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Phase II study of pomalidomide in combination with prednisone in patients with myelofibrosis and significant anemia

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Abstract

We evaluated pomalidomide with prednisone for myelofibrosis (MF) with significant anemia (hemoglobin <10g/dL). Patients (n=29; 18 RBC-transfusion dependent) received 0.5 mg pomalidomide daily in continuous 28-day cycles with prednisone given for the first 3 cycles only. Six (21%) patients responded (median response duration 11.4 months), including four who achieved RBC-transfusion-independence per the Delphi criteria and two who achieved clinical improvement (in platelets and spleen, respectively) per the International Working Group for Myelofibrosis Research and Treatment criteria. Grade 3 toxicity occurred in 1 patient (fatigue). Pomalidomide with prednisone is safe therapy with modest activity in patients with MF and anemia.

Keywords

myelofibrosis; pomalidomide; anemia

1 Introduction

Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs) are clonal malignancies characterized by unchecked proliferation of terminally differentiated myeloid cells.[1] Anemia is the most prevalent hematological aberrancy seen in myelofibrosis (MF)

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and is noted in approximately 75% of patients with MF.[2, 3] Progressive anemia may cause fatigue, dyspnea and organ dysfunction. Furthermore, anemia is independently associated with increased morbidity and mortality in MF.[2, 4] Erythropoietin analogues, androgens, splenectomy and corticosteroids have been used with limited success to treat MF-associated anemia.[5, 6] While JAK2 inhibitors have been shown to significantly abrogate splenomegaly and constitutional symptoms, they have little to no effect on improving erythropoiesis in patients with MF.[7, 8] Thus, novel therapeutic agents are needed that are focused on improving erythropoiesis and significant anemia in patients with MF.

The immunomodulatory agents (IMiDs) thalidomide and lenalidomide have been shown to improve anemia, thrombocytopenia and splenomegaly in select patients with MF.[9-13] Pomalidomide is a potent second-generation IMiD that has been shown to have a better toxicity and safety profile than thalidomide and lenalidomide. An initial phase II, randomized double-blinded 4-arm trial evaluated the efficacy and safety of pomalidomide as therapy for patients with MF and significant anemia.[14] The International Working Group for Myelofibrosis Research and Treatment 2006 (IWG-MRT) response rate in the pomalidomide 0.5 mg/day plus prednisone arm was the highest (response rate of 36%) but was not statistically significantly different from response rates in other groups.[14, 15] Subsequent studies have evaluated the clinical activity of single-agent pomalidomide in MF patients with significant anemia, with reported response rates ranging from 17%-37%.[16-20] While these studies were being conducted, we performed a phase 2 study of the combination of pomalidomide and prednisone to further evaluate whether the combination could be effective in treating patients with MF and significant anemia [17]. The results of this study are presented herein.

2. Patients and Methods

2.1. Patient eligibility

Eligibility criteria included the following: patients ≥ 18 years of age with a diagnosis of primary, post-polycythemia vera or post-essential thrombocythemia MF requiring therapy[21]; total hemoglobin level <10 g/dL or presence of transfusion dependency at screening; performance status ≤2 by the Eastern Cooperative Oncology Group (ECOG) scale; serum creatinine ≤ 2.0 mg/dL; serum bilirubin < 3.0 times the upper limit of the normal range; blood transaminase level ≤ 3 times the upper limit of the normal range; absolute neutrophil count ≥ 1.0×10^9/L and platelet count ≥ 50×10^9/L. Patients must not have been treated with growth factors, cytotoxic chemotherapeutic agents (e.g. hydroxyurea and anagrelide), corticosteroids, or experimental therapy for at least 4 weeks prior to study enrollment and must have recovered from the toxic effects of such therapy (to ≤ grade 1) at the time of enrollment. Women of childbearing age must have had a negative pregnancy test and all patients were required to use effective methods of contraception during study participation. This was a single center study supported by Celgene Corporation, Summit, NJ, USA. All patients gave written informed consent and the protocol was approved by the Institutional Review Board at MD Anderson.

2.2. Treatment Schedule

Pomalidomide was administered at a dose of 0.5 mg daily in continuous 28-day cycles. Concomitant prednisone was administered at a dose of 30 mg/day for the first cycle, 15 mg/day for the second cycle and 15 mg every other day for the third cycle, based on prior experience when combined with IMiDs. The dose of pomalidomide was determined on the basis of prior studies and could not be further escalated or de-escalated.[14, 17, 19] Pomalidomide was to be continued for at least 6 months if tolerated. Subjects manifesting a clinical benefit (including those who were deemed to be deriving clinical benefit by the treating physician but had not achieved a clinical response according to defined response criteria) could continue therapy beyond 6 months until either disease progression or intolerable toxicity warranted treatment discontinuation. Subjects showing no clinical benefit at 6 months were taken off-study. Low-dose aspirin prophylaxis was recommended for patients with platelet count > 75×10^9/L. Growth factor support was excluded, with the exception of filgrastim or pegfilgrastim, which could be administered to patients who developed prolonged neutropenia or neutropenic fever. Study accrual began in July 2011 and was completed in March 2013.

2.3. Response evaluation

Responses were adjudicated in two ways: For patient with baseline hemoglobin <10 g/dL, clinical improvements (CI) in hemoglobin were assessed by the 2006 IWG-MRT criteria, which require a minimum hemoglobin increase of 2.0 g/dL from baseline (without transfusion support), sustained for a duration of at least 8 weeks.[15] However, the attainment of transfusion independence was assessed on the basis of the RAND-Delphi expert-consensus panel definitions of red blood cell–transfusion dependence and independence.[22] The Delphi consensus criteria are more clinically robust than IWG-MRT criteria for assessment of transfusion dependence in clinical trials. Transfusion dependency is defined as monthly red blood cell transfusions of at least 2 units during the prior 3 months with a hemoglobin level of less than 8.5 g/dL that was not associated with clinically overt bleeding. The Delphi criteria define transfusion independence as becoming transfusion independent for at least 3 months. The National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), version 3.0 was used to assess toxicity. [23]

2.4. Study design and statistical schema

This was a two-stage (MiniMax), single center, phase II trial designed to assess the efficacy of low-dose pomalidomide in combination with prednisone in patients with MF. The primary efficacy endpoint of this trial was best overall response, which included complete remission (CR), partial remission (PR) or clinical improvement (CI). Responses were judged starting after the first 6 cycles of therapy, using the IWG-MRT and/or Delphi consensus criteria.[15, 22] The largest success proportion where the combination would be considered unpromising was 5%, representing the probability of a response by chance. The smallest success proportion that would support subsequent studies with the combination regimen was 20%.

In accordance with the two-stage design, an interim analysis was conducted after the first 20 evaluable subjects had been observed for at least 6 cycles to permit early reporting of

efficacy results and permit early stoppage of the study if there was strong evidence that the study regimen was inactive. If 1 or fewer treatment successes were observed in these 20 subjects, the treatment regimen would have been considered inactive and the study would be closed. If 2 or more treatment successes were observed in these 20 subjects, decisions about activity would await the final analysis after the accrual of all patients. Since >1 more treatment success was documented after accrual of the first 20 patients, the study continued till all patients were accrued (n=29).

3. Results

Twenty-nine patients with primary, post-PV, or post-ET MF with anemia were enrolled. Patient characteristics are summarized in Table 1. Twenty patients (69%) had received prior therapy: 2 patients (7%) had received anagrelide alone, 2 patients (7%) had received hydroxyurea alone and 4 patients (14%) had received anagrelide and hydroxyurea, 6 patients (21%) had received thalidomide or lenalidomide; 3 patients (10%) had received danazol, and 1 patient each had received epoetin alfa, pegylated-interferon, and AZD1480 (an ATP-competitive JAK-1 and 2 inhibitor).

Twenty-three patients remain alive after a median follow-up of 18.4 months (range, 3.4-27.0 months). The median time on study was 6.4 months (range, 2.5-24.8 months) and the median number of cycles administered was 6 (range, 1-26). At the time of paper submission, 5 patients are still being treated, with a median time on study of 15.0 months (range, 9.0-25.0 months). Of the 29 patients enrolled, 2 (of the 5 who remain on study) have achieved a documented response, including CI in spleen size in one patient and transfusion independence (per the Delphi consensus criteria) in the other patient. Time to response in these patients was 173 and 31 days, respectively. Their responses have been maintained for 7.3 months and 14.4 months, respectively. One patient experienced self-limiting grade 1 drug-related diarrhea and constipation and the other patient had no drug-related toxicities. The remaining 3 patients who are still being treated did not achieve a documented response but were deemed to derive clinical benefit and were allowed to continue therapy on the study. Clinical benefit in these 3 patients included: (1) reduced disease-related symptoms and improvement in hemoglobin that did not meet the IWG-MRT criteria for clinical improvement in a patient who remains on study after 25 months (26 cycles), (2) reduced fatigue and reduced frequency of red blood cell transfusions that did not meet the documented Delphi criteria for transfusion independence response in a patient who remains on study after 9 months (10 cycles), and (3) improved performance status and reduced frequency of red blood cell transfusions that did not meet the documented Delphi criteria for transfusion independence response in a patient who remains on study after 10 months (11 cycles). The remaining 24 patients discontinued treatment for the following reasons: lack of response in 18 patients, progressive disease in 2 patients, loss of response in 1 patient, grade-3 toxicity in 1 patient, and patient preference in 2 patients.

Eighteen patients (62%) were transfusion dependent at baseline and 4 (22%) achieved transfusion independence as defined by Delphi consensus criteria (Table 2). The median time to transfusion independence was 92 days (range, 31-130 days) and the response was maintained for a median of 11.4 months (range, 2.0-22.0 months). Among the 4 patients

who achieved transfusion independence, one also had IWG-defined CI in hemoglobin (sustained improvement in hemoglobin ≥ 2 g/dl that was maintained for > 8 weeks). One patient had an IWG-defined CI in platelet counts: the platelet counts improved from 50 × 10^9/L at baseline to > 100 × 10^9/L after 25 days on treatment, and the response was maintained for 19.5 months. One patient had an IWG-defined CI in spleen size. At baseline, the patient had splenomegaly palpable at 9 cm below left costal margin, which resolved after 6 months of therapy. The spleen response lasted 7.3 months. Another patient had baseline splenomegaly of 5 cm that resolved after 8 weeks of therapy but was not counted as CI because his baseline spleen size was ≤ 5 cm. In total, protocol defined responses were identified in 6 (21%) of 29 patients enrolled with a median response duration of 11.4 months (range, 2.0 – 22.0). One of the six responders had received prior therapy with lenalidomide. The median time on study for all responding patients was 13.7 months (range, 6.7-19.0 months) with a median of 15 cycles (range, 7–19 cycles).

Overall, the combination of low-dose pomalidomide and prednisone was well tolerated. The most common toxicities, seen in 5 patients, involved the gastrointestinal system (including nausea, abdominal pain and bloating, constipation, and diarrhea). (All grade 1; Table 3) The only drug-related grade 3-4 toxicity was grade 3 fatigue in one patient. No patients had to discontinue treatment due to drug-related toxicities. In addition, no episodes of thrombosis or thrombocytosis were noted. Six deaths were documented during follow-up after the patients had discontinued treatment and were attributed to progressive disease in 2 patients, pneumonia in 1 patient, myocardial infarction in 1 patient, sepsis in 1 patient, and unknown cause in 1 patient.

4. Discussion

In our current study, 29 patients were treated with pomalidomide in combination with a prednisone taper during the first 3 cycles of therapy with a modest anemia response of 22%. Responses were not associated with the presence or absence of the *JAK2V617F* mutation. A recently completed phase 3 randomized trial evaluated pomalidomide versus placebo in transfusion-dependent patients with MF (RESUME trial).[16] The Delphi consensus response criteria, which were specifically formulated to accurately evaluate “RBC-transfusion-independence” in transfusion-dependent MF patients in clinical trials, were used in the RESUME trial..[22] Two hundred and fifty-two patients were randomized 2:1 to receive pomalidomide 0.5 mg/day or placebo. The Delphi-defined response rate was 16% in both groups. Interestingly, response rates for improvements in platelet counts (secondary endpoint of the study) were significantly higher for patients treated with pomalidomide (22%) than for those who received placebo (0%). These results suggest some clinical activity of pomalidomide that was not adequately assessed by the initial trial design. Additional research designs and improved response criteria need to be developed if we hope to accurately identify patients with MF who have a high likelihood of responding to anti-anemia/cytopenia medications.

Preliminary results of another clinical study evaluating activity of pomalidomide in combination with prednisone in MF have recently been presented (ClinicalTrials.gov identifier: NCT00949364).[24] Eligible patients were either RBC-transfusion-dependent or

had significant cytopenias (hemoglobin <10.0 g/dL and/or neutrophils <1.0 × 10^9/L and/or platelets <50 × 10^9/L). Patients were enrolled in one of two cohorts. Patients enrolled in cohort 1 (n=38) received pomalidomide 2 mg/day. If no response was achieved after 3 months, prednisone 30 mg/day was added at the start of cycle 4. Cohort 2 consisted of two treatment arms with pomalidomide (0.5 mg/day): in arm 1 (n=27) patients started pomalidomide alone and prednisone was added at the start of cycle 4 if no response was achieved; in arm 2 (n=31) patients started pomalidomide alone and prednisone was added at the start of cycle 7 if no response was achieved. Overall response rates were 34%, 19% and 16%, respectively. Both anemia and platelet responses were observed more often in cohort 1, suggesting that higher dose of pomalidomide (2 mg/day) and earlier initiation of prednisone might be better than other tested approaches, contrary to the initial results of a study of pomalidomide in MF published in 2009. [20]

Finally, an ongoing clinical study is evaluating pomalidomide in combination with ruxolitinib (ClinicalTrials.gov identifier: NCT01644110). The possible complimentary efficacy profile and non-overlapping toxicities of ruxolitinib and pomalidomide suggest that combining the two drugs may help alleviate the significant comorbidities experienced by patients with MF. That study is currently underway Results from these last two ongoing studies may finally answer the question of whether there remains a role for pomalidomide therapy in patients with MF.

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Highlights

- We evaluated pomalidomide with prednisone for myelofibrosis with significant anemia.
- Lower-dose of pomalidomide (0.5 mg/day) in combination with prednisone was administered.
- The combination has modest efficacy with an overall response rate of 21%.
- Four of eighteen transfusion dependent patients achieved transfusion independence.
- The combination was well tolerated with only one grade 3 toxicity (fatigue).

Table 1

Patient characteristics (N=29)

Characteristic	Number (%)
Age, years [range]	69 [48-88]
Men	20 (69)
Splenomegaly	8 (28)
ECOG performance status	
0	8 (28)
1	21 (72)
JAK 2V617F positive	15 (52)
Diagnosis	
PMF	27 (93%)
Post-ET MF	2 (7%)
Transfusion dependent (Delphi criteria)	18 (62)
Median white blood cell count, 10^9/L [range]	4.8 [1.0-36.2]
Bone marrow blasts ≥ 1%	19 (65)
Platelets, 10^9/L [range]	177 [35-1191]
Karyotype	
Diploid	16 (55)
Abnormal	10 (35)
Indeterminate	3 (10)
Prior treatment	21 (72)

Abbreviations: ECOG, Eastern cooperative oncology group; PMF, primary myelofibrosis; Post-ET MF, post-essential thrombocythemia myelofibrosis

Table 2

Characteristics of responding patients

DX	Age	JAK 2	Cyto	Prior RX	Spleen size at baseline (cm)	TSF Dependent	Response CI	Med time to response (d)	Resp duration (m)	Still on therapy	Status
PMF	68	−	Diploid	None	0	Yes	TSF	130	1.5	No	Alive
PMF	68	+	Abnormal	None	20	Yes	TSF	129	8.4	No	Alive
PMF	57	−	Abnormal	Pegasys	0	Yes	TSF	31	14.4	Yes	Alive
PMF	75	+	Diploid	Proc, HU, Revlimid	8	Yes	TSF & HGB	55	22.0	No	Dead
PMF	58	−	Diploid	Steroids	0	Yes	PLT	13	19.5	No	Alive
PMF	74	+	Abnormal	AG	9	No	SPLN	73	7.3	Yes	Alive

Abbreviations: Dx, diagnosis; PMF, primary myelofibrosis; Pos, positive; Neg, negative; Cyto, cytogenetics; RX, treatment; Proc, procrit; HU, hyrdoxyurea; AG, anagrelide; TSF, transfusion; CI, clinical improvement; HGB, hemoglobin; PLT, platelets; SPLN, spleen; d, days; Resp, response; m, months;

Table 3

Therapy-related toxicities in patients receiving pomalidomide in combination with prednisone (total number of events)

Side Effects	Grade			
	1	2	3	4
Extremity cramping	1	1		
GI symptoms	5			
Edema-Feet	1			
Fatigue			1	
Urinary Frequency	1			
Blurring vision	1			
Hypothyroidism	1			
Myelosuppression		3		