Long-term outcome of pomalidomide therapy in myelofibrosis

Kebede H. Begna,[1] Animesh Pardanani,[1] Ruben Mesa,[2] Mark R. Litzow,[1] William J. Hogan,[1] Curtis A. Hanson,[3] and Ayalew Tefferi[1]*

Ninety-four Mayo Clinic patients with myelofibrosis (MF) participated in two consecutive clinical trials of pomalidomide (0.5–3.5 mg/day), with or without prednisone. Overall anemia response was 27% and increased to 53% in *JAK2*V617F-positive patients with <10 cm palpable splenomegaly and <5% circulating blasts; response rate was 0% in mutation-negative patients with either ≥10 cm splenomegaly or ≥5% circulating blasts (*P* = 0.0001). Median duration of anemia response was 16 months. Treatment effect on splenomegaly was negligible. To date, pomalidomide therapy has been discontinued in 86 (91%) patients at a rate of 68% at 1 year and 89% at 2 years. Grade 1 sensory neuropathy developed in 4 (13%) of 30 patients treated for ≥1 year. Risk-adjusted survival in pomalidomide-treated primary MF patients (*n* = 72) was similar to their counterparts not exposed to the drug (*n* = 471; *P* = 0.19). Long-term follow-up of pomalidomide treatment in MF reveals palliative value for a select group of patients and treatment-emergent sensory neuropathy. Am. J. Hematol. 87:66–68, 2012. © 2011 Wiley Periodicals, Inc.

Introduction

Pomalidomide is an immunomodulatory drug that is structurally related to both lenalidomide and thalidomide [1]. All three drugs display anti-angiogenic, anti-tumor necrosis factor-α, and T cell modulatory effect, but the precise mechanism of action in vivo is poorly understood. Thalidomide [2], lenalidomide [3], and pomalidomide [4] have all been shown to have therapeutic activity in myelofibrosis (MF), including primary (PMF), post-polycythemia vera (post-PV MF), and post-essential thrombocythemia (post-ET MF). Higher doses (100–400 mg/day) of thalidomide were associated with an increased adverse drop-out rate whereas low-dose (50 mg/day) thalidomide, alone or in combination with prednisone, was better tolerated and alleviated anemia in approximately 20% of treated patients with MF [5–7]. Lenalidomide (5–10 mg/day), with or without prednisone, also alleviated anemia in a similar proportion of patients with MF [3,8,9], and was most useful in the presence of del(5q) [10]. Two recent studies reassessed treatment response using the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria [11]; one study reported up to 38% response rate for lenalidomide plus prednisone therapy [12] whereas the other study reported 28% response rate for thalidomide-based therapy [13]. However, in a prospective multi-center study [8], the combination of lenalidomide and prednisone resulted in only 19% anemia response and 23% overall response. Regardless, the use of thalidomide or lenalidomide in MF is limited by the respective occurrence of peripheral neuropathy [12] and moderate to severe myelosuppression [8], in the majority of treated patients.

We have recently communicated the short-term results of two consecutive clinical trials using pomalidomide therapy for MF [4,14,15]. The maximum tolerated dose of pomalidomide in MF was 3 mg/day (dose-limiting toxicity was myelosuppression) but doses higher than 2 mg/day were associated with more myelosuppression and other toxicities and were not necessarily more effective [15]. In a phase-2 randomized study, pomalidomide alone at 2 mg/day was shown to be as active (23% response rate), in the treatment of anemia, as prednisone plus pomalidomide at 0.5 (36% response rate) or 2 mg/day (16% response rate) [4]. In an extension of the above-mentioned phase-1 study [15], low-dose pomalidomide (0.5 mg/day), as a single agent, was given to 58 patients and induced a 17% anemia response, which was predicted by the absence of marked splenomegaly, presence of *JAK2*V617F, and lower circulating levels of monocyte chemotactic protein-1, interleukin (IL)-2R, IL-15, and IL-8 [16]. Pomalidomide treatment was also beneficial in terms of alleviating thrombocytopenia but its effect on splenomegaly was negligible. Peripheral neuropathy was mentioned in only one (2%) of 58 patients treated in one of the studies [15]. In the current study, we describe the long-term follow-up of 94 Mayo Clinic patients with MF who have participated in the aforementioned consecutive clinical trials [4,14,15], focusing on duration of treatment benefit, long-term toxicity, and survival effect.

Patients and Methods

The current study includes all Mayo Clinic patients who participated in two consecutive clinical trials using pomalidomide-based therapy for MF (*ClinicalTrials.gov Identifiers: NCT00463385 and NCT00669578*) [4,14,15]. All studies were approved by the Mayo Clinic Institutional Review Board and supported by Celgene Corporation, Summit, NJ, USA. Eligibility criteria that were common to all three studies were diagnosis of PMF, post-PV MF, or post-ET MF [17], a hemoglobin level of <10 g/dL or presence of red cell transfusion dependency and a platelet count of $\geq 20 \times 10^9$/L. Prior therapy with lenalidomide or thalidomide was allowed. Oral pomalidomide (0.5–3.5 mg/day) was administered daily in either 21-day or 28-day cycles. Response was assessed by the IWG-MRT criteria [11]. Statistical analyses were performed using Stat-View (SAS Institute, Cary, NC). Survival of pomalidomide-treated PMF patients was compared to other PMF patients from the Mayo Clinic database, after matching the two populations for disease stage according to the Dynamic International Prognostic Scoring System (DIPSS)-plus [18] and hematologic study entry criteria. Survival data were prepared by the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazard regression model was used for multivariable analysis. *P* values less than 0.05 were considered significant.

Results and Discussion

From May, 2007 to January, 2010, 94 Mayo Clinic patients with MF (73 PMF, 11 post-ET MF, and 10 post-PV MF) were enrolled in two consecutive clinical trials that

[1]Division of Hematology, Mayo Clinic, Rochester, Minnesota; [2]Division of Hematology, Mayo Clinic, Scottsdale, Arizona; [3]Division of Hematopathology, Mayo Clinic, Rochester, Minnesota

Conflict of interest: AT served as the principal investigator of the pomalidomide clinical trials and all other authors were co-investigators.

*Correspondence to: Ayalew Tefferi, MD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: tefferi.ayalew@mayo.edu

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TABLE I. Clinical and Laboratory Features of 94 Patients with Primary or Post-Polycythemia Vera/Essential Thrombocythemia Myelofibrosis at the Time of Study Entry for Treatment with Pomalidomide Alone or with Prednisone

Variables	All patients (n = 94)	Anemia responders (n = 27)	Anemia non-responders (n = 67)	P value
Age (years); median (range)	67 (37–87)	67 (43–86)	67 (37–87)	0.7
Age >65 years; *n* (%)	54 (57%)	15 (56%)	40 (60%)	0.2
Males; *n* (%)	61 (67%)	15 (56%)	46 (68%)	0.2
Myelofibrosis subtype:				
PMF/post-PV MF/post-ET MF (*n*)	73/10/11	21/4/2	52/6/9	0.5
Hemoglobin, g/dL; median (range)	8.9 (6.6–11.6)	8.8 (7.5–11.6)	8.9 (6.6–11.6)	0.8
Hemoglobin <10 g/dL; *n* (%)	94 (100)	27 (100%)	67 (100%)	0.8
Transfusion requiring; *n* (%)	73 (77%)	20 (74%)	53 (79%)	0.6
Leukocyte count, $\times 10^9$/L; median (range)	6.8 (1.5–204)	6.4 (1.6–204)	7 (1.5–180)	0.7
Leukocyte count >25 $\times$ 10^9/L; *n* (%)	11 (12%)	3 (11%)	8 (12%)	0.9
Platelets, $\times$ 10^9/L; median (range)	139 (20–1233)	118 (32–910)	154 (20–1233)	0.5
Platelets <100 $\times$ 10^9/L; *n* (%)	32 (34%)	12 (44%)	20 (30%)	0.3
Peripheral blood blast %; median (range)	1 (0–18)	1 (0–4)	1 (0–18)	0.06
PB blasts ≥1%; *n* (%)	61 (65%)	14 (52%)	47 (70%)	0.09
PB blast ≥5%; *n* (%)	10 (11%)	0	10 (15%)	0.03
Constitutional symptoms; *n* (%)	26 (28%)	5 (19%)	21 (31%)	0.2
Spleen size cm; median (range) (n = 90)	8 (0–26)	4 (0–22)	11 (0–26)	0.006
Palpable spleen size < 10 cm; *n* (%)	48 (53%)	22 (81%)	26 (41%)	0.0005
Splenectomy; *n* (%)	4 (4%)	0	4	
DIPSS-plus[a] risk group; *n* (%)				0.77
Low	0	0	0	
Intermediate-1	1	0	1	
Intermediate-2	54 (57%)	15 (56%)	39 (58%)	
High	39 (41%)	12 (44%)	27 (41%)	
*JAK2*V617F; *n* (%)	71 (76%)	23 (85%)	48 (71%)	0.16
Serum erythropoietin level, mIU/mL;				
median (range) (*n* evaluable =74)	93 (4.4–4864)	106 (4.4–1447)	86 (6–4864)	0.4
Serum erythropoietin level >100 mIU/mL; *n* (%)	34/74 (46%)	12/24 (50%)	22/50 (44%)	0.3
Cytogenetic categories (*n* evaluable = 91)				0.8
Normal	53 (58%)	16 (59%)	37 (58%)	
Favorable	25 (27%)	8 (30%)	17 (27%)	
Unfavorable[b]	13 (14%)	3 (11%)	10 (15%)	
Transplanted; *n* (%)	5 (5%)	0	5 (7%)	0.4
Deaths; *n* (%)	40 (43%)	6 (22%)	34 (51%)	0.01
Leukemic transformations, *n* (%)	6 (6%)	1 (4%)	5 (7%)	0.5

[a] DIPSS, Dynamic International Prognostic Scoring System-plus; MK, monosomal karyotype; PB, peripheral blood; WBC, white blood cell count.

[b] Unfavorable karyotype includes complex karyotype or any single or two abnormalities that includes +8, −7/7q−, −5/5q−, inv(3), i(17q), 12p−, or 11q23 rearrangement. PMF, primary myelofibrosis; PV, polycythemia vera; ET, essential thrombocythemia.

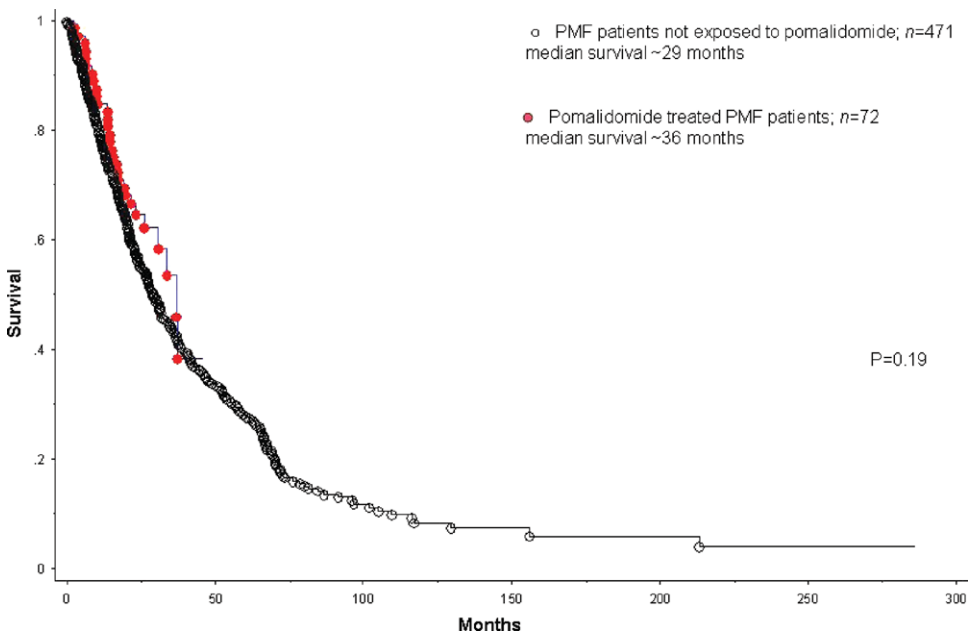

Figure 1. Comparison of survival data between 72 pomalidomide-treated patients with primary myelofibrosis (PMF) and 471 PMF patients not exposed to pomalidomide therapy. The two study populations were matched for their Dynamic International Prognostic Scoring System (DIPSS)-plus [18] risk profile (only patients with high or intermediate-2 risk disease were considered), hemoglobin and platelet counts that were consistent with study eligibility criteria (all patients had a hemoglobin level of <10 g/dL and platelet count of >20 $\times$ 10^9/L). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

included pomalidomide; 19 were enrolled in a phase-1 dose escalation study (2.5–3.5 mg/day) [14], 58 in an extension of the phase-1 study using low-dose single agent pomalidomide (0.5 mg/day) [15], and 17 in a phase-2 randomized study (2 mg/day alone or either 2 or 0.5 mg/day in combination with a short course of prednisone

therapy) [4]. Patient characteristics at study entry are outlined in Table I and additional patient and protocol details are as previously described [4,14,15]. Follow-up information was updated in August, 2011 (median time from drug initiation was 27 months; range 20–52 months). To date, pomalidomide therapy has been discontinued in 86 (91%) patients at a rate of 68% at 1 year and 89% at 2 years (median treatment duration was 7 months; range 1–32). Eight (9%) patients remained on treatment for a median duration of 34 months (range 22–51).

Overall anemia response, per IWG-MRT criteria, was 27% and was more likely to occur in the absence of marked splenomegaly defined as palpable spleen size $\geq$10 cm (46% vs. 12%; $P = 0.0005$), presence of $<$5% circulating blasts (32% vs. 0%; $P = 0.03$), or presence of *JAK2*V617F (32% vs. 17%; $P = 0.17$). Anemia response rate in the absence of marked splenomegaly, presence of $<$5% circulating blasts and absence of *JAK2*V617F was 53% compared to 21% or 0%, respectively, in the presence of one or two of the following: marked splenomegaly, $\geq$5% circulating blasts, absence of *JAK2*V617F ($P = 0.0001$). In addition, a 50% or more increase in circulating basophil count in the first month of treatment predicted anemia response ($P = 0.008$). Response was not affected by karyotype, DIPSS-plus risk profile, or leukocyte count. Median response duration was 16 months (range 2–50 months). Only one (1%) patient met IWG-MRT criteria for spleen response. Among 34 patients with baseline platelet count of $<100 \times 10^9$/L, 20 (59%) experienced a $\geq$50% increase in platelet count, which was predicted by the presence or absence of anemia response (50% vs. 14%; $P = 0.03$).

Grade 1 sensory neuropathy developed in 4 (13%) of 30 patients treated for $\geq$12 months. Symptoms were described as numbness of the hands and feet, occasionally involving lips and face. In all instances, symptoms of neuropathy first developed while patients were receiving $\geq$2 mg/day dose and onset ranged from 2 to 39 cycles into treatment. Three of the four patients with drug-induced neuropathy remained on a reduced dose (0.5 mg/day) with stable symptoms for a period of 34–45 cycles. One of these patients also experienced progressive chorea that was felt to be unrelated to pomalidomide therapy. None of the patients were previously exposed to thalidomide or lenalidomide therapy.

Risk-adjusted survival was similar in PMF patients who were ($n = 72$) or were not ($n = 471$) exposed to pomalidomide therapy (Fig. 1; $P = 0.19$). The control PMF population for the survival comparison was selected from the Mayo Clinic database of patients with PMF and the two study populations were matched for DIPSS-plus risk profiles and hematologic study eligibility criteria.

The current long-term follow-up data on pomalidomide-treated patients with MF reveals palliative value in a selected group of patients with anemia and highlights the development of treatment-emergent sensory neuropathy, whose incidence might increase with treatment duration. An ongoing placebo-controlled, phase-3 study (*ClinicalTrials.gov Identifier: NCT01178281*) is expected to further clarify the role of pomalidomide therapy in MF-associated anemia.

Author Contributions

AT and KHB designed the study, contributed patients, collected data, performed the statistical analysis and wrote the paper. AP contributed patients and participated in data analysis. RM, MRL, and WJH contributed patients. CAH reviewed histopathology. All authors approved the final draft of the paper.

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