Predictors of response to pacritinib therapy and survival among 60 Mayo Clinic patients with myelofibrosis treated outside of clinical trials

Pacritinib (PAC) is a relatively selective JAK2 (*vs*. JAK1) inhibitor (JAKi) and is one of four JAKi approved by the US Food and Drug Administration (FDA) for use in myelofibrosis (MF) with the other three being ruxolitinib, fedratinib, and momelotinib.[1] All four JAKi have been shown to reduce spleen size, alleviate symptoms, and reverse cachexia in patients with primary or secondary MF, although with variable potency and different toxicity profiles.[1] However, none of these drugs have been shown to modify the natural history of the disease or effect morphologic or molecular remissions.[2] JAKi treatment-associated improvement in MF-associated anemia has been reported for pacritinib and momelotinib while ruxolitinib and fedratinib are often associated with exacerbation of anemia.[3] The erythropoietic effect of pacritinib and momelotinib has been attributed to alleviation of ineffective erythropoiesis through inhibition of the activin A receptor type-I (ACVR1).[4]

In one of the first clinical trial reports involving PAC, 35 patients with MF were treated in a phase II study and received PAC at 400 mg once daily.[5] A ≥35% spleen volume reduction was achieved in 31% and a ≥50% reduction in total symptom score was achieved in 48% of the patients; anemia responses were not reported. Response rates reported in subsequent controlled studies were less impressive. PERSIST-1[6] included JAKi-naïve patients (N=327), regardless of baseline platelet count, and compared PAC (400 mg once daily) with best available therapy (BAT), excluding JAKi. The ≥35% reduction in spleen volume at week 24 was 19% (intent-to-treat, ITT) or 25% (in evaluable patients), and symptom response rate was 25% (ITT) and 41% (evaluable). Transfusion resolution was reported in 25% of patients. PERSIST-2[7] included JAKi-naïve and ruxolitinib-treated (48%) MF patients with platelet count <100x10^9/L (N=311) and compared PAC (400 mg once daily or 200 mg twice daily) with BAT (45% treated with ruxolitinib). The ≥35% spleen volume reduction rate at week 24 for PAC 200 mg twice daily was 22% and was lower in patients who had received ruxolitinib (13%). The corresponding response rates were 32% for ≥50% reduction in total symptom score and 25% for anemia response in patients with baseline hemoglobin level <10 g/dL.

More recent studies have painted a rosier picture regarding treatment response to PAC in patients with MF. A post-hoc analysis of PERSIST-2 suggested that 25-37% of transfusion-dependent patients achieved a ≥12-week transfusion-free period[8] and that PAC responders, as opposed to BAT responders, had a survival advantage compared to non-responders.[9] It should be noted that these observations were communicated under the full coordination of and with medical writing support from the drug companies.[9] Regadless of this, claims of erythropoietic efficacy have led to the broader use of the drug in anemic patients with MF, regardless of platelet count, although the FDA label restricts its use in patients with platelet count <50x10^9/L.[10] The current study sought to clarify the erythropoietic value of PAC in a real-world setting, and identify determinants of treatment response and survival in the context of other risk factors.

The current retrospective study was conducted under an institutional review board approved minimum risk protocol that allowed retrospective collection and analysis of data from patient records. A Mayo Clinic enterprise-wide database search for PAC-treated patients with primary or secondary MF was conducted from centers in Rochester (MN), Jacksonville (FL), and Scottsdale (ARZ), USA. Diagnostic criteria were those of the International Consensus Criteria.[11] Institutional protocols were followed in processing cytogenetic analysis and multi-gene next-generation sequencing. Treatment responses were adjudicated by the International Working Group and European LeukemiaNet (IWG-ELN)[12] and the revised IWG-ELN[13] criteria for spleen and anemia response, respectively, and measured at any time on treatment. Transfusion-dependent anemia (TDA) was defined according to the revised IWG-ENL criteria.[13] Because of the retrospective nature of the study, as well as the lack of systematic and accurate documentation, the total symptom score was not considered in the current study. Conventional statistical methods were employed for comparisons of groups and survival analysis (JMP Pro 17.0.0 software SAS Institute, Cary, NC, USA).

A total of 60 MF patients (median age 70 years, males 62%, primary MF 63%) received PAC upfront (N=19; 32%) or after failing treatment with another JAKi (N=41; 68%), including ruxolitinib (N=39; 65%). Reasons for discontinuing ruxolitinib included drug intolerance in 41% of patients, suboptimal response in 25%, and relapse after initial response 33%. The initial dose of PAC was 200 mg twice daily in 19 patients and 100 mg twice daily or once daily in 41 patients. Clinical and laboratory features at time of initiation of PAC therapy are outlined in Table 1. Driver mutations included *JAK2* (60%), *CALR* (27%), and *MPL* (10%). Other mutations, evaluable in 56 patients, included *ASXL1* (34%), *TET2* (23%), *SF3B1* (16%), *U2AF1* (13%), *IDH1* or *IDH2* (13%), *DNMT3A* (11%), and *SRSF2* (11%) (Table 1). Dynamic International Prognostic

Table 1. Clinical, laboratory, and outcome data in 60 patients with myelofibrosis, receiving pacritinib therapy outside of clinical trials, stratified by pre-pacritinib exposure to other JAK2 inhibitors.

Variables at initiation of pacritinib therapy	All patients N=60 (100%)	JAK2 inhibitor-experienced N=41 (68%)	JAK2 inhibitor-naïve N=19 (32%)	*P*
Demographics				
Median age in years (range)	70 (51-86)	71 (51-86)	69 (51-79)	0.25
Males, N (%)	37 (62)	28 (68)	9 (47)	0.12
Clinical and laboratory variables				
Transfusion dependent, N (%)	24 (40)	21 (51)	3 (16)	<0.01*
Hemoglobin <10 g/dL, N (%)	45 (75)	29 (71)	16 (84)	0.25
Platelets <50×10^9/L, N (%)	15 (25)	11 (27)	4 (21)	0.63
Leukocytosis >32×10^9/L, N (%)	10 (17)	8 (20)	2 (11)	0.37
Palpable splenomegaly >15 cm, N (%)	41 (76)	31 (82)	10 (63)	0.14
DIPSS$^+$ risk groups, N (%) High risk Intermediate-2 Intermediate-1	 29 (48) 28 (47) 3 (5)	 23 (56) 17 (41) 1 (2)	 6 (32) 11 (58) 2 (10)	0.13
Mutations and karyotype				
Unfavorable karyotype, N (%)	21 (36)	14 (35)	7 (37)	0.89
Driver mutations, N (%) *JAK2* *CALR* *MPL* Triple negative	 36 (60) 16 (27) 6 (10) 2 (3)	 28 (68) 9 (22) 4 (10) 0 (0)	 8 (42) 7 (37) 2 (10) 2 (10)	0.06
Other mutations, N (%), N evaluable = 56 *ASXL1* *TET2* *SF3B1* *U2AF1* *IDH1/2* *DNMT3A* *SRSF2*	 19 (34) 13 (23) 9 (16) 7 (13) 7 (13) 6 (11) 6 (11)	 13 (35) 7 (19) 8 (22) 6 (16) 6 (16) 4 (11) 2 (5)	 6 (32) 6 (32) 1 (5) 1 (5) 1 (5) 2 (10) 4 (21)	 0.79 0.29 0.09 0.21 0.21 0.97 0.08
High molecular risk mutations (*ASXL1/U2AF1 Q157/SRSF2*), N (%)	24 (43)	15 (41)	9 (47)	0.63
Pacritinib response and toxicity				
IWG-ELN response categories, N (%) Anemia response (N evaluable = 47) Spleen response (N evaluable = 49)	 1 (2) 9 (18)	 1 (3) 4 (11)	 0 (0) 5 (36)	 0.36 0.06
Median time in mth from pacritinib start to spleen response (range)	6 (1-9)	8 (6-9)	3 (1-6)	<0.01*
Median duration of spleen response in mth (range)	12 (2-28)	3 (2-15)	13 (2-28)	0.16
Side effects, N (%) Gastrointestinal symptoms Peripheral edema Dyspnea Neutropenia grade ≥3 Rash and swelling	 33 (55) 18 (30) 15 (25) 11 (19) 6 (10)	 23 (56) 13 (32) 10 (24) 9 (22) 1 (2)	 10 (53) 5 (26) 5 (26) 2 (11) 5 (26)	 0.80 0.67 0.87 0.3 <0.01*
Treatment-emergent thrombocytopenia grade ≥3, N (%) Pre-treatment platelet count >100×10^9/L Pre-treatment platelet count 50-100×10^9/L Pre-treatment platelet count >100×10^9/L	27 (46) 10 (37) 11 (41) 6 (22)	24 (59) 8 (33) 10 (42) 6 (25)	3 (17) 2 (67) 1 (33) 0 (0)	<0.01*
Follow-up and transplant status				
Pacritinib treatment discontinuation, N (%)	53 (88)	38 (93)	15 (79)	0.14
Median follow-up time in mth from start of pacritinib therapy (range)	19 (1-33)	19 (1-33)	19 (1-32)	0.72
Median duration of treatment with pacritinib in mth (range)	6 (1-32)	6 (1-22)	6 (1-32)	0.5
Acute myeloid leukemia transformation, N (%)	7 (12)	4 (10)	3 (16)	0.51
Allogeneic stem cell transplant, N (%)	11 (18)	7 (17)	4 (21)	0.71
Deaths, N (%)	24 (40)	19 (46)	5 (26)	0.13

DIPSS: Dynamic International Prognostic Scoring System; IWG-ELN: International Working Group and European LeukemiaNet; mth: months; N: number. *P<0.05 was considered statistically significant.

Table 2. Clinical, laboratory, and outcome data in 60 patients with myelofibrosis, receiving pacritinib therapy outside of clinical trials, stratified by spleen response.

Variables at pacritinib	All patients N=60 (100%)	Spleen responders N=9 (18%)	Spleen non-responders N=40 (82%)	*P*
Demographics				
Median age in years (range)	70 (51-86)	66 (51-75)	74 (51-86)	<0.01*
Males, N (%)	37 (62)	5 (56)	24 (60)	0.81
Clinical and laboratory				
Transfusion-dependent, N (%)	24 (40)	2 (22)	18 (45)	0.19
Hemoglobin <10 g/dL, N (%)	45 (75)	5 (56)	31 (78)	0.20
Platelets <50×10^9/L, N (%)	15 (25)	2 (22)	10 (25)	0.86
Leukocytosis >32×10^9/L, N (%)	10 (17)	0 (0)	7 (18)	0.08
Palpable spleen >15 cm, N (%)	41 (76)	7 (78)	30 (77)	0.96
Mutations and karyotype				
Unfavorable karyotype, N (%)	21 (36)	1 (11)	15 (38)	0.09
Driver mutations, N (%) *JAK2* *CALR* *MPL* Triple negative	 36 (60) 16 (27) 6 (10) 2 (3)	 6 (67) 2 (22) 0 (0) 1 (11)	 25 (63) 10 (25) 5 (12) 0 (0)	0.14
Other mutations, N (%), N evaluable = 56 *ASXL1* *TET2* *SF3B1* *U2AF1* *IDH1/2* *DNMT3A* *SRSF2*	 19 (34) 13 (23) 9 (16) 7 (13) 7 (13) 6 (11) 6 (11)	 1 (13) 1 (13) 0 (0) 1 (13) 0 (0) 0 (0) 1 (13)	 16 (43) 8 (22) 7 (19) 5 (13) 6 (16) 5 (13) 3 (8)	 0.08 0.54 0.08 0.94 0.11 0.15 0.7
High molecular risk mutations (*ASXL1/U2AF1 Q157/SRSF2*), N (%)	24 (43)	2 (25)	18 (49)	0.21
Pacritinib response and toxicity				
IWG-ELN response categories, N (%) Anemia response (N evaluable = 47) Symptoms response (N evaluable = 58)	 1 (2) 14 (24)	 0 (0) 7 (78)	 1 (3) 5 (12)	 0.56 <0.01*
Side effects, N (%) Gastrointestinal symptoms Peripheral edema Dyspnea Neutropenia grade ≥3 Rash and swelling	 33 (55) 18 (30) 15 (25) 11 (19) 6 (10)	 3 (33) 3 (33) 1 (11) 2 (22) 2 (22)	 28 (70) 14 (35) 10 (25) 6 (15) 4 (10)	 0.04* 0.92 0.34 0.61 0.35
Treatment-emergent thrombocytopenia grade ≥3, N (%) Pre-treatment platelet count <50×10^9/L Pre-treatment platelet count 50-100×10^9/L Pre-treatment platelet count >100×10^9/L	27 (46) 10 (37) 11 (41) 6 (22)	2 (22) 2 (22) 0 (0) 0 (0)	21 (53) 4 (21) 2 (11) 13 (68)	0.09
Follow-up and transplant status				
Pacritinib treatment discontinuation, N (%)	53 (88)	5 (56)	37 (92)	0.01*
Median follow-up time from start of pacritinib therapy in mth (range)	19 (1-33)	22 (6-32)	19 (1-33)	<0.01*
Median duration of treatment with pacritinib in mth (range)	6 (1-32)	17 (6-23)	6 (1-32)	0.051
Acute myeloid leukemia transformation, N (%)	7 (12)	1 (11)	6 (15)	0.76
Allogeneic stem cell transplant, N (%)	11 (18)	2 (22)	4 (10)	0.34
Deaths, N (%)	24 (40)	1 (11)	18 (45)	0.04*

IWG-ELN: International Working Group and European LeukemiaNet; mth: months; N: number. *P<0.05 was considered statistically significant.

Scoring System (DIPSS)[14] risk distribution was high (48%), intermediate-2 (47%), and intermediate-1 (5%). Unfavorable karyotype[15] was noted in 36%. At the time of PAC treatment initiation, 40% of the patients displayed TDA, 25% a platelet count <50x10^9/L, and 76% palpable splenomegaly >15 cm below the left costal margin. In most instances, presenting features were similar between patients with or without pre-PAC exposure to JAKi (Table 1).

Initial PAC dosing was 100 mg twice or once daily (N=41) or 200 mg twice daily (N=19). PAC dose was increased in 44% of patients who had started at 100 mg twice or once daily and decreased in 55% of those who had started at 200 mg twice daily. Median duration of treatment with PAC was six months (range, 1-32). Among 47 patients evaluable for anemia response, including 23 with non-TDA and 24 with TDA, only one (2%), receiving 200 mg twice daily, responded; none of the patients with TDA responded. Forty-nine patients were evaluable for spleen response, achieved in 9 (18%) patients, including 5 (36%) of 14 who were JAKi-naïve and 4 (11%) of 35 JAKi-treated (P=0.06) cases. Spleen responses were less likely in older patients (10% *vs*. 33% ≥70 years *vs*. <70 years; P=0.04) and in those with marked leukocytosis (0% *vs*. 21% in patients with *vs*. without leukocyte count ≥20x10^9/L; P=0.02) or higher DIPSS scores (4% *vs*. 23% *vs*. 100% in DIPSS high, intermediate-2, and intermediate-1 risk disease, respectively; P<0.01). Although not significant, unfavorable karyotype (6% *vs*. 25%; P=0.09) or *ASXL1* (6% *vs*. 25%; P=0.08), DNMT3A (0% *vs*. 20%; P=0.15), *SF3B1* (0% *vs*. 21%; P=0.08), or *IDH1/IDH2* (0% *vs*. 21%; P=0.11) mutations were associated with inferior spleen response; spleen response rates were 60% (6 of 10 patients) *versus* 5.7% (2 of 35 patients) in the absence *versus* presence of any one of these risk factors. Initial PAC dose level of 100 mg twice daily (N=29; response rate 14%) *versus* 200 mg twice daily (N=15; response rate 20%) *versus* 100 mg once daily (N=5; response rate 40%) did not appear to affect spleen response rate (P=0.42), as was the case for instances of dose increments (P=0.96) or dose reductions (P=0.7) (Table 2).

At a median follow-up of 19 months (range 1-33), PAC was discontinued in 88% of the patients due to intolerance (58%), suboptimal response (54%), or transition to allogeneic stem cell transplant (ASCT) (10%). Treatment-emergent adverse events (TEAE) were more frequent with the 200 mg *versus* the 100 mg twice daily dose schedule (Table 1). Grade 3/4 neutropenia occurred in 22% and thrombocytopenia in 46%, including 22% in patients with baseline platelet count >100x10^9/L and 41% in those with baseline counts of 50-100x10^9/L (Table 1). Up to the time of writing, 24 (40%) deaths, 11 (18%) ASCT, and 7 (12%) leukemic transformations have been documented. The overall 12-month post-PAC survival was 78%, including 80% in JAKi-naïve and 73% in JAKi-treated cases. In multivariable analysis, TDA (Hazard Ratio [HR] 7.8; 1.7-35.4), leukocyte count ≥32x10^9/L (HR 7.0; 2.1-23.4), platelet count <50x10^9/L (HR 6.4; 1.7-24.6), and HMR mutations (HR 6.6; 1.6-26.1) were identified as independent risk factors for transplant-censored post-PAC survival; significance was not reached for age (P=0.97), gender (P=0.37), pre-treatment palpable spleen size >15 cm (P=0.97), spleen response to PAC (P=0.41), unfavorable karyotype (P=0.47), or JAKi-naïve *versus* JAKi-treated cases (P=0.69). Similar results were apparent during multivariable analysis of survival that was not censored for trans-

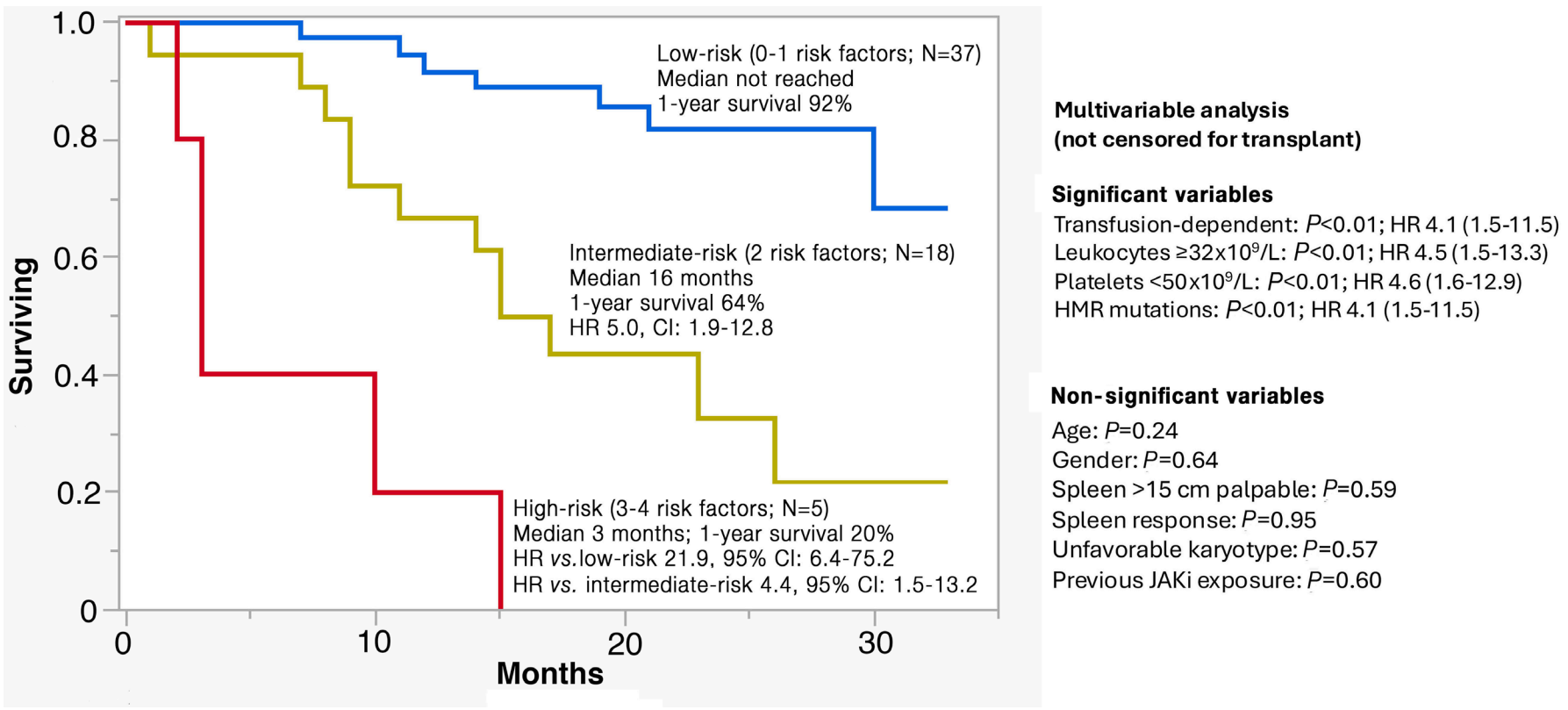

Figure 1. Post-pacritinib survival data among 60 patients with myelofibrosis. Analysis was not censored for transplant and 68% had received another JAK2 inhibitor therapy prior to starting treatment with pacritinib. Risk factors: 1) transfusion-dependent anemia; 2) leukocytes ≥32x10^9/L; 3) platelets <50x10^9/L; 4) high molecular risk (HMR) mutations including *ASXL1, SRSF2* or *U2AF1Q157*. CI: Confidence Interval; HR: Hazard Ratio; JAKi: JAK inhibitor; N: number.

plant (Figure 1). A working risk model that was based on the presence or absence of the aforementioned four risk factors resulted in three risk categories with significantly different survival outcome (Figure 1): low (N=37; median not reached), intermediate (N=18; median 16 months), and high (N=5; median 3 months). Median post-PAC survival in patients previously exposed to ruxolitinib (N=39) was 26 months and no statistical difference was observed when this was stratified according to causes of ruxolitinib discontinuation (*P*=0.3).

Despite recent reports on the drug's mechanistically unique erythropoietic activity,[4,8] the anemia response rate seen with PAC in the current real-world study of MF patients was underwhelming; only one (2.4%) of 41 JAKi-treated and none of 19 JAKi-naïve patients met the revised IWG-MRT criteira for anemia response. Clinically-vetted spleen response rate was higher (18%) and notably predicted by the presence or absence of specific clinical (e.g., marked leukocytosis) or molecular (e.g., HMR mutations) features. Predictors of response also influenced post-PAC survival and fully accounted for the apparent survival advantage for treatment responders, observed in univariate analysis. Taken together, these observations raise questions regarding the current therapeutic role of PAC in MF, in the context of currently available and arguably more potent alternatives, which, incidentally, might also be safe to use in thrombocytopenic patients, with dose adjustments.[16] At the same time, the high-risk nature of cytopenic patients with MF should be recognized and might have contributed to the poor treatment results seen in the current study. Regardless of this, our observations underscore the need to account for other risk factors before evaluting survival according to treatment response.

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Contributions

MA and AT designed the study, collected data, performed the analyses, and wrote the paper. JMP, AAK, MH, JF, KHB, CYAY, AP, NG and AT participated in patient care. All authors reviewed the final draft of the paper.

Data-sharing statement

Please email the corresponding author.

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