

## Improvement of Anaemia in Patients with Primary Myelofibrosis by Low-Dose Thalidomide and Prednisone

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**Summary:** Background: A combination of low-dose thalidomide and corticosteroids is a treatment option for anaemic patients with primary myelofibrosis (PMF) who are not eligible for allogeneic hematopoietic stem cell transplantation. Methods: We describe the outcomes of 13 patients with PMF treated with thalidomide 50 mg daily in combination with prednisone 0.5 mg/kg daily. Treatment responses were seen in 10/13 (77%) patients with a median onset of therapeutic effect at 4 weeks (range 3–7 weeks) after treatment initiation. Improvements of anaemia and thrombocytopenia and reduction in splenomegaly were observed in 70%, 38%, and 30% of patients, respectively. Four of six initially transfusion-dependent patients became transfusion independent following the therapy. The median duration of treatment response was 18 months (range 3–35 months). The treatment was well tolerated, with only one patient discontinuing therapy due to toxicity. Responders included both patients with and without JAK2 V617F, and included patients with both newly diagnosed and longstanding PMF. Conclusions: Our retrospective analysis confirmed that the therapy with low-doses thalidomide with prednisone in patients with PMF achieves significant response rate in anaemia with low treatment toxicity.

**Keywords:** Primary myelofibrosis; Immunomodulatory agents; Thalidomide; Treatment

### Introduction

Primary myelofibrosis (PMF) is a clonal disorder of haematopoiesis from the group of Philadelphia-negative myeloproliferative diseases. The median survival of patients with PMF is approximately 3.5 to 10 years depending on the presence of risk factors such as higher age, anaemia, blasts in peripheral blood, and constitutional symptoms. The International Prognostic Scoring System (IPSS) and the Dynamic IPSS (DIPSS) are used to stratify patients into risk groups and to select appropriate treatment (1–4).

Younger patients (<65–70 years) with advanced disease should be considered for allogeneic haematopoietic stem cell transplantation (HSCT). HSCT remains the only curative treatment option for PMF (5–11). In contrast, conventional treatments are intended to influence the main symptoms of PMF resulting from splenomegaly and anaemia and to maintain or improve the quality of life but have no or minimal impact on the survival of patients. Anaemia is often the most disabling symptom of PMF, being present in about 20% of patients at diagnosis and in up to 50% of patients after 3.5 years of disease duration. Various drugs including danazol and erythropoietin have been proposed for the treatment of anaemia in the past but are usually ineffective for PMF-associated anaemia (12, 13).

Immunomodulatory drugs (IMiDs) such as thalidomide, lenalidomide, and pomalidomide have recently been shown to improve anaemia associated with PMF. These agents exhibit pleiotropic effects, reducing the levels of cytokines (transforming growth factor-beta, platelet-derived growth factor), inhibiting angiogenesis (vascular endothelial growth factor, basic fibroblastic growth factor), and triggering immunomodulation (increased production of T cells and NK cells). Other mechanisms of action that may be beneficial in patients with PMF include the induction of apoptosis by inhibition of nuclear kappa B (NF  $\kappa$ -B) and by activation of the caspase-8 death receptor pathway (14). Thalidomide and pomalidomide have also been found to be potent regulators of erythropoiesis, promoting the survival of erythrocyte progenitors and increasing the expression of foetal haemoglobin (HbF) (15).

Several groups have published reports on treatment of PMF using thalidomide at different doses ranging from 50 to 800 mg per day. Improvements of anaemia in these studies have been achieved in 16 to 70% of patients. However, up to 50% of patients receiving higher doses of thalidomide had to discontinue the treatment due to adverse events. In an effort to reduce the toxicity, we have explored a treatment regimen using low-dose thalidomide (50 mg daily) in combination with prednisone (0.5 mg/kg/day). The treat-

ment produced significant clinical benefit with markedly low toxicity (16–22).

## Patients and Methods

Thirteen patients (10 men, 3 women) were treated with low-dose thalidomide with prednisone in the period from 11/2005 to 7/2015 at our institution. All patients had a primary form of PMF. The median age was 66 years (range 52–81 years) and 5/13 (38%) patients were positive for JAK2V617 mutation. The median time from diagnosis to the start of thalidomide treatment was 22 months (range 1–156 months).

Symptoms resulting from progressive anaemia were the reason for treatment initiation in all patients. Six patients were transfusion-dependent prior to the onset of therapy. In all cases, patients received no previous therapy for PMF. Initial median values at the start of treatment were as follows: haemoglobin 8 g/dL (range 6–9 g/dL), platelet count  $182 \times 10^9/L$  (range  $15\text{--}650 \times 10^9/L$ ), leukocyte count  $5.93 \times 10^9/L$  (range  $2.64\text{--}13.6 \times 10^9/L$ ), and the median initial palpable spleen size was 10 cm below the costal margin (range 1–15 cm).

Treatment with thalidomide 50 mg daily and prednisone 0.5 mg/kg/day was administered for at least 3 months and was then discontinued if no therapeutic effect was seen. After 3 months of treatment, the dose of prednisone was gradually tapered to a maintenance dose of 5 to 10 mg/day in patients with ongoing treatment.

Therapeutic responses were evaluated according to the International Working Group – Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European Leukemia Net (ELN) criteria (23).

## Results

Therapeutic responses were achieved in 10/13 (77%) patients. According to the IWG-MRT criteria, five patients achieved partial remission (PR) and further five patients clinical improvement (CI). Peripheral blood parameters of patients after 3 months of treatment were as follows: median haemoglobin 9.9 g/dL (range 8–10.6 g/dL), median platelet count  $251 \times 10^9/L$  (range  $87\text{--}1020 \times 10^9/L$ ), median leukocyte count  $6.31 \times 10^9/L$  (range  $4.01\text{--}18.67 \times 10^9/L$ ). In 5/13 (38%) patients, there was an increase in platelet count  $\geq 50\%$  of the initial values and 4/13 patients (30%) had a reduction in spleen size of  $\geq 50\%$  compared to the initial size. Transfusion dependence resolved in 4/6 initially transfusion-dependent patients.

In accordance with published data, the treatment responses occurred rapidly, after median treatment duration of only four weeks (range 3–7 weeks). The median duration of response was 15 months (range 3–35 months). Responders included both patients with and without JAK2 V617F, and included patients with both newly diagnosed and long-standing PMF.

Summary of patient characteristics and treatment responses is shown in Table 1.

**Tab. 1:** Characteristics for 13 patients with PMF treated by low-dose thalidomide with prednisone.

Sex	Age	DIPSS	JAK2 status	Time from diagnosis (months)	Transfusions requirement	Time to response (weeks)	IWG-MRT response	Response duration (months)	Adverse events	Reasons of withdrawal therapy
F	52	High	neg	156	no	5	PR	35	–	HSCT
F	76	High	pos	22	yes	4	PR	34	neuropathy	death (CV reason)
M	66	High	neg	3	yes	6	CI	25	–	lack of effect
M	55	High	neg	30	yes	4	CI	3	neutropenia gr. II, pneumonia	adverse events
F	57	High	neg	146	no	3	CI	5	constipation	HSCT
M	69	High	neg	9	yes	–	SD	–	–	
M	64	Int-2	neg	54	no	–	SD	–	–	
M	79	High	neg	1	no	5	CI	14	–	lack of effect
M	72	High	pos	1	no	3	PR	10	–	lack of effect
M	81	High	pos	3	yes	3	PR	12	neuropathy, tiredness	continuing
M	68	High	pos	6	yes	–	SD	–	–	
M	57	Int-1	pos	108	no	6	PR	20	tiredness	continuing
M	59	Int-1	neg	39	no	3	CI	20	–	continuing

Haematological toxicity led to treatment discontinuation in a single patient who developed grade 2 neutropenia with infection, and even in that patient anaemia had improved. No thrombotic complications were seen. Antithrombotic prevention was not routinely applied but was administered in one elderly patient with cardiovascular risk factors. Non-haematological toxicity was observed in four patients, including two cases of grade 1–2 neuropathy with worsening of chronic constipation in one of the two patients, and fatigue in two other patients. The reason for treatment discontinuation was allogeneic unrelated transplantation in two patients. In three cases, treatment was discontinued after 9, 14, and 25 months, respectively, because of the loss of therapeutic effect. One patient died of a cardiovascular cause unrelated to PMF (end stage of heart failure).

## Discussion

Several series and case studies have been published on the possible use of IMiDs therapy in patients with PMF. The first experience was published in 2001 by Barosi et al. (16), reporting on a group of 21 patients treated with an initial thalidomide dose of 100 mg daily and gradually increased to 400 mg daily. Therapeutic responses were achieved in 13 patients (62%), including improvement of anaemia, thrombocytopenia, and reduction of spleen size in 43%, 67%, and 31% of patients, respectively. However, 91% of patients discontinued the treatment within 6 months due to toxicity or lack of treatment response.

Elliott et al. (17) used thalidomide in a dose of 200–400 mg daily in a series of 15 patients with similar results, achieving improvements of anaemia and thrombocytopenia, and reduction in spleen size in 20%, 60%, and 25% of patients, respectively. Again, premature treatment discontinuation was required in 80% of patients.

In the largest study ( $n = 63$ ) to-date which was published in 2004 by Marchetti et al. (18), the doses of thalidomide ranged from 50 to 400 mg daily. In 11 patients (26%), the treatment had beneficial effect on anaemia, including eight patients who became transfusion independent. Improvements in thrombocytopenia occurred in 22% of patients and a reduction in spleen size in 19% of patients. The median tolerated dose of thalidomide in this study was 100 mg daily, and only 13% of patients tolerated a higher dose. Despite this relatively low dose of thalidomide, a high proportion of patients (49%) discontinued the therapy due to toxicity during the first six months after its initiation.

The cohort published by Thomas et al. (19) included 44 patients who received thalidomide in a dose of 100–800 mg daily. Treatment responses were achieved in 41% of patients, with 20% patients experiencing improvement of anaemia and 21% of thrombocytopenia, and

31% a reduction in spleen size. These studies have shown that although intermediate and high doses of thalidomide may accomplish some clinical objectives, they are generally poorly tolerated. In these studies, haematological

toxicity prompted treatment discontinuation in 25–91% of patients. The obvious way forward was to explore the effect of low-dose thalidomide and look for possible combination regimens.

In 2003, Mesa et al. (20) published a paper describing the effect of thalidomide 50 mg daily and 30 mg of prednisone given daily over three months in a group of 21 patients. An increase in haemoglobin was observed in 70% of patients and 40% of patients became transfusion independent. Improvements in platelet counts occurred in 75% of patients but only 19% of patients had a reduction in spleen size. The response usually persisted even after gradual discontinuation of corticosteroids. In this study, only 5% of patients discontinued treatment due to adverse events.

Similar results were obtained in a 2008 study by Weinkove et al. (21), in which 15 patients were treated with thalidomide 50 mg daily and 13 of them also received concomitant prednisone 30–60 mg daily. The responses evaluated according to the European Network for Myelofibrosis (EUMNET) criteria (24) were as follows: 27% of patients achieved a major response, 7% a moderate response, and 33% a minor response, while 27% had no treatment response. Only three patients discontinued treatment because of toxicity. The median time to best response was 7.5 weeks (range 2–15 weeks).

Another recent work using a combination of thalidomide with corticosteroids was published in 2011 by Thapaliya et al. (25). Their cohort included 50 patients with PMF divided into three arms. All patients received 50 mg of thalidomide with low-dose corticosteroids. The first subgroup received no additional treatment, cyclophosphamide 25 mg daily was added to the second group, and etanercept 25 mg twice weekly was added in the third subgroup. Therapeutic responses were achieved in 28% of patients and the response rates were similar in all three study arms, suggesting no benefit of cyclophosphamide or etanercept. Improvement of anaemia was the most commonly observed type of response, occurring in 22% of patients, while 8% of patients had a reduction in spleen size. The median duration of response reached 8.5 months. A possible synergistic action of corticosteroids may potentiate the cytotoxic effect of IMiDs, reducing the levels of some interleukins and possibly decreasing the toxicity of IMiDs treatment.

Several studies have been published on the treatment of PMF with IMiDs other than thalidomide (lenalidomide, pomalidomide) (26–29). In studies, lenalidomide has been associated with the lower response rates and higher toxicity (myelosuppression). The response rates achieved with pomalidomide are similar to those of thalidomide, ranging from 19 to 30%. The principal disadvantage of pomalidomide is the high cost of treatment and the risk of myelosuppression which can occur in as many as 25–88% of patients. In 2010, the first results were published of a multicentre study using pomalidomide 2 mg/day plus placebo, pomalidomide 2 mg/day plus prednisone, pomalidomide

0.5 mg/day plus prednisone and prednisone plus placebo (29). Response rates for clinical improvement in anaemia were 23%, 16%, 36% and 19% in the four arms. The results of this trial demonstrated once again that the best effect in PMF can be expected with the combination of low-dose IMiDs with prednisone.

## Conclusion

Our retrospective analysis confirmed that therapy with low-doses thalidomide with prednisone in patients with PMF achieves significant response rate in anaemia with low treatment toxicity. A clinically meaningful increase in haemoglobin levels was observed in 10/13 (77%) patients. The onset of response was very rapid and the median duration of response was 15 months. Responders included both patients with and without JAK2 V617F. The use of low-dose IMiDs in combination with corticosteroids thus represents a valid therapeutic option for patients with PMF who are not eligible for allogeneic HSCT.

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