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ORIGINAL ARTICLE

A phase-2 trial of low-dose pomalidomide in myelofibrosis

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In a previous study, we reported on the safety and efficacy of low-dose (0.5 mg) pomalidomide and prednisone and pomalidomide alone (2 mg/day), for the treatment of anemia associated with myelofibrosis (MF). The current study examined the value of low-dose pomalidomide alone. The main eligibility criterion was transfusion-dependency or hemoglobin <10 gm per 100 ml. Anemia response was assessed by International Working Group criteria. Pomalidomide (0.5 mg/day) was given to 58 patients (median age 68 years); 46 (79%) were transfusion-dependent and 42 were *JAK2*V617F positive. Anemia response was documented only in the presence of *JAK2*V617F (24 vs 0%; $P=0.03$) but was not further affected by mutant allele burden ($P=0.39$); 9 of the 10 anemia responders became transfusion independent. Anemia response in *JAK2*V617F-positive patients was predicted by the presence of pomalidomide-induced basophilia in the first month of therapy (38 vs 6%; $P=0.02$) or absence of marked splenomegaly (38 vs 11%; $P=0.05$). A total of 14 (58%) of 24 patients with a platelet count of $\leqslant 100\times10^9$ cells/l experienced a >50% increment in platelet count. There were no spleen responses. Grade 3 or 4 thrombocytopenia/neutropenia occurred in 2%/0% of patients. Low-dose pomalidomide is effective in the treatment of anemia associated with *JAK2*V617F-positive MF; response is predicted by early drug-induced basophilia.
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Introduction

Pomalidomide is an immunomodulatory drug that is structurally related to both lenalidomide and thalidomide. All three drugs display anti-angiogenic, anti-TNF-α and T-cell modulatory activity, but the precise mechanism of their therapeutic activity is poorly understood.[1] Lenalidomide and thalidomide, in combination with dexamethasone, are Food and Drug Administration approved for use in relapsed and newly diagnosed multiple myeloma, respectively.[2–4] Single-agent lenalidomide is approved for use in the treatment of transfusion-dependent anemia in low/intermediate-1 myelodysplastic syndromes with del(5q).[5]

Thalidomide, lenalidomide and pomalidomide have all been used in the treatment of primary, post-polycythemia vera or post-essential thrombocythemia myelofibrosis (MF). In this regard, higher doses (100–400 mg/day) of thalidomide were associated with an increased adverse dropout rate.[6–8] Low-dose (50 mg/day) thalidomide in combination with prednisone is better tolerated, and it alleviates anemia in approximately a quarter of treated patients with MF.[9–13] However, as a single agent, the anti-anemia activity of thalidomide is limited and long-term use has been associated with neuropathy. Lenalidomide (5–10 mg/day) with or without prednisone also improves anemia in approximately 25% of patients with MF, but the drug's utility is limited by its association with substantial myelosuppression.[14–16] Lenalidomide is most useful in del(5q)-associated MF.[17]

The maximum tolerated dose of pomalidomide was 2 mg/day in relapsed or refractory multiple myeloma[18] and 3 mg/day in MF.[19] At 2 mg/day, the drug, in combination with dexamethasone, has shown remarkable activity in relapsed multiple myeloma, including patients refractory to either lenalidomide or bortezomib.[20] In a phase-2 randomized study ($n=84$), pomalidomide either alone (2 mg/day) or in combination with prednisone (0.5 or 2 mg/day) was shown to be safe (no neuropathy and <10% severe myelosuppression) and effective (25% response rate) in treating anemia associated with MF.[21] In the current study, we evaluated single agent low-dose (0.5 mg/day) pomalidomide therapy in MF patients with anemia and looked for predictors of response.

Patients and methods

This was a single center study supported by Celgene Corporation, Summit, NJ, USA. Approval for the study was obtained from the Mayo Clinic Institutional Review Board and informed consent was obtained from all study patients. The study is registered at ClinicalTrials.gov (no. NCT00669578). Eligibility criteria included diagnosis of primary, post-polycythemia vera or post-essential thrombocythemia MF,[22] a hemoglobin level of <10 gm per 100 ml or presence of red cell transfusion dependency (defined as documentation of transfusion of at least two units of packed red blood cells, for a hemoglobin level of <8.5 gm per 100 ml, during the 4-week period before study entry), an absolute neutrophil count $\geqslant 1\times10^9$ cells/l, a platelet count $\geqslant 20\times10^9$ cells/l, a creatinine level ⩽2 mg per 100 ml, direct bilirubin level <2× the upper limit of normal and blood transaminase level ⩽3× the upper limit of normal unless attributed to extramedullary hematopoiesis. Patients who failed prior therapy with lenalidomide or thalidomide were eligible for the study, whereas those with history of deep vein thrombosis or pulmonary embolism in the year before study entry were not.

Oral pomalidomide (0.5 mg) was administered daily and a 28-day therapy constituted a cycle of treatment. After six cycles of treatment at 0.5 mg/day, it was allowed to increase the dose to 2 mg/day in the absence of drug side effects. Response was assessed by the International Working Group for Myeloproliferative Neoplasms Research and Treatment criteria.[23] Toxicity was assessed by the National Cancer Institute Common Terminology Criteria for Adverse Events version 3. Statistical

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analyses were performed using Stat-View (SAS Institute, Cary, NC, USA). Differences in the distribution of continuous variables between categories were analyzed by either Mann–Whitney *U*- or Kruskal–Wallis test. A χ^2 test was used to compare categorical variables.

Results

A total of 58 patients were enrolled into the current study and their baseline characteristics are depicted in Table 1. All 58 patients belonged to high or intermediate-2 risk category according to the Dynamic International Prognostic Scoring System[24] and 79% of the patients were red cell transfusion-dependent at the time of study entry. A total of 42 (72%) patients were positive for *JAK2*V617F.

A total of 49 (84%) patients completed at least three cycles of pomalidomide therapy; the reasons for treatment discontinuation, in the first three months of therapy, in the remaining nine (16%) patients, were disease progression ($n=3$), lack of therapeutic effect ($n=5$) and gastrointestinal bleeding not attributed to protocol treatment ($n=1$). At the time of this writing, the total number of adverse events that were at least possibly related to pomalidomide therapy was 19 (33%). Grade 3 or 4 adverse events were infrequent (7%; Table 2). Specifically, there were no occurrences of thrombosis and only 1 (2%) patient had grade 1 neuropathy possibly related to the study drug. Grade 3/4 neutropenia or thrombocytopenia occurred in 0 and 2% of the patients, respectively. A more than 50 or 100% increase in absolute basophil count occurred in 58 and 48% of the patients, respectively, during the first month of therapy, but was not associated with any ill-effects. None of the patients stopped treatment because of adverse events. To date, four deaths have been documented: one acute myeloid leukemia (~4 months off therapy because of disease progression), one cryptococcal meningitis and sepsis (~4 weeks off therapy because of acute illness) and two unknown causes (~2 weeks and 4 months off therapy because of lack of response or streptococcal viridans sepsis, respectively).

In all, 10 (17%; CI 8–27%) patients achieved an anemia response as per International Working Group for Myeloproliferative Neoplasms Research and Treatment criteria; 9 of the 10 anemia responders became red blood cell transfusion independent. Among patients who received ⩾three cycles of pomalidomide therapy, the anemia response rate was 20% (95% CI 9–32%); median time to response was 2.3 months (range 1–4.6) and median duration of response to date was 8.3+ months (range 5.5–12.8+ months). There were no correlations between anemia response and age ($P=0.75$), sex ($P=0.7$), leukocyte count ($P=0.74$), platelet count ($P=0.06$), cytogenetic risk category ($P=0.73$), MF subtype (primary vs post-ET vs post-PV; $P=0.2$) or the Dynamic International Prognostic Scoring System score ($P=0.17$).[24] Instead, anemia response was significantly associated with the presence of JAK2*V617F* (24 vs 0%; $P=0.03$), absence of marked splenomegaly (29 vs 7%; $P=0.04$) and occurrence of drug-induced basophilia (>50% increase in absolute basophil count) in the first month of therapy (27 vs 4%; $P=0.02$) (Table 3). Among the 42 *JAK2*V617F-positive cases, anemia response was not further affected by mutant allele burden ($P=0.39$), but was significantly higher in the absence of marked splenomegaly (38 vs 11%; $P=0.05$) or presence of drug-induced basophilia (38 vs 6%; $P=0.02$). In contrast, cytogenetic risk category ($P=0.96$) or leukocytosis ($P=0.27$) did not affect anemia response.

Pomalidomide therapy also resulted in a >50% increase in platelet count in 14 (58%) of 24 patients with baseline platelet count of $\leqslant 100\times10^9$ cells/l, whereas it had little effect on leukocyte count, serum lactate dehydrogenase level or spleen size (0% response rate by International Working Group for Myeloproliferative Neoplasms Research and Treatment criteria). Among the 14 patients with platelet response, median platelet count increased from 82×10^9 cells/l (range, 32–100) to 160×10^9 cells/l (range, 61–332). Platelet response was documented in 6 (86%) of 7 anemia responders and 8 (47%) of 17 anemia non-responders ($P=0.08$). Platelet response did not correlate with MF subtype ($P=0.30$), cytogenetic risk category ($P=0.35$), spleen size ($P=0.47$), leukocytosis ($P=0.48$), *JAK2* mutational status ($P=0.71$) or drug-induced basophilia ($P=0.52$).

Table 1 Baseline clinical and laboratory features of 58 patients with myelofibrosis who received low dose (0.5 mg/day) pomalidomide

Parameter	*Number (%)*
Total number of study patients	58 (100)
Median age, years	68
Range	45–87
Males	44 (76%)
Myelofibrosis subtype	
Primary	46 (79%)
Post-ET	7 (12%)
Post-PV	5 (9%)
DIPSS[24a]	
Int-2/high	42 (72%)/16 (28%)
Number of transfusion-dependent patients at base line	46 (79%)
Leucocyte count median, $\times/10^9$ cells/l	7.3
Range	1.5–180.9
Platelet count median, $\times/10^9$ cells/l	136
Range	20–1233
Spleen size ⩾10 cm, *n*[b]	27 (49%)
Number of *JAK2V617F*-positive patients	42 (72%)
Number of patients with abnormal cytogenetics[c]	23 (42%)
Cytogenetic risk category[25]	
Favorable/unfavorable	46/9

Abbreviations: DIPSS, dynamic international prognostic scoring system; ET, essential thrombocythemia, PV, polycythemia vera.
[a]DIPSS for primary myelofibrosis; for practical purposes, DIPSS was used here to also risk stratify post-polycythemia vera and post-essential thrombocythemia myelofibrosis.
[b]Spleen size available in 55 patients (three were status post splenectomy at study entry).
[c]Cytogenetic information available in 55 patients (three had insufficient metaphases).

Table 2 Adverse events as per the National Cancer Institute Common Terminology Criteria in 58 patients with myelofibrosis treated with pomalidomide 0.5 mg/day

Adverse events	*All grades*	*Grade 1 or 2*	*Grade 3 or 4*
AE (probable/possible) related to pomalidomide	19 (33%)	15 (26%)	4 (7%)
Anemia	5 (8%)	2 (3%)	3 (5%)
Thrombocytopenia	6 (10%)	5 (9%)	1 (2%)
Neutropenia	4 (7%)	4 (7%)	0
Fatigue/asthenia	2 (4%)	2 (4%)	0
Increase in serum alkaline phosphatase	1 (2%)	1 (2%)	0
Neuropathy (on the basis of symptom)	1 (2%)	1 (2%)	0

Table 3 Baseline and post-treatment parameters of 10 patients with myelofibrosis who responded to treatment with low dose (0.5 mg/day) pomalidomide

Sex/age	*MF subtype*	*JAK2V617F status*	*Spleen size (cms)*	*Karyotype*	*Pre-treatment hemoglobin (g/dl)*	*Post-treatment hemoglobin (g/dl)*[a]	*Response duration (months)*
M/66	Primary	Pos.	7	47,XY, +14[10]/ 94, idemx2[1]/46,XY[9]	8.2	11.3	8.3+
F/59	Primary	Pos.	1	46,XX, del(20)(q11.2q13.3) [14]/ 46,XX[1]	7.5	9.8	8.2+
M/78	Post-PV	Pos.	21	46,XY, del(20)(q11.2q13.3) [19] /46, XY[1]	Tx-dependent	9.2	7.4+
M/63	Primary	Pos.	0	46, XY[16]	Tx-dependent	9.1	12.8+
M/72	Primary	Pos.	8	46, XY[20]	Tx-dependent	9.1	12.2+
M/70	Primary	Pos.	1	46, XY[20]	Tx-dependent	9.2	9.2+
M/86	Primary	Pos.	0	46,XY, del(20)(q11.2q13.1) [1]/46,XY[29]	Tx-dependent	10	8.3+
M/51	Primary	Pos.	6	43,XY, −2, −6, −10, del(20) (q11.2q13.3)[1]/46,XY[5]	Tx-dependent	9.2	5.5[b]
F/76	Primary	Pos.	0	46, XX[30]	Tx-dependent	10.7	6.6[b]
M/61	Post-PV	Pos.	12	46,XY, del(7)(p13p15)[10]/ 46,sl,del(20)(q11.2q13.1)[9]/ 47,sd11,+8[1]	Tx-dependent	11.1	8.2+

Abbreviations: F, female, M, male, MF, myelofibrosis; Pos., positive; PV, polycythemia vera.
[a]Best hemoglobin response.
[b]Lost response.
All responses signified improvement in anemia according to the International Working Group for Myelofibrosis Research and Treatment criteria.

Discussion

The current study demonstrates the safety and therapeutic value of single agent low-dose pomalidomide in the treatment of anemia associated with *JAK2*V617F-positive MF, especially in the absence of marked splenomegaly. The latter is consistent with the lack of effect of the drug on splenomegaly and raises the prospect of combination therapy with other drugs with favorable effect on splenomegaly such as hydroxyurea or JAK inhibitors. Such an approach is specially appealing, considering the fact that low-dose pomalidomide was not myelosuppressive and might instead be associated with improved platelet count. We currently do not have a cogent explanation for the effect of *JAK2* mutational status on anemia response and the issue is further confounded by the lack of additional effect from mutant allele burden. It is possible that *JAK2*V617F-negative MF includes a disease spectrum that is biologically different than mutation-positive disease. The observation that pomalidomide response might be predicted by the presence or absence of early drug-induced basophilia carries substantial practical value and facilitates dynamic treatment decision making. Incidentally, there was no additional benefit in terms of anemia response from increasing the pomalidomide dose to 2 mg/day; this was done in 16 patients with lack of response at the 0.5 mg/day dose level. Regardless, the value of low-dose (0.5 mg/day) pomalidomide is currently being evaluated in an international phase-3 randomized study.

Conflict of interest

The authors declare no conflict of interest.

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