Pomalidomide Is Active in the Treatment of Anemia Associated With Myelofibrosis

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ABSTRACT

Purpose

Thalidomide and lenalidomide can alleviate anemia in myelofibrosis. However, their value is undermined by their respective potential to cause peripheral neuropathy and myelosuppression. We therefore evaluated the safety and therapeutic activity of another immunomodulatory drug, pomalidomide.

Methods

In a phase II randomized, multicenter, double-blind, adaptive design study, four treatment arms were evaluated: pomalidomide (2 mg/d) plus placebo, pomalidomide (2 mg/d) plus prednisone, pomalidomide (0.5 mg/d) plus prednisone, and prednisone plus placebo. Pomalidomide was administered for up to 12 28-day treatment cycles. Prednisone (30 mg/d) was given in a tapering dose schedule during the first three cycles. Response was assessed by International Working Group criteria.

Results

Eighty-four patients with myelofibrosis-associated anemia were randomly assigned to the aforementioned treatment arms: 22, 19, 22, and 21, respectively. Response in anemia was documented in 20 patients, including 15 who became transfusion independent. Response rates in the four treatment arms were 23% (95% CI, 5% to 41%), 16% (95% CI, 0% to 33%), 36% (95% CI, 16% to 56%), and 19% (95% CI, 2% to 36%). The corresponding figures for patients receiving ≥ 3 cycles of treatment ($n = 62$) were 38%, 23%, 40%, and 25%. Response to pomalidomide with or without prednisone was durable (range, 3.2 to 16.9+ months) and significantly better in the absence of leukocytosis (37% v 8%; $P = .01$); *JAK2V617F* or cytogenetic status did not affect response. Grade ≥ 3 toxicities were infrequent and included (in each treatment arm) neutropenia (9%; 16%; 5%; 5%), thrombocytopenia (14%; 16%; 9%; 5%), and thrombosis (9%; 5%; 0%; 0%).

Conclusion

Pomalidomide therapy at 0.5 or 2 mg/d with or without an abbreviated course of prednisone is well tolerated in patients with myelofibrosis and active in the treatment of anemia.

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INTRODUCTION

Lenalidomide and pomalidomide are second generation IMiDs immunomodulatory drugs that are created by chemical modification of thalidomide with the intent to reduce toxicity and enhance anticancer and immunological activity.¹ In the United States, thalidomide is approved by the US Food and Drug Administration for use in acute erythema nodosum leprosum² and, in combination with dexamethasone, in newly diagnosed multiple myeloma.³ Lenalidomide is approved for use in low/intermediate-1 risk myelodysplastic syndrome

associated with transfusion-dependent anemia and a deletion 5q cytogenetic abnormality⁴ and, in combination with dexamethasone, in relapsed multiple myeloma.^{5,6} Pomalidomide is currently not US Food and Drug Administration–approved but is known to have therapeutic activity in multiple myeloma.^{7,8} All three drugs display antiangiogenic, anti-tumor necrosis factor (TNF) $-\alpha$, and T-cell costimulatory activity.¹ Lenalidomide and pomalidomide are more potent than thalidomide in this regard, and were also recently shown to inhibit T-regulatory cell proliferation and suppressor function.⁹ The composite effect of these immune

and cytokine modulatory properties is believed to underlie the mechanism of action for these drugs and the rationale for investigating their therapeutic value in a variety of other conditions including myelofibrosis.

The abnormal cytokine milieu in myelofibrosis is believed to contribute to its cardinal disease features including anemia, constitutional symptoms, cachexia, and extramedullary hematopoiesis.¹⁰ Therefore, based on their aforementioned anticytokine and antiangiogenic properties, it was reasonable to explore the therapeutic activity of immunomodulatory compounds in myelofibrosis. Single-agent thalidomide, at dose levels of ≥ 100 mg/d, is poorly tolerated in patients with myelofibrosis and long-term use causes peripheral neuropathy.¹¹⁻¹⁶ Furthermore, if one were to apply the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria,¹⁷ the anemia response rates seen with single-agent thalidomide therapy might be as low as 10% and unlikely to exceed 20%. The same can be said regarding the antianemia effect of lenalidomide in myelofibrosis, in the absence of a deletion 5q cytogenetic abnormality.^{18,19} Lenalidomide use in myelofibrosis is further limited by its potential to cause severe myelosuppression.¹⁸ Therefore, we studied pomalidomide, hoping for better toxicity profile and improved erythropoietic activity in myelofibrosis.

METHODS

Study Design

The current study was a phase II, prospective, randomized, multicenter, double-blind, active-control, parallel-group study to determine the safety of and to select a treatment regimen of pomalidomide either as single-agent or in combination with prednisone to study further in patients with myelofibrosis. Study patients were randomly assigned to four treatment arms: pomalidomide (2 mg/d) and placebo, pomalidomide (2 mg/d) and prednisone, pomalidomide (0.5 mg/d) and prednisone, and prednisone and placebo (active control). The primary objective of the statistical analysis was to select, for further study, one of the pomalidomide regimens. An adaptive selection design using a Bayesian β prior/binomial likelihood model with regular monitoring was used to potentially eliminate early those regimens that were unlikely to be effective and, ultimately, to select the most effective pomalidomide regimen.²⁰ A maximum of 80 subjects were expected to enroll in the current study, 20 per treatment arm, barring early stopping.

Protocol Therapy

Pomalidomide 2 or 0.5 mg/d (or placebo) was administered for up to 12 28-day treatment cycles with the option to continue treatment beyond that point in the presence of treatment response and absence of unacceptable toxicity. These doses of pomalidomide were selected based on previous observations from Schey et al⁷ who established the maximum tolerated dose (MTD) of pomalidomide in refractory/relapsed multiple myeloma at 2 mg/d. Prednisone (or placebo) was given in combination with pomalidomide (or placebo) in a tapering dose schedule during the first three cycles only: starting dose of 30 mg/d during the first cycle, 15 mg/d the second cycle, and 15 mg every other day the third cycle. Pomalidomide (or placebo) dose reduction by 50% was allowed in case of adverse events that warranted such an action. Dose escalation was not allowed. During or within 28 days of protocol therapy, use of growth factors or any other treatment for myelofibrosis was not allowed. The usual strict guidelines for contraception (and avoidance of breast feeding) while on immunomodulatory compound therapy were followed for both male and female patients.²¹

Patients

Multiple centers (n = 10) from the United States and Europe participated in this study after institutional review board approval. Eligibility criteria included a diagnosis of primary, postpolycythemia vera, or postessential throm-

bocythemia myelofibrosis, according to the WHO criteria.²² Additional requirements included a hemoglobin level lower than 10 g/dL or RBC transfusion dependence (the latter required documentation of transfusion with ≥ 2 units of packed RBCs, for a hemoglobin level of < 8.5 g/dL, during the 28 days before protocol entry),¹⁷ an absolute neutrophil count $\geq 1 \times 10^9/L$, a platelet count $\geq 50 \times 10^9/L$, a creatinine level ≤ 2 mg/dL, direct bilirubin level lower than 2 times the upper limit of normal, and blood transaminase level ≤ 3 times the upper limit of normal unless attributed to extramedullary hematopoiesis. Patients with prior exposure to pomalidomide, lenalidomide, or thalidomide were excluded. Also excluded were patients with history of deep vein thrombosis or pulmonary embolism within 1 year of study entry. Response was assessed by the IWG-MRT criteria.¹⁷ Toxicity was assessed by the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.²³

RESULTS

A total of 104 patients were screened and 84 fulfilled protocol eligibility criteria and were randomly assigned to one of four treatment arms: pomalidomide (2 mg/d) plus placebo (n = 22), pomalidomide (2 mg/d) plus prednisone (n = 19), pomalidomide (0.5 mg/d) plus prednisone (n = 22), and prednisone plus placebo (n = 21). The four treatment arms were well balanced in terms of baseline patient characteristics including disease duration and prior therapy (Table 1).

Response Rates and Duration

After a median treatment period of 4.6 months (range, 0.3 to 18) for all patients and 10 months (range, 6 to 17.7) for patients still on-study, a total of 20 responses were documented and all signified improvement in anemia and none represented reduction in spleen size. Responders included 15 patients who became RBC transfusion independent. Response rates among the four treatment arms were: 23% (pomalidomide 2 mg/d plus placebo; 95% CI, 5% to 41%), 16% (pomalidomide 2 mg/d plus prednisone; 95% CI, 0% to 33%), 36% (pomalidomide 0.5 mg/d plus prednisone; 95% CI, 16% to 56%), and 19% (prednisone plus placebo; 95% CI, 2% to 36%). The corresponding figures for patients receiving at least three cycles of treatment (n = 62) were 38%, 23%, 40%, and 25%. Median response duration was 6.5 months (range, 2.3 to 16.9). Median time to response in the four arms was 2 months (range, 1 to 7), 3 months (range, 1 to 3), 2 months (range, 1 to 7), and 3 months (range, 1 to 4). To date, three of the four prednisone responders have relapsed after response duration of 2.3 to 5.5 months (Table 2). The median response duration in the 16 patients who responded to pomalidomide with or without prednisone was 7.8 months (range, 3.2 to 16.9) and two have relapsed during this period (Table 2).

Predictors of Response

Univariate analysis in patients receiving pomalidomide (0.5 or 2 mg/d) with or without prednisone (n = 63) did not show a correlation between response and Lille score²⁴ (P = .31), myelofibrosis subtype (primary v postessential thrombocythemia v postpolycythemia vera; P = .50), platelet count (P = .64), RBC transfusion dependency at baseline (P = .58), age (P = .32), or sex (P = .96). Similarly, the presence of either JAK2V617F (number assessable = 84) or abnormal cytogenetics (number assessable = 47) did not affect response; 11 (31%) of 36 JAK2V617F-positive patients responded as opposed to 5 (19%) of 27 mutation-negative patients (P = .28); six

Table 1. Baseline Clinical and Laboratory Features of 84 Patients With MF Who Were Randomly Assigned to One of Four Treatment Arms to Receive Pomalidomide and/or Prednisone

Parameter	All Patients		Pomalidomide (2 mg/d) + Placebo		Pomalidomide (2 mg/d) + Prednisone		Pomalidomide (0.5 mg/d) + Prednisone		Prednisone + Placebo	
	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	84		22		19		22		21	
Median age, years	67		68		67		70		67	
Range	36-86		50-83		36-80		43-86		44-80	
Male	57	68	17	77	13	68	13	59	14	67
MF subtype										
Primary	60		16		15		13		16	
Post-ET	14		2		2		7		3	
Post-PV	10		4		2		2		2	
Median disease duration, years	1.12		0.6		1.1		1.7		1.4	
Range	0.01-14.3		0.04-6.27		0.03-13		0.01-10.9		0.05-14.3	
Previous therapy*										
None	23	28	6	27	6	32	6	27	5	24
Non-cytotoxic	56	66	15	68	12	63	13	59	16	76
Cytotoxic	15	18	2	9	3	16	5	23	5	24
Lille ²⁴ intermediate/high risk group	66/18		15/7		15/4		19/3		17/4	
Transfusion dependent at baseline	65	77	17	77	15	79	16	73	16	76
Median leukocyte count, $\times 10^9/L$	7.5		10		8.2		6.4		7.3	
Range	2.7-50.4		3.1-50.4		3.2-50		3.1-20.5		2.7-25.8	
Leukocyte count	29	35	11	50	8	42	6	27	4	19
Median platelet count, $\times 10^9/L$	203		190		232		209		201	
Range	50-1,237		57-624		50-572		50-1,237		67-691	
Spleen size, > 10 cm	44	52	14	64	11	58	8	36	11	52
JAK2V617F positive	50	60	13	59	12	63	11	50	14	67
Abnormal cytogenetics†	21 of 47	45	5 of 12	42	5 of 12	42	5 of 12	42	6 of 11	55

NOTE. Please see text for additional information regarding treatment dose and schedule for both pomalidomide and prednisone.

Abbreviations: MF, myelofibrosis; ET, essential thrombocythemia; PV, polycythemia vera.

*Please note that the number of patients does not always add up since some patients received both cytotoxic and non-cytotoxic therapy.

†Cytogenetic information was available in only 47 patients.

(40%) of 15 patients with abnormal cytogenetics responded as opposed to four of 21 without ($P = .17$). None of the six responders with abnormal cytogenetics had complex abnormalities; the simple cytogenetic lesions included monosomy 7 $\pm$ r(7) in two patients and del(13q), del(20q), der(6)t(1q;6p), and trisomy 9 in one patient each. The latter patient also had a t(X;14)(q26;q32) abnormality. Two patients with del(5q) were randomly assigned to the prednisone only arm and did not respond. Leukocyte count higher than $10 \times 10^9/L$ or palpable spleen size ≥ 10 cm correlated with lower response rate; two (8%; 95% CI, 0% to 19%) of 25 patients with leukocytosis responded as opposed to 14 (37%; 95% CI, 22% to 52%) of 38 without ($P = .01$); five (15%; 95% CI, 3% to 27%) of 33 patients with marked splenomegaly responded as opposed to 11 (37%; 95% CI, 20% to 54%) of 30 without ($P = .05$). However, only leukocytosis remained significant during multivariable analysis (Table 3).

Treatment Effect on Other Blood Parameters

This study did not include patients with platelet counts of lower than $50 \times 10^9/L$ or absolute neutrophil counts of lower than $1 \times 10^9/L$; therefore, the drug's effect on clinically relevant thrombocytopenia or neutropenia could not be accurately assessed. However, a greater than 50% increase in platelet count was recorded in six (43%) of 14 patients who received pomalidomide (0.5 or 2 mg/d) with or

without prednisone and had baseline platelet counts in the range of 50 to $100 \times 10^9/L$ (baseline platelet counts of 64 to $86 \times 10^9/L$ increased to peak levels of 148 to $293 \times 10^9/L$). Unlike our previous experience with lenalidomide, serum lactate dehydrogenase level was seldom affected by pomalidomide with or without prednisone therapy (normalized in only two responders) and treatment-induced changes in leukoerythroblastosis or peripheral blood CD34-positive cell count were infrequent (data not shown).

Treatment Effect on Histology, Cytogenetics, or JAK2V617F Allele Burden

Follow-up bone marrow examination was available in four responders who completed 1 year of treatment with pomalidomide with or without prednisone. In three of these patients, overall bone marrow cellularity, degree of fibrosis, or cytogenetic findings did not change (Table 2; patients 5, 7, and 12). In one patient (Table 2; patient 6), bone marrow fibrosis decreased from grade 3+ to grade 1. This patient received pomalidomide 2 mg/d plus prednisone and also had a partial cytogenetic remission after 1 year of protocol therapy; number of metaphases with monosomy 7 and r(7) decreased from 18 of 20 to three of 20 metaphases examined. However, the patient developed, after 16 months of therapy, marked leukocytosis with eosinophilia, basophilia, and pleural effusion. A repeat bone marrow examination at the time revealed monosomy 7 and r(7) in all metaphases

Table 2. Baseline and Post-Treatment Parameters of 20 Patients With Myelofibrosis Who Responded to Treatment With Pomalidomide and/or Prednisone

Patient No.	Patient Age/Sex	MF Subtype	Lille Score	JAK2 Status	Karyotype	Treatment Arm*	Hemoglobin Level (g/dL)		Response Duration (months)
							Pretreatment	Post-Treatment†	
1	75/M	Primary	High	Neg	der(6)t(1q;6p)	POM	Tx dependent	9	3.2 (relapsed)
2	50/M	Primary	High	Neg	NA	POM	Tx dependent	13.3	9.2+
3	69/M	Primary	High	Neg	Normal	POM	8.1	10.9	6.4+
4	54/M	Primary	Int	Pos	+9	POM	Tx dependent	12.7	8.3+
5	79/M	Primary	Int	Pos	20q-	POM	Tx dependent	12.1	9.2+
6	63/F	Primary	Int	Pos	-7 and r(7)	POM/pred	9.9	16.0	14 (off-study)‡
7	68/M	Post-ET	High	Pos	Normal	POM/pred	Tx dependent	10.6	15.3+
8	65/F	Primary	Int	Pos	-7	POM/pred	Tx dependent	11	6.4+
9	72/M	Primary	Int	Pos	13q-	pom/pred	Tx dependent	10.8	4.1+
10	70/M	Post-ET	Int	Pos	NA	pom/pred	Tx dependent	10	6.5+
11	66/F	Primary	Int	Pos	NA	pom/pred	9.7	15.2	4.6+
12	60/M	Post-PV	High	Pos	Normal	pom/pred	Tx dependent	12.2	16.9+
13	43/M	Primary	Int	Neg	NA	pom/pred	Tx dependent	11.7	9.7+
14	59/F	Post-ET	Int	Neg	NA	pom/pred	Tx dependent	9.9	6.1+
15	59/M	Primary	Int	Pos	NA	pom/pred	Tx dependent	9.3	8.3+
16	86/F	Post-ET	Int	Pos	Normal	pom/pred	Tx dependent	11.6	14+
17	61/F	Primary	Int	Pos	Normal	Pred	Tx dependent	11.8	5.5 (relapsed)
18	58/F	Post-PV	Int	Pos	NA	Pred	8.3	12.4	2.8 (off-study)§
19	76/M	Primary	Int	Pos	NA	Pred	Tx dependent	9.4	2.3 (relapsed)
20	67/M	Primary	High	Neg	Normal	Pred	8.6	11.3	2.3+

NOTE. All responses signified improvement in anemia according to the International Working Group for Myelofibrosis Research and Treatment Criteria.¹⁷ Abbreviations: M, male; High, high risk; Neg, negative; POM, pomalidomide 2 mg/day; Tx, red blood cell transfusion; F, female; Pos, positive; pom, pomalidomide 0.5 mg/day; pred, prednisone; NA, not available; ET, essential thrombocythemia; PV, polycythemia vera; MF, myelofibrosis; Int, intermediate risk.

*Please see text for treatment dose and schedule for both pomalidomide and prednisone.

†Best hemoglobin response.

‡Patient developed grade 3 pleural effusion attributed to drug.

§Patient experienced progressive splenomegaly.

examined. Granulocyte DNA-derived *JAK2V617F* allele burden was measured in four responding patients at baseline and after variable follow-up time; in one of these patients who showed an increase in her hemoglobin to 16 g/dL (Table 2; patient 6), mutant allele burden increased from 18% to 48% after 1 year of treatment; there was no change in the other three patients (Table 2; patient 12 from 3% to 3.3% after 1 year of treatment; patient 7 from 21% to 19% after 3 months of treatment; patient 8 from 9% to 9% after 5 months of treatment).

Treatment Toxicity

At the time of this writing, all patients still on-study have completed six cycles of treatment. Twenty-two patients (26%) discontinued treatment before the completion of three cycles because of, according to documents provided by the treating physician, lack of efficacy/progressive disease in nine patients, adverse events in six patients, withdrawal of consent in four patients and death unrelated to drug therapy in three patients. A total of eight deaths were documented during protocol therapy and were attributed to progressive

Table 3. Response Rates Among 84 Pomalidomide-Treated Patients With Myelofibrosis

Treatment Arm*	All 84 Patients			Among 55 Patients Without Leukocytosis†		Among 29 Patients With Leukocytosis		Among 62 Patients Who Completed 3 Cycles of Treatment	
	No.	%	95% CI	No.	%	No.	%	No.	%
Pomalidomide (2 mg/d) + placebo	5 of 22	23	5 to 41	4 of 11	36	1 of 11	9	5 of 13	38
Pomalidomide (2 mg/d) + prednisone	3 of 19	16	0 to 33	3 of 11	27	0 of 8	0	3 of 13	23
Pomalidomide (0.5 mg/d) + prednisone	8 of 22	36	16 to 56	7 of 16	44	1 of 6	17	8 of 20	40
Prednisone	4 of 21	19	2 to 36	3 of 17	18	1 of 4	25	4 of 16	25

NOTE. All responses signified improvement in anemia according to the International Working Group for Myelofibrosis Research and Treatment. The Table also outlines additional information on response rates in patients with and without leukocytosis based on significant influence on multivariable analysis (see text). Response rates restricted to patients who have completed three cycles of protocol therapy are also provided.

*Please see text for treatment dose and schedule for both pomalidomide and prednisone.

†Leukocytosis was defined as a leukocyte count of $> 10 \times 10^9/L$.

disease in three patients, sepsis or pneumonia in three patients, a combination of progressive disease and infection in one patient, and cerebral hemorrhage in one patient; among the eight deaths, three were on the pomalidomide 2 mg/d plus prednisone arm, two were on the pomalidomide only 2 mg/d arm, two were on the prednisone only arm, and one was on the pomalidomide 0.5 mg/d plus prednisone arm. In general, grade ≥ 3 adverse events were infrequent (Table 4) and included neutropenia (8%), thrombocytopenia (11%), pneumonia/sepsis (11%), and venous thrombosis (4%). Most patients receiving pomalidomide with or without prednisone experienced eosinophilia and/or basophilia and one patient in addition developed grade 3 pleural effusion with marked eosinophilia in the pleural fluid that resolved completely with treatment discontinuation. Two patients experienced asymptomatic increase in platelet count that exceeded $1,000 \times 10^9/L$.

DISCUSSION

This study identifies pomalidomide, at a dose level of 0.5 to 2 mg/d, with or without a short course of concomitant prednisone therapy, as a well-tolerated drug in patients with myelofibrosis. The study also demonstrates the drug's erythropoietic activity, especially in the absence of leukocytosis. The observed anemia response rates of up to 40% are particularly notable considering the study's utilization of the strict IWG-MRT criteria for response and the fact that 81% of the responders were RBC transfusion dependent at baseline. By comparison, using single-agent thalidomide or lenalidomide in myelofibrosis, we have previously reported anemia response rates of 20% and 22%, respectively.^{12,18} The overall findings from this study also suggest that pomalidomide at the lower dose level (0.5 mg/d), combined with a

short course of prednisone therapy, might be as effective as the drug at the higher dose level (2 mg/d), and possibly less toxic. Furthermore, the responses seen at the lower pomalidomide dose level were maintained for several months beyond the discontinuation of concomitant prednisone therapy and are thus likely the result of pomalidomide and not prednisone effect. However, this study was not designed or adequately powered to either compare the different treatment arms or clarify the additional value of prednisone during pomalidomide therapy in myelofibrosis. After all, it is possible that prednisone can modify the effect of IMiDs immunomodulatory compounds by suppressing inflammatory stimuli. Therefore, additional studies are required to validate single-agent pomalidomide activity at 0.5 mg/d.

The underlying mechanism for the salutary effect of pomalidomide for myelofibrosis-associated anemia is not readily apparent and the available data on the drug's effect on normal erythropoiesis are not always consistent. For example, a recent study showed that both pomalidomide and lenalidomide favorably modulated human erythropoiesis by promoting survival of erythroid progenitors and enhancing fetal hemoglobin expression.²⁵ These observations are somewhat at odds with a previous study where pomalidomide suppressed erythroid colony formation and instead increased the frequency of myeloid colonies.²⁶ Regardless, these in vitro observations do not necessarily recapitulate in vivo drug effects that take into account the presence of clonal erythropoiesis and an aberrant cytokine milieu. Pomalidomide is known to upregulate interferon- γ , interleukin (IL)-2, IL-5, and IL-10 and downregulate TNF- α , IL-1 β , IL-11, and IL-12 and the composite effect of such cytokine modulation might be favorable in terms of ineffective erythropoiesis and over-ride any direct

Table 4. Adverse Events Graded at ≥ 3 per the National Cancer Institute Common Toxicity Criteria for Adverse Events Version 3²³ and Occurring in Two or More Patients

Adverse Event	All Patients		No. of Events			
	No.	%	Pomalidomide (2 mg/d) + Placebo	Pomalidomide (2 mg/d) + Prednisone	Pomalidomide (0.5 mg/d) + Placebo	Prednisone
No. of patients	84		22	19	22	21
Fatigue/asthenia	10	12	1	4	3	2
Pneumonia/sepsis	9	11	3	3	2	1
Thrombocytopenia	9	11	3	3	2	1
Anemia	8	10	2	3	1	2
Neutropenia	7	8	2	3	1	1
Hyperglycemia/diabetes	4	5	0	1	1	2
Dyspnea	4	5	2	0	2	0
Venous thrombosis	3	4	2	1	0	0
Bleeding	3	4	2	0	0	1
Diarrhea	3	4	0	2	0	1
Memory impairment	3	4	1	1	1	0
Nausea/vomiting	2	2	0	2	0	0
Abdominal pain	2	2	0	0	0	2
Pulmonary hypertension	2	2	1	0	0	1
Respiratory failure	2	2	1	1	0	0
Hyperuricemia	2	2	0	0	1	1
Arrhythmia/bradycardia	2	2	0	2	0	1
Cardiac failure	2	2	1	0	0	1
Hyperbilirubinemia	2	2	0	1	0	1
Myalgia	2	2	1	0	1	0
Dizziness	2	2	0	1	1	0

drug action.^{27,28} In this regard, it is important to mention that the anti-TNF- α activity of pomalidomide is much more potent than that of both thalidomide and lenalidomide¹; TNF- α markedly and directly inhibits human erythropoiesis.²⁹ Furthermore, it is possible that IMiDs immunomodulatory compounds promote opposing effects on normal and clonal cells.^{30,31} The latter scenario provides an explanation for lenalidomide's effect in restoring normal blood counts while eradicating the del(5q) clone in patients with myelodysplastic syndrome and for our observation of a patient who experienced a robust increase in hemoglobin level while achieving a partial cytogenetic remission.

For evaluating predictors of anemia response, we considered all patients receiving pomalidomide with or without prednisone ($n = 63$). Multiple parameters including myelofibrosis subtype, JAK2V617F mutational status, cytogenetic findings, leukocyte and platelet counts, spleen size, duration of disease, disease stage, and presence or absence of RBC transfusion history at baseline. On multivariable analysis, only leukocytosis, which was often associated with marked splenomegaly, came out as a significant negative predictor of response. It is possible that anemia in myelofibrosis patients with leukocytosis or marked splenomegaly is etiologically different and less amenable to treatment with IMiDs immunomodulatory compound (ie, it might reflect more a clone-intrinsic rather than cytokine-mediated ineffective erythropoiesis). It is also possible that the benefit of pomalidomide in patients with leukocytosis or marked splenomegaly was undermined by the dynamics of their disease progression, which might have necessitated intervention with alternative therapy and premature interruption of the study drug; unlike our previous experience with lenalidomide,¹⁸ and to some degree with thalidomide,¹² pomalidomide had little effect on splenomegaly. Therefore, considering the fact that the drug exerted minimal myelosuppression, it is reasonable to consider additional studies that allow combination therapy with pomalidomide and a cytoreductive drug.

We were particularly encouraged by the relatively low incidence of grade ≥ 3 neutropenia and thrombocytopenia associated with pomalidomide therapy: 5% and 9% at the lower 0.5 mg/d dose level and 9% to 16% and 14% to 16% at the higher 2 mg/d dose levels. These figures compare favorably to those seen in our previous study of lenalidomide therapy (10 mg/d) in myelofibrosis; 40% and 24%, respectively.¹⁸ However, it is possible that higher doses of pomalidomide could produce a similar degree of myelosuppression, and in this regard, it is important to recall that the drug causes dose-dependent myelosuppression in multiple myeloma.⁷ Schey et al⁷ have previously established the MTD of pomalidomide in refractory/relapsed multiple myeloma at 2 mg/d. In this particular study, dose limiting toxicity was neutropenia.⁷ We are currently conducting a phase I study to determine the MTD of pomalidomide in myelofibrosis and preliminary results suggest that pomalidomide doses higher than 2 mg/d might be associated with higher incidences of grade 3 or grade 4 neutropenia and thrombocytopenia. Grade ≥ 3 nonhematologic toxicity in this study were also infrequent (Table 4) and included thrombosis that occurred in three patients (4%); in a previous phase I study of pomalidomide in multiple myeloma, the incidence of drug-attributed thrombosis was 13%.⁷ Other untoward effects of the drug, including thrombocytosis, eosinophilia, and basophilia, have previously been noticed during treatment with other IMiDs immunomodulatory compounds and are probably mediated by drug-induced cytokine

changes. For example, IL-5 is a well known eosinophilopoietic cytokine and is known to be upregulated by pomalidomide and this might have contributed to the drug-induced eosinophilia seen in this study.²⁷

We underscore the need for validating the current experience considering the relatively low overall response rate in terms of anemia. Also, controlled studies are needed to assess the impact of pomalidomide on survival or leukemic transformation in PMF. Similarly, longer follow-up of this study is needed to accurately assess pomalidomide's effect on bone marrow histology, cytogenetics, and JAK2V617F allele burden. Finally, additional studies are needed to evaluate safety and efficacy of the drug at the lower dose level (eg, 0.5 mg/d) in patients with baseline platelet counts of lower than $50 \times 10^9/L$ and absolute neutrophil count of lower than $1 \times 10^9/L$.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Bartlett JB, Dredge K, Dalglish AG: The evolution of thalidomide and its IMiD derivatives as anticancer agents. *Nat Rev Cancer* 4:314-322, 2004
2. Haslett PA, Roche P, Butlin CR, et al: Effective treatment of erythema nodosum leprosum with thalidomide is associated with immune stimulation. *J Infect Dis* 192:2045-2053, 2005
3. Rajkumar SV, Hayman S, Gertz MA, et al: Combination therapy with thalidomide plus dexamethasone for newly diagnosed myeloma. *J Clin Oncol* 20:4319-4323, 2002
4. List A, Dewald G, Bennett J, et al: Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 355:1456-1465, 2006
5. Weber DM, Chen C, Niesvizky R, et al: Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 357:2133-2142, 2007
6. Dimopoulos M, Spencer A, Attal M, et al: Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 357:2123-2132, 2007
7. Schey SA, Fields P, Bartlett JB, et al: Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J Clin Oncol* 22:3269-3276, 2004
8. Streetly MJ, Gyertson K, Daniel Y, et al: Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. *Br J Haematol* 141:41-51, 2008
9. Galustian C, Meyer B, Labarthe MC, et al: The anti-cancer agents lenalidomide and pomalidomide inhibit the proliferation and function of T regulatory cells. *Cancer Immunol Immunother* 58:1033-1045, 2008
10. Tefferi A: Pathogenesis of myelofibrosis with myeloid metaplasia. *J Clin Oncol* 23:8520-8530, 2005
11. Barosi G, Grossi A, Comotti B, et al: Safety and efficacy of thalidomide in patients with myelofibrosis with myeloid metaplasia. *Br J Haematol* 114:78-83, 2001
12. Elliott MA, Mesa RA, Li CY, et al: Thalidomide treatment in myelofibrosis with myeloid metaplasia. *Br J Haematol* 117:288-296, 2002
13. Abgrall JF, Guibaud I, Bastie JN, et al: Thalidomide versus placebo in myeloid metaplasia with myelofibrosis: A prospective, randomized, double-blind, multicenter study. *Haematologica* 91:1027-1032, 2006
14. Ochonisky S, Verroust J, Bastuji-Garin S, et al: Thalidomide neuropathy incidence and clinico-electrophysiologic findings in 42 patients. *Arch Dermatol* 130:66-69, 1994
15. Thomas DA, Giles FJ, Albitar M, et al: Thalidomide therapy for myelofibrosis with myeloid metaplasia. *Cancer* 106:1974-1984, 2006
16. Mileskin L, Stark R, Day B, et al: Development of neuropathy in patients with myeloma treated with thalidomide: Patterns of occurrence and the role of electrophysiologic monitoring. *J Clin Oncol* 24:4507-4514, 2006
17. Tefferi A, Barosi G, Mesa RA, et al: International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). *Blood* 108:1497-1503, 2006
18. Tefferi A, Cortes J, Verstovsek S, et al: Lenalidomide therapy in myelofibrosis with myeloid metaplasia. *Blood* 108:1158-1164, 2006
19. Tefferi A, Lasho TL, Mesa RA, et al: Lenalidomide therapy in del(5)(q31)-associated myelofibrosis: Cytogenetic and JAK2V617F molecular remissions. *Leukemia* 21:1827-1828, 2007
20. Thall PF, Simon R: Practical Bayesian guidelines for phase IIB clinical trials. *Biometrics* 50:337-349, 1994
21. Castaneda CP, Zeldis JB, Freeman J, et al: RevAssist: A comprehensive risk minimization programme for preventing fetal exposure to lenalidomide. *Drug Saf* 31:743-752, 2008
22. Vardiman JW, Brunning RD, Harris NL: WHO histological classification of chronic myeloproliferative diseases, in Jaffe ES, Harris NL, Stein H, et al (eds): World Health Organization Classification of Tumors: Tumours of the Haematopoietic and Lymphoid Tissues. Lyon, France, International Agency for Research on Cancer Press, 2001, pp 17-44
23. Cancer Therapy Evaluation Program: Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. Rockville, MD, National Cancer Institute. <http://ctep.cancer.gov/forms/>
24. Dupriez B, Morel P, Demory JL, et al: Prognostic factors in agnogenic myeloid metaplasia: A report on 195 cases with a new scoring system. *Blood* 88:1013-1018, 1996
25. Moutouh-de Parseval LA, Verhelle D, Glezer E, et al: Pomalidomide and lenalidomide regulate erythropoiesis and fetal hemoglobin production in human CD34+ cells. *J Clin Invest* 118:248-258, 2008
26. Koh KR, Janz M, Mapara MY, et al: Immunomodulatory derivative of thalidomide (IMiD CC-4047) induces a shift in lineage commitment by suppressing erythropoiesis and promoting myelopoiesis. *Blood* 105:3833-3840, 2005
27. Schafer PH, Gandhi AK, Loveland MA, et al: Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. *J Pharmacol Exp Ther* 305:1222-1232, 2003
28. Kaushansky K: Lineage-specific hematopoietic growth factors. *N Engl J Med* 354:2034-2045, 2006
29. Rusten LS, Jacobsen SE: Tumor necrosis factor (TNF)-alpha directly inhibits human erythropoiesis in vitro: Role of p55 and p75 TNF receptors. *Blood* 85:989-996, 1995
30. Jacobs-Helber SM, Roh KH, Bailey D, et al: Tumor necrosis factor-alpha expressed constitutively in erythroid cells or induced by erythropoietin has negative and stimulatory roles in normal erythropoiesis and erythroleukemia. *Blood* 101:524-531, 2003
31. Verhelle D, Corral LG, Wong K, et al: Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34+ progenitor cells. *Cancer Res* 67:746-755, 2007