and were

Table 7. Comparison of patients in the thalidomide group according to whether they completed or did not complete treatment.

	Discontinued treatment n=16	*Complete treatment n=10*	*p value*
Age (years)	67.9±8.1	68.0 ± 8.6	ns
Age < 60 years	1	1	ns
Weight loss	7	3	ns
Body mass index	25.1±32.	24.8 ± 2.0	ns
Not transfused patients	1	4	ns
Hemoglobin (g/dL, not transfused)	8.1	8.9±1.0	not available
RBC units/ 3 months	12.3±9.2	11.2±9.5	ns
Spleen clinical size > 10 cm	8	5	ns
Abnormal EMG	4	5	ns
ECOG performance grade > 0	14	8	ns
Dupriez score: high risk	9	4	ns
Severity score > 4	14	3	< 0.001
Leukocytes ($\times 10^9$/L)	28.4±40.3	6.8±5.5	ns
Leukocytes > 15×10^9/L	6	1	ns
Platelets ($\times 10^9$/L)	135.9±206.9	158.7±79.8	ns
Platelets > 500×10^9/L	1	0	ns
Bone marrow: type 2-3	9	6	ns
γ-GT (IU/L)	100.8±80.5	38.4±31.4	< 0.05
Lactate dehydrogenase (IU/L)	1376±931	1392±1478	ns

Clinical and biological data were compared between patients who completed the 6 month thalidomide treatment and patients who discontinued thalidomide before completion of the study. Quantitative data: mean ± standard error; Kruskal-Wallis non-parametric test. Qualitative data: patient frequency; χ^2 or Fisher's test when appropriate. ns: not significant.

Table 8. Mean characteristics of patients with effective treatment according to randomization group.

Patient	*Group*	*Sex*	*Age*	*MMM duration (months)*	*3-months RBC transfusion (units)*		*Hemoglobin (g/dL)*	
					Before	*Trial end*	*Day 0*	*Day 180*
1	T	1	60	24	0	0	9.0	11.0
2	T	1	70	58	4.7	3.7		
3	T	2	51	54	2	0		
4	T	2	67	160	8.7	0		
5	P	2	63	233	0	0	8.3	10.6
6	P	1	67	60	4.7	3.7		
7	P	1	80	8	1.3	0.7		
8	P	2	51	30	0.7	0		
9	P	1	55	69	0.7	0		
10	P	1	77	11	2.3	0		

T: thalidomide; P: placebo.

not transfused during the subsequent 6 months (Table 8, patients #8 and #9).

According to the randomized double-blind trial design, our study provides objective information about the evolution of anemia in non-treated patients. An improvement of anemia was noted in 23% of the patients in the placebo group (6 out of 26 patients). This suggests that the natural history of disease comprises spontaneous periods of remission from anemia. These observations are of importance since results of previously published large non-randomized studies indicated that the percentages of patients having an increase in hemoglobin concentration while taking thalidomide was close to the percentage in our placebo group, i.e 22% of patients in Marchetti's study,[19] and 29% in Barosi's study.[16] Only the Mayo Clinic study indicated a higher percentage of efficiency on anemia with the addition of steroids to the thalidomide treatment: with this treatment anemia improved in 62% of the 21 included patients.[21] So, previously published results, indicating that thalidomide has around 20% efficacy at improving anemia, could possibly simply reflect a placebo effect. The 62% efficacy observed by Mesa could quite possibly reflect the effect of steroids rather than the effect of thalidomide.

As in other trials,[16,19] thalidomide was poorly tolerated in our patients. More than half the patients discontinued thalidomide after 4 months of treatment, due to adverse events. Thrombotic complications, such as deep vein thrombosis, however, were not observed. While our trial demonstrated little efficacy for thalidomide in the treatment of anemia in MMM, the significant positive changes observed in spleen size, plasma volume, and γ-GT do encourage randomized studies with thalidomide in MMM. Our trial also strongly suggests that in forthcoming trials thalidomide should be given preferentially to patients with a severity score < 4 and a normal γ-GT level in order to increase compliance.

J-FA, RZ, J-MC contributed to the study design, conduction, analysis and writing; J-MC contributed to statistical analysis and data entry; J-FA, IG, J-NB, MF, J-FR, LL-T, FB, PC, BS, CB, PR, ML, BV, CH, KG, FL, FR, JD, CA, MM, FI, RZ, J-MC contributed to study planning, case ascertainement, data collection, and interpretation of results.

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