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REVIEW

Thalidomide and lenalidomide in primary myelofibrosis

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ABSTRACT

Primary myelofibrosis is a clonal haematopoietic stem cell disease, characterised by marrow stromal fibrosis, extramedullary haematopoiesis, splenomegaly, hepatomegaly and progressive cytopenia. Therapeutic options once cytopenia has developed are limited to supportive care, such as erythrocyte transfusions and growth factors. The aetiology has become more clear, especially since JAK-2 mutations were found, resulting in increased production of cytokines. The immune-modulating drug thalidomide and its derivative lenalidomide have shown to be effective in reducing cytopenia, most probably by inhibiting the cytokine responses. In some patients the bone marrow fibrosis disappears. We describe the experience with these drugs in a cohort of 14 patients for thalidomide and seven for lenalidomide (in six patients lenalidomide was given after thalidomide and one patient received lenalidomide upfront). Thalidomide gave clinical improvement in 6/14 patients, but its use was limited mainly due to toxicity, especially the development of neuropathy. The drug could be given for a median period of 15.5 months in responding patients. Lenalidomide was effective in 4/7 of the patients, in some patients with no response on thalidomide. Due to the more favourable toxicity profile, the median duration of therapy was 19 months, with 3/4 patients on therapy longer than 19 months. These data are discussed in view of the clinical studies published. We conclude that lenalidomide is preferred in myelofibrosis, given a higher response rate and more favourable toxicity profile. If no response the addition of prednisone can be considered. In some patients it can normalise haemoglobin and make them transfusion independent.

KEYWORDS

Myeloproliferative neoplasm, myelofibrosis, thalidomide, lenalidomide

INTRODUCTION

Primary myelofibrosis (PMF), also known as idiopathic fibrosis or myelofibrosis with myeloid metaplasia, is a clonal haematopoietic stem cell disorder characterised by intense bone marrow stromal reaction including collagen fibrosis, osteosclerosis and neoangiogenesis. Typical clinical features include extramedullary haematopoiesis with marked splenomegaly, hepatomegaly and progressive cytopenias in advanced stages.[1,2]

The median survival is estimated to be five to seven years, but exceeds ten years in younger patients with good prognostic features.[3,4] Older age, anaemia, leukocytosis, constitutional symptoms and peripheral blast are the major risk factors.[1] Current therapy for patients with PMF such as hydroxyurea, interferon or corticosteroids has not shown to improve the overall survival and as such, these drugs serve palliative purposes. The only possibility to cure the disease is a haematopoietic stem cell transplantation, but this is limited to younger patients and even then associated with a relatively high morbidity and mortality.[6]

Apart from primary myelofibrosis, fibrosis may also develop in later stages of other myeloproliferative neoplasms such as polycythemia vera (PV) and essential thrombocytosis (ET). These patients, who initially show high blood counts and need cytoreductive therapy, eventually develop cytopenia, bone marrow fibrosis, splenomegaly and become transfusion dependent, often referred to as 'spent phase'.

The pathogenesis of PMF has not been fully elucidated, but there is increasing evidence that various cytokines such as transforming growth factor (TGF), platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF) and tumour necrosis factor (TNF) contribute to the changes in the microenvironment of the bone marrow that lead to collagen fibrosis, osteosclerosis and angiogenesis.[1,4,7] The JAK-2 mutation, found in about 50% of the PMF and ET patients and almost all PV patients, results in constitutively activated JAK-2 signalling and enhanced cytokine production. Due to JAK-2 mutations in the pseudokinase domain of the gene, the kinase inhibitory part of the gene is lost, resulting in enhanced signalling and increased production of cytokines. Interestingly, patients diagnosed with the JAK-2 mutation seem to be characterised by a more symptomatic myeloproliferative disorder. However, the prognostic relevance of the JAK-2 mutation has not been elucidated yet.[8]

Thalidomide, showing potent antiangiogenic and cytokine-modulating activity, has proved to be effective in patients with myelofibrosis.[6,9,11-15] The thalidomide analogue, lenalidomide, has also been studied for its effect in myelofibrosis.[7] *In vitro* cell line models show a much more potent activity for lenalidomide than thalidomide.[16]

The experience with these drugs for treatment of myelofibrosis in the Netherlands is limited. Nevertheless, we observed clinical effects in some patients. In this report we summarise the experience with thalidomide and the switch of a number of patients to lenalidomide in a university (UMC St Radboud, Nijmegen) and a general hospital (CWZ Nijmegen). Based on the literature and our own data, we give recommendations on the use of thalidomide and lenalidomide in myelofibrosis.

PATIENTS AND METHODS

We reviewed clinical data from all patients in our database who have been treated with thalidomide and/or lenalidomide for chronic idiopathic myelofibrosis, either primary or secondary after PV or ET. The first patient started treatment in February 2004, the follow-up was until evaluation in February 2009. For thalidomide, patients of the UMC Radboud and the Canisius Wilhelmina Hospital, both located in Nijmegen, were included. The indication for treatment was myelofibrosis and cytopenia, in most cases anaemia. The initial treatment in 14/15 patients was thalidomide; based on toxicity or no response 6/14 switched to lenalidomide, one patient started upfront on lenalidomide. In some patients prednisone was also given next to thalidomide or lenalidomide. Lenalidomide for compassionate use was provided by Celgene, the Netherlands.

We defined a major response as a normalisation of blood counts and for patients who were transfusion dependent to become transfusion independent. If there was an increase in blood counts or a decrease in spleen size but no normalisation we designated the response as limited. In individual patients bone marrow biopsy was done before and after treatment to show changes in marrow fibrosis.

RESULTS

Thalidomide treatment

Fourteen patients were treated with thalidomide at a dose of 50 to 100 mg for a median of eight months, varying between one and 37 months (*table 1*). Of these 14 patients

Table 1. *Patient data before and after treatment with thalidomide*

UPN	Sex	Jak2	TD	Dose (mg)	Duration of thalidomide therapy (months)	Before-after				
						Hb (mmol	WBC (10^9/l	PLT (10^9/l	Spleen (cm)	Response
1	M	Neg	No	50-100	11	5.4-4.9	6.1-2,8	35-92	Stable	Limited
2	F	Neg	TD	100	3	6.7-TD	12.8-2.8	463-373	No change	No
3	M	Pos	No	100	4	7.4-6.7	11.7-12.3	515-815	No change	No
4	M	Nd	No	50	7	7.4-6.2	6.0-3.8	36-63	Stable	No
5	M	Nd	TD	100	20	3.8-9.5	9.2-9.5	42-226	Decreased to normal	Major
6	M	Pos	No	50	15	5.4-7.4	9.6-8.2	62-113	NA	Limited
7	F	Pos	TD	50	3,5	4.4-5.2	19.8-5.8	958-763	NA	No
8	M	Pos	No	50	1	6.2-5.5	19.0-9.2	177 – 299	Decrease	Limited
9	M	Nd	No	50	16	6.4-TD	35.8-3.8	423-184	NA	No
10	M	Pos	No	100-50	37	5.7-6.5	7.0-4.4	86-227	Splenectomy	Limited
11	F	Neg	No	50	4	5.7-4.7	7.5-2.5	60-45	NA	No
12	F	Nd	TD	100	16	5.2-5.8	8.4-6.6	380-570	Stable	Limited
13	M	Nd	TD	50-100	8	4.1-4.0	18.7-6.9	491-563	NA	No
14	M	Nd	TD	100-150	8	5.0-4.8	2.0-1.6	97-89	Increase	No

UPN = unique personal number; Hb = haemoglobin; WBC = white blood count; PLT = platelets; TD = transfusion dependent; NA = not available; NE = not evaluable; Nd = not determined.

the JAK-2 mutation was determined in eight: five were positive and three were negative. The major reason to start treatment was anaemia. In case of anaemia the only treatment option is supportive care, including blood transfusions and erythropoietin. Two patients are still on thalidomide after 10 and 20 months, respectively. In 12 patients the thalidomide treatment was stopped. The reason to stop treatment was due to side effects such as constipation, tiredness and concentration weakness in three patients at 1, 7 and 15 months, neuropathy in four patients after 1, 4, 10 and 37 months and neuropathy as well as therapy resistance in one patient at 20 months. In three patients thalidomide was stopped due to lack of effect after 3, 4 and 4 months, respectively. One patient received an allotransplant after eight months of thalidomide treatment, with no significant improvement at that time. One patient (UPN 7), already in a poor clinical condition at the start of treatment, died after a hip fracture. Five out of the 14 patients who started on thalidomide showed an increase in haemoglobulin level of >1 mmol/l. Three of six patients who were dependent on erythrocyte transfusions at the start of thalidomide became transfusion independent, also designated as a major response. The median treatment duration was 15.5 months in responding patients (between 1 and 37 months). One out of 14 patients showed a normalisation of the haemoglobin, increasing from 3.8 mmol/l to normal levels.

In 6/14 patients a thrombocytosis was present at the start of thalidomide, in seven patients a low platelet count. Among the seven patients with a platelet count below 100 x 10^9/l, five showed an increase, from a median of 42 to a median of 113. The response in spleen size was not evaluated in five patients. Only two out of nine patients showed a decrease in spleen size. The spleen size stabilised in three patients under thalidomide therapy. Three out of the 14 patients showed a response in both haemoglobin and platelets; in one of these the spleen size normalised (one was splenectomised, the third showed a stable spleen size). In two of these three responding patients the improvement in myelofibrosis was confirmed by a decrease in fibrosis in the marrow biopsy. In one of these three responding patients thalidomide was given in combination with prednisone.

Lenalidomide treatment

Seven patients received lenalidomide, 6/7 had been treated before with thalidomide (all except patient 15, *table 2*). The starting dose was 10 mg in five patients, 15 mg in one patient and 25 mg in another patient. In one patient lenalidomide 10 mg had to be stopped after three weeks due to pancytopenia, in a second patient after three months due to diarrhoea, despite lowering the dose. Patient 8 could not be evaluated, because lenalidomide therapy was only given for six days. Patient 3 stopped after six months of treatment because he underwent a haematopoietic stem cell transplantation (SCT); at the time of SCT the platelets had already normalised and the spleen was reduced in size. A response was also observed in three other patients, all of whom have been on lenalidomide treatment for more than 19 months.

Among the five patients with symptomatic anaemia, three patients responded. A reduction in spleen size occurred in 3/4 patients. One patient had a platelet count below 100 x 10^9/l, which normalised after lenalidomide treatment. Patient 1 was red blood cell transfusion dependent during lenalidomide therapy, but he became transfusion independent when he received a combination of lenalidomide and prednisone (25 mg). Interestingly, patient 3 did not respond to thalidomide, but he did respond to lenalidomide. In two patients thalidomide neuropathy was the reason to switch to lenalidomide. To summarise, lenalidomide had to be stopped due to side effects in 2/7 patients, was effective in 4/7 patients, in one patient only after the combination with prednisone.

DISCUSSION

Our results on thalidomide treatment for myelofibrosis show improvement in haematopoiesis in 6/14 patients, a

Table 2. *Patient data before and after treatment with lenalidomide*

Patient	Sex	Dose (mg)	Duration of lenalidomide therapy (months)	Before-after				
				Hb (mmol/l)	WBC (10^9/L)	PLT (10^9/L)	Spleen (cm)	Response
1	M	10-15	>48	5.4-4.4	5.5-1.4	35-152	Decrease	Major
2	F	10	3	4.6-TD	3.6-1.8	222-455	No change	No
3	M	10	6	7.0-6.6	11.7-5.2	702-299	Decrease	Major
8	M	15	6 days	6.6-7.3	5.5-39.4	57-84	No change	NE
9	M	10	3 weeks	4.4-4.2	3.9-1.4	246-44	NA	NE
10	M	25	>19	7.2-8.0	5.8-4.8	216-194	NA	Major
15	M	10	>19	6.3-8.2	5.6-6.6	430-381	Decreased to normal	Major

Hb = haemoglobin; WBC = white blood count; PLT = platelets; TD = transfusion dependent; NA = not available; NE = not evaluable.

raise in haemoglobin, including transfusion independency, reduction in thrombocytopenia as well as reduction in spleen size and bone marrow fibrosis. The major drawback of thalidomide treatment is the toxicity, constipation, weakness but especially neurotoxicity. Due to this toxicity the mean duration of therapy was only 11 months.

In the literature we found nine studies and one case report evaluating the effect of thalidomide (with or without prednisone) in patients with myelofibrosis (*table 3*).

In the largest trial, by Marchetti *et al.*,[17] 63 patients were enrolled and patients who received more than one month of treatment were evaluated. In this trial anaemia ameliorated in 11 out of 49 (22%) patients, red blood cell transfusions could be stopped in seven out of 18 (39%) transfusion-dependent patients and nine of those transfusion-dependent patients had a 50% reduction of transfusion requirement. Thrombocytopenia improved in 20 patients (41%) and a 50% reduction in spleen size occurred in 19% of the patients. However, 51% of the patients had discontinued thalidomide after six months of treatment. Significant side effects such as paresthesias, tremors, altered hearing, seizures, depression or extrapyramidal symptoms occurred in 38 patients (60%) and four patients had a toxicity grade 3 or more. The median of maximum tolerated thalidomide dose was 100 mg daily; only eight patients (13%) could tolerate higher doses of thalidomide daily (300 mg). The main reasons for discontinuing treatment were pneumonia, neutropenia, rash, leukaemic transformation, neuropathy and venous thromboembolism.

In the study by Thomas *et al.*,[12] 44 patients were treated with thalidomide with an average tolerated dose of 400 mg for the median duration of three months. Forty-one patients were evaluable, because three patients discontinued treatment within 15 days for a grade 3 rash or for rapidly progressive disease with splenic infarction. Also in this study, a significant number of patients showed improvement of anaemia (20%), thrombocytopenia (21%) and splenomegaly (31%). After thalidomide treatment, five out of 24 patients became transfusion independent. Dose-related toxicities included fatigue (50%), constipation (48%), rash or pruritis (37%), sedation (35%), peripheral oedema (29%), tremors (23%), peripheral neuropathy (22%), and orthostasis. Similar findings have been described in three other studies with lower numbers of patients,[6,9,18] all evaluating the effect of thalidomide monotherapy in patients with myelofibrosis.

Abgrall *et al.*[13] reported in a prospective placebo-controlled trial that thalidomide (400 mg/day) compared with placebo did not demonstrate significant efficacy and was associated with considerable side effects. After two months, 40% of the thalidomide group (26 patients) had discontinued study participation and after four months 56% had discontinued treatment. In the placebo group (26 patients), these figures were 20 and 32%, respectively. Furthermore, only ten patients in the thalidomide group completed the six months of treatment. In most cases, thalidomide therapy was discontinued prematurely due to intolerance related to the initial high treatment dose.

In summary these studies suggest that thalidomide monotherapy in moderate and high doses (200 to 800 mg) produces a response rate of 20 to 50%. However, treatment is poorly tolerated with high dropout rates. Interestingly, three studies[8,11,15] and one case report[14] showed that the combination of low-dose thalidomide (50 mg) and prednisone was better tolerated and more efficacious than thalidomide alone. In the Mesa trial,[8] 21 patients participated and 20/21 patients completed the first three months of therapy. An improvement of anaemia was observed in 13/21 (62%). Transfusions could be stopped in four out of ten transfusion-dependent patients (40%) and in seven patients the need for transfusions decreased. Thrombocytopenia improved in 6/8 patients and 4/21 patients showed a reduction

Table 3. *Thalidomide studies*

Recent studies	No. of patients	Dose (mg)	Pred.	Responders / evaluable patients				TID / TD after therapy
				Hb	PLT	WBC	Spleen	
Weinkove *et al.*,[15] 2008	15	50	+	5/7	0	0	4/13	2/7
Berrebi *et al.*,[14] 2008	1	50	+	1/1	1/1	1/1	1/1	1/1
Abgrall *et al.*,[13] 2006	52	400	-	NS	NS	NS	S	NR
Thomas *et al.*,[12] 2006	44	100-800	-	7/35	5/24	NR	9/29	5/24
Benatatos *et al.*,[11] 2005	5	50	+	5/5	2/2	4/5	1/5	3/3
Marchetti *et al.*,[17] 2004	63	50-400	-	11/49	20/49	0	20/47	7/18
Mesa *et al.*,[8] 2003	21	50	+	13/20	6/8	NR	4/20	4/10
Piccaluga *et al.*,[6] 2002	12	100-600	-	3/4	2/2	2/4	7/11	2/4
Elliott *et al.*,[18] 2002	15	50-400	-	3/13	12/13	NR	3/12	1/5
Barosi *et al.*,[9] 2001	21	100-400	-	3/13	2/3	4/5	4/13	1/7

Hb = haemoglobin; WBC = white blood count; PLT = platelets; NR = not reported; NS = not significant with placebo; S = significant with placebo; TID = transfusion independent (Hb); TD = transfusion dependent (Hb); Pred. = prednisone.

of splenomegaly. Especially fatigue, constipation, depression, bradycardia and orthostatic symptoms were significantly reduced by this low-dose thalidomide-prednisone regimen. In agreement with this Mesa trial, the case report[14] and the other two studies[11,15] showed similar responses to the combination therapy. To study the effect of low-dose thalidomide after the discontinuation with prednisone, 12 patients who responded were enrolled in the second phase of the Mesa trial (thalidomide monotherapy 50 mg/day for three months). After discontinuation of prednisone, clinical responses were maintained in eight out of 13 (62%) in terms of anaemia, four out of six (66%) in terms of thrombocytopenia and two out of four (50%) patients in terms of splenomegaly.[8]

We treated seven patients with lenalidomide, six after previous thalidomide treatment. Our results show a response in 4/7 patients, interestingly also in a patient not responding to thalidomide, but more importantly lenalidomide could be continued for much longer. The median time was 19 months instead of 15.5 months for thalidomide. The toxicity in lenalidomide was diarrhoea in one patient and cytopenia, as is known for this drug. Tefferi *et al.*[7] presented two phase II studies (Mayo Clinic Rochester and M.D. Anderson Houston) involving single-agent lenalidomide at a dose of 10 mg for three or four months (*table 4*). Overall, anaemia ameliorated in 10/68 patients (22%). After the lenalidomide treatment, four patients (12%) became transfusion independent. In eight (17%) of 46 patients, with a baseline haemoglobin level below 100 g/l, the haemoglobin level normalised. Furthermore, thrombocytopenia improved in six patients (50%) and 14 patients (33%) showed a reduction in their spleen size. The most common adverse events in both studies were neutropenia, thrombocytopenia, fatigue and pruritus. Of the eight patients with the major anaemia response, all patients received a maximum of six months therapy. In the Mayo Clinic study, two patients were still in remission two and five months after treatment discontinuation. In the M. D. Anderson clinical trial, three patients have not relapsed after six to 36 weeks. However, the other three patients relapsed off therapy. In our patients we continued lenalidomide as long as a response was observed. Quintas-Cardama[20] reported 40 patients treated with lenalidomide 10 mg for 21 days in a 28-day cycle and prednisone 30 mg in the first cycle, than 15 mg for two more cycles. They report a 30% response for anaemia and 42% for splenomegaly. These authors also report a reduction in JAK-2 in all eight JAK-2 patients, with 4/8 more than 50% reduction. In this study lenalidomide was continued indefinitely, as in our patients, with a median response duration of 18 months (3.5 to >24 months). The major side effects were haematological, neutropenia (58%), anaemia (42%) and thrombocytopenia (13%), for which reason they advise close monitoring of blood counts. Tefferi *et al.*[21] in a recent trial reported that another immune-modulating drug, pomalidomide, showed increased activity in myelofibrosis compared with prednisone, in a randomised trial. The lowest dose of pomalidomide plus prednisone seemed most effective, showing a 36% response of the anaemia. Haematological toxicity was infrequent; perhaps pomalidomide has a superior toxicity profile compared with lenalidomide but it is not available, even for compassionate use.

In conclusion, thalidomide is effective in about 30% of patients with primary myelofibrosis, especially if given at a low dose of 50 mg and in combination with prednisone. However, the toxicity of the drug limits the duration of therapy and especially the neuropathy will not resolve once established and may disable patients for the rest of their life. Lenalidomide at a dose of 10 mg in combination of prednisone, as used in the trials of Tefferi *et al.* and Quintas-Cardama *et al.* shows similar response rates, but less toxicity, although haematological toxicity may be a concern as reported by Quintas-Cardama *et al.* Based on the literature data and our own limited experience we suggest that in patients with myelofibrosis and cytopenia it is worthwhile to consider treatment with lenalidomide. Other treatment options are limited; perhaps JAK-2 inhibitors may become an alternative in the near future. If lenalidomide treatment is considered it seems rational to start at a low dose (5 to 10 mg), given the cytopenia as side effect, and preferably in combination with prednisone. If a response is seen, prednisone can be stopped in view of the potential side effects of long-term prednisone treatment.

Table 4. *Recent lenalidomide studies*

Recent studies	No. of patients	Dose (mg)	Responders / evaluable patients				TID / TD after therapy
			Hb	PLT	WBC	Spleen	
Tefferi *et al.*,[7] 2006	68	10	10/46	6/12	NR	14/42	4/34
Quintas-Cardama *et al.*,[20] 2009	40	10	7/23	0/6	0/2	10/24	NR

Hb = haemoglobin; WBC = white blood count; PLT = platelets; NR = not reported; TID = transfusion independent (Hb); TD = transfusion dependent (Hb).

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