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Outcomes of patients with myelofibrosis treated with compassionate use pacritinib: a sponsor independent international study

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Abstract

Myelofibrosis (MF) is a chronic yet progressive myeloid neoplasm in which only a minority of patients undergo curative therapy, hematopoietic stem cell transplantation. Ruxolitinib, a JAK1/2 inhibitor, is the lone therapy approved for MF, offering a clear symptom and spleen benefit at the expense of treatment-related cytopenias. Pacritinib (PAC), a multi-kinase inhibitor with specificity for JAK2, FLT3, and IRAK1 but sparing JAK1, has demonstrated clinical activity in MF with minimal myelosuppression. Due to an FDA-mandated full clinical hold, the randomized phase 3 PERSIST trials were abruptly stopped and PAC was immediately discontinued for all patients. Thirty-three patients benefitting from PAC on clinical trial prior to the hold were allowed to resume therapy on an individual, compassionate-use basis. This study reports the detailed outcomes of 19 of these PAC retreatment patients with a median follow-up of 8 months. Despite a median platelet count of $49 \times 10^9/L$ at restart of PAC, no significant change in hematologic profile was observed. Grade 3/4 adverse events of epistaxis (n=1), asymptomatic QT prolongation (n=1) and bradycardia (n=1) occurred in 3 patients within the first 3 months of re-treatment. One death due to catheter associated sepsis occurred. The median time to discontinuation of PAC therapy on compassionate use for all 33 patients was 12.2 (95% CI: 8.3 - NR) months. PAC retreatment was associated with modest improvement in splenomegaly without progressive myelosuppression and supports the continued development of this agent for the treatment of MF second line to ruxolitinib or in the setting of treatment-limiting thrombocytopenia.

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Keywords

Myelofibrosis; pacritinib; JAK inhibitor

Background

Myelofibrosis (MF) is a clonal hematopoietic malignancy characterized by progressive splenomegaly, debilitating systemic symptoms, and limiting cytopenias often requiring transfusion support (1). Hyperactivity of the JAK-STAT signaling pathway is the unifying pathobiological theme of this molecularly heterogeneous disease (2). Ruxolitinib (Jakafi, Incyte) is the only therapy approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for MF, and the majority of patients benefit from symptom improvement and spleen reduction, at the expense of myelosuppression (3, 4). Although ruxolitinib was a major milestone in drug development for MF, this therapy does not effectively induce pathologic and molecular remissions, and therefore, disease progression can occur in treated patients (5). Outcomes in this population are dismal with a median survival after ruxolitinib discontinuation of 14 months, and even worse for those with a platelet count $<100 \times 10^9/L$ at the time of discontinuation (6).

Pacritinib (CTI Biopharma) is an oral multi-kinase inhibitor with selectivity against JAK2, FLT3, and IRAK1 (7). Pacritinib (PAC) was evaluated in two multi-centered, randomized, phase 3 trials in patients with advanced myelofibrosis (MF). The PERSIST-1 trial enrolled patients with MF irrespective of baseline platelet count and without previous exposure to ruxolitinib (8). These patients were randomized in a 2:1 fashion to PAC 400 mg daily versus best available therapy (BAT), excluding ruxolitinib. The primary endpoint of 35% or greater spleen volume reduction (SVR) at 24 weeks of therapy was superior in the PAC arm compared to BAT, 19.1% versus 4.7%. The PERSIST-2 trial included MF patients with baseline thrombocytopenia ($<100 \times 10^9/L$) and palpable splenomegaly and compared PAC at doses of 200 mg twice daily and 400 mg once daily to BAT including ruxolitinib (9). The co-primary endpoints of SVR and total symptom score (TSS) reduction for the combined PAC twice daily and once daily arms compared to BAT were not significant ($p=0.001$ for SVR and 0.079 for TSS) but were significant when assessing the PAC 200 mg twice daily cohort compared to BAT, (SVR: 21.6% vs 2.8%; $p<0.007$ and TSS: 32.4% vs 13.9%, $p<0.011$).

On February 9, 2016, a full clinical hold was placed on PAC due to concerns by the FDA surrounding an OS detriment focused on increased bleeding and cardiovascular events based upon the interim analyses of PERSIST-2 and consistent with the results from PERSIST-1. Shortly after the full hold order, the FDA allowed patients who were benefiting from PAC therapy, based on investigator assessment, to enroll in single patient compassionate use protocols. The hold was lifted on January 5, 2017 after review of the complete data set from PERSIST-2 and on acceptance of a dose searching protocol (PAC 203; ClinicalTrials.gov Identifier: NCT03165734) for patients with MF who failed to benefit from ruxolitinib.

Due to this hold, immediate cessation of PAC therapy was mandated for all patients enrolled on clinical trials. This abrupt discontinuation of PAC therapy prevented appropriate study

follow up, and the experience of patients that resumed PAC on a compassionate care (CC) basis has not been reported. We conducted a sponsor-independent analysis of the outcomes of patients treated with CC-PAC after withdrawal from therapy on clinical trial.

Methods

This study was conducted in accordance with the declaration of Helsinki and each participating center obtained approval from their institutional review board prior to data collection. Only patients enrolled in the CC-PAC single patient investigational new drug (IND) program through the FDA were included in this retrospective study. Patients treated with CC-PAC were additionally required to be monitored for bleeding and cardiac treatment emergent adverse events at baseline and every three months on therapy with a complete blood count, coagulation profile, electrocardiogram and echocardiogram (or multi-gated acquisition scan). The local treating physician provided the requested data in a paper case report form (CRF) and this was entered centrally (Mount Sinai) into an electronic database. Additional analysis to determine the probability of remaining on CC-PAC were performed on the de-identified follow-up data of the entire cohort of patients treated on the compassionate care program. This data was provided courtesy of CTI Biopharma but analyzed independently by the authors.

Statistical analyses were performed with the SAS Version 9.4 (SAS Institute Inc., Cary, North Carolina) software package. Continuous patient-related, disease-related, and treatment-related variables were summarized by median [Q1–Q3] while categorical variables were summarized by N (%). The method of Kaplan-Meier was used to estimate the overall survival (OS), follow-up and CC-PAC exposure distributions while taking into account censored observations. Linear mixed models of natural log transformed lab values (WBC, hemoglobin, platelet and spleen length) were used to compare geometric means of values over time.

Results

CRFs were completed on a total of 19 of 33 patients receiving CC-PAC from 7 centers in 2 countries (U.S. and New Zealand). The baseline demographics of these patients at the start of initial PAC therapy on the PERSIST clinical trial program are shown in Table 1. This was predominantly an advanced MF population with splenomegaly and a measurable symptom burden by the TSS. Approximately 20% of PAC treated patients at baseline had received previous ruxolitinib therapy and 40% were red blood cell transfusion-dependent.

The median duration of PAC therapy on clinical trial prior to the clinical hold was 8.5 months (range, 3.6–11.1). A median duration of 4 months (range, 1.8–14.8) occurred between stopping PAC on clinical trial due to the FDA hold and initiating CC-PAC. Five of the 19 patients received an alternative MF therapy in the interim prior to starting CC-PAC [ruxolitinib 5 mg twice daily n=2; hydroxyurea n=2, decitabine n=1].

The baseline demographics of these patients at the start of CC-PAC therapy are shown in Table 2. All 19 patients included in this analysis received CC-PAC at 200mg BID. The median duration of follow up in this CC-study was 8 months (range, 3–9.5), and median

duration of CC-PAC exposure was 8 months (range, 0.4–9.5). This was computed as months to stopping CC-PAC therapy (either by completing full 9 months or discontinuing prior to 9 months). Patients were censored if they were not followed for full 9 months of study either because they started therapy less than 9 months ago or were lost to follow up (Figure 1; Table 5).

There was a significant difference between mean palpable spleen length at month 3 (11.3 cm) and 6 (12.1 cm) compared to baseline (14.3 cm) [$p=0.0009$]. At 6 months of therapy in 15 patients, there was no significant change from baseline in hematologic parameters (Table 3). At months 3, 6, and 9 there were 44%, 47%, and 50% of patients, respectively, experiencing at least one treatment emergent adverse event regardless of attribution and these were almost exclusively grade 1/2 (Table 4). Three patients experienced grade 3 adverse events of epistaxis, QT prolongation, and bradycardia. There were no clinically significant treatment emergent changes in echocardiogram findings in any of the treated patients.

Seven patients discontinued treatment with CC-PAC for reasons that included: sepsis/death ($n=1$), disease progression/acute myeloid leukemia ($n=2$), lack of efficacy ($n=1$), surgery for ovarian cancer ($n=1$), patient decision ($n=1$), and physician decision ($n=1$). There were no dose holds or modifications while on CC-PAC. One patient died while on CC-PAC from complications of a central line associated bacterial infection. The 9-month probability of survival was 94% (CI, 63–99%).

Duration of treatment was available for the entire cohort of 33 patients treated on the compassionate use protocol (Courtesy of CTI Biopharma). Median time to discontinuation of CC-PAC was 12.2 (95% CI: 8.3 - NR) months. The probability of remaining on CC-PAC at 6, 12, and 18 months was 75%, 54%, and 42%, respectively (Figure 2).

Discussion

PAC therapy is associated with spleen and symptom improvement in patients with MF regardless of prior ruxolitinib treatment (PERSIST-2), and subset analyses of this prior ruxolitinib exposure population confirms activity in these patients (manuscript in preparation). This analysis of the outcomes of patients previously treated with PAC on clinical trial, who were then transitioned to compassionate use after mandatory study discontinuation, is the first report of the real-world experience of PAC therapy in MF. In a population of patients with advanced MF, the current study did not identify any significant treatment-emergent adverse events. Moreover, there was modest improvement in palpable spleen length over the duration of CC-PAC treatment. The median time on PAC for the full 33 patients treated on the compassionate care protocol was approximately 1 year, with 42% still on treatment for over 18 months. Despite PAC treatment interruption of a median of 4 months, and a median PAC treatment on clinical trial of 8.5 months, half the patients continued to receive PAC treatment for an additional 12 months on CC-PAC. This corresponds to approximately 24 months (20 months of cumulative PAC therapy) since start of PAC on clinical trial which appears favorable compared to the reported median survival of 14 months after ruxolitinib discontinuation (6).

Limitations of this retrospective study include short follow up, absence of standardized patient reported outcome (PRO) for symptom burden and objective radiographic assessment of change in spleen volume. There were also significant gaps between treatment on trial and the start CC-PAC. It is unclear how this interruption in JAK inhibitor therapy may have affected efficacy of PAC and the overall outcomes in this analysis. Additionally, the inclusion of a control population of patients that discontinued PAC therapy on clinical trial and then received alternative agents to CC-PAC would have allowed for a relevant comparator of outcomes. Nevertheless, PAC was well tolerated in the CC setting and significant bleeding events were uncommon with only a single patient experiencing grade 3 epistaxis. These results demonstrate safety and efficacy of PAC outside of a formal clinical trial context and confirm the unmet need for PAC in patients with MF and thrombocytopenia where alternative therapeutic options including ruxolitinib are limited.

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Figure 1. Duration of Pacritinib Treatment on Compassionate Care Program and Reasons for Discontinuation

Duration of treatment in months for the 19 individual patients detailed in this report. Patients remaining on treatment at the time of this analysis and patients that had discontinued are indicated by color and the reasons for discontinuation are shown in the key.

Figure 2. Kaplan-Meier Estimation of the Time to Discontinuation of Pacritinib in Patients in the Compassionate Use Program
Median time to discontinuation is estimated at 12.2 (95% CI: 8.31 – NA) months in 33 patients receiving pacritinib on a compassionate basis after initially stopping pacritinib treatment on clinical trial due

Table 1

Baseline Demographics at Entry on PERSIST-2, N=19

Age, median [q1–q3]	71 [64–74]
Male	10 (53%)
MF Diagnosis	
Primary-MF	11 (58%)
PPV-MF	6 (32%)
PET-MF	2 (11%)
Genotype	
<i>JAK2</i> ^{V617F} positive	11 (58%)
MPLW515L/K	1 (5%)
CALR Exon 9 Insertion/Type 1	1 (5%)
CALR Exon 9 Insertion/Type 2	0 (0%)
Triple Negative	6 (32%)
% VAF, median [q1–q3]	36.6 [8.0–50.0]
Number of MF Directed Therapies prior to Pacritinib, median [q1–q3]	1 [1–1]
Received Prior Ruxolitinib	4 (21%)
Duration of Ruxolitinib therapy (months), median [q1–q3]	7.5 [2–18]
Transfusion Dependent Prior to pacritinib	
Yes	7 (37%)
No	11 (58%)
Unknown	1 (5%)
WBC (10³/μl), median [q1–q3]	6.9 [3.4–15.0]
Hemoglobin (g/dL), median [q1–q3]	10.2 [8.7–11.3]
Platelet (10³/μL), median [q1–q3]	49.0 [33.0–85.0]
Spleen length by palpation (cm), median [q1–q3]	14.0 [9.0–18.0]
TSS, median [q1–q3]	15.6 [8.6–23.4]
DIPSS risk category	
Int-1	4 (21%)
Int-2	9 (47%)
High	5 (26%)
Unknown	1 (5%)

Range: [q1 q3]

Data expressed as n (%) unless otherwise stated

Table 2

Baseline Demographics at Entry on Compassionate Care Pacritinib, N=19

Interim MF Directed Therapies	
Yes	5 (26%)
No	14 (74%)
<hr/>	
WBC ($10^3/\mu\text{L}$), median [q1–q3]	6.2 [3.2–17.6]
<hr/>	
Hemoglobin (g/dL), median [q1–q3]	9.9 [8.7–12.2]
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Platelet ($10^3/\mu\text{L}$), median [q1–q3]	49.0 [37.0–63.0]
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Spleen length by palpation (cm), median [q1–q3]	15.0 [8.0–18.0]
<hr/>	
Ejection Fraction%, median [q1–q3]	62 [59–65]
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Transfusion Dependent	
Yes	9 (47%)
No	10 (53%)

Range: [q1–q3]

Data expressed as n (%) unless otherwise stated

Table 3

Hematologic and spleen parameters over time on Compassionate Care Pacritinib, N=19

	Baseline	3 Months	6 Months	9 Months
	N=19	N=17	N=15	N=6
WBC ($10^3/\mu\text{L}$)				
Median[q1–q3]	6.2 [3.2–17.6]	7.8 [4.3–9.5]	8.0 [4.3–15.4]	8.1 [1.5–26.5]
Min-Max	1.1–102.6	1.0–21.1	1.2–51.2	1.3–31.9
Mean [SD] *	8.3 (3.2)	6.5 (2.1)	7.0 (2.8)	6.9 (3.9)
Hemoglobin (g/DL)				
Median[q1–q3]	9.9 [8.7–12.2]	10.1 [8.5–11.7]	9.9 [8.7–12.5]	12.3 [9.7–14.0]
Min-Max	7.4–15.6	6.3–14.3	8.1–14.3	8.0–14.1
Mean [SD] *	10.1 (1.2)	9.8 (1.3)	10.3 (1.2)	11.5 (1.3)
Platelet ($10^3/\mu\text{L}$)				
Median[q1–q3]	49.0 [37.0–63.0]	49.0 [39.0–103.0]	57.0 [34.0–118.0]	62.5 [40.0–105.0]
Min-Max	19.0–312.0	17.0–287.0	23.0–245.0	19.0–194.0
Mean [SD] *	54.1 (2.0)	59.1 (2.2)	60.9 (2.1)	62.2 (2.2)
Spleen length by palpation (cm)				
N	19	14	12	4
Median[q1–q3]	15.0 [8.0–18.0]	11.0 [7.0–17.0]	13.5 [7.0–17.0]	17.0 [8.0–20.5]
Min-Max	0–36	0–24	0–23	0–23
Mean (SD)	14.3 (8.4)	11.4 (6.7)	12.1 (7.2)	14.3 (9.9)

Data expressed as median [range] unless otherwise stated; range: [q1–q3]

* Geometric Mean and SD provided due to skewness of distribution and inappropriate use of arithmetic mean

Table 4Treatment-Emergent Adverse Events of Interest on Compassionate Care Pacritinib by grade, N=18¹

	At Any Grade	At Grade 3 or 4
All events	10 (56%)	3 (17%)
Bleeding events	3 (17%)	1 (6%)
Epistaxis	2 (11%)	1 (6%)
Hematemesis	1 (6%)	0 (0%)
Cardiovascular events	2 (11%)	2 (11%)
QT Prolongation	1 (6%)	1 (6%)
Bradycardia ²	1 (6%)	1 (6%)
Assessment Period		
3-month events (N=18)	8 (44%)	3 (17%)
6-month events (N=15)	7 (47%)	0 (0%)
9-month events (N=6)	3 (50%)	0 (0%)

¹ one patient did not have AEs evaluated yet² with premature atrial contractions

Data expressed as # (%) of patients experiencing at least 1 AE overall and at each assessment

Table 5

Overall Survival and Duration of Compassionate Care Pacritinib Exposure, N=19

Overall Survival	
Deaths, n (%)	1 (5%)
9-month survival probability (95% CI)	0.94 (0.63, 0.99)
CC-PAC Exposure	
Discontinued CC-PAC therapy within 9 months [*] , n (%)	7 (37%)
Completed CC-PAC therapy 9 months, n (%)	6 (31.5%)
Censored for CC-PAC exposure, n (%)	6 (31.5%)
Median CC-PAC Exposure in months (95% CI)	8.3 (6.9–9.1)

^{*} discontinued Pacritinib by 9 months of start of PAC Compassionate Care for any reason