A retrospective analysis of pacritinib treatment outcomes in myelofibrosis patients with and without monocytosis

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CONCLUSIONS

- While monocytosis in MF is not a cardinal finding, it is present in a sizable minority of patients and is a known predictor of poor outcomes in MF. By contrast, outcomes with pacritinib do not appear inferior in MF patients with monocytosis compared to those without.
- Given this, and the dire need for new therapies for chronic myelomonocytic leukemia (CMML), particularly the proliferative type (MP-CMML), these data provide rationale to study pacritinib in patients with CMML, which is actively being planned.

INTRODUCTION

- While sustained monocytosis has been described as a high-risk feature in patients with MF[1], it is also a core diagnostic component for CMML.
- The presence of driver mutations such as JAK2V617F, bone marrow fibrosis, and extramedullary hematopoiesis can be seen in both entities.
- Pacritinib is a JAK2 inhibitor approved for MF, and also has potency in the inhibition of CSF1R and IRAK1[2], both which are kinases upregulated in CMML.
- While pacritinib has not yet been tested in CMML, it has shown preclinical activity in murine CMML models.[3]
- As MF and CMML occur along a clinical spectrum, treatment outcomes in patients with MF with monocytosis might inform therapies in CMML.

AIM

- To retrospectively analyze clinical outcomes of MF patients with vs without monocytosis treated with pacritinib across two phase 3 studies (PERSIST-1 and PERSIST-2).

METHODS

- Patients treated with pacritinib on the PERSIST-1 (JAK-inhibitor naïve) and PERSIST-2 (JAK-inhibitor naïve or ruxolitinib refractory with platelets ≤100 x 10^9/L) trials were included.
- Patients were stratified based on the presence (≥10% monocytes and absolute monocyte count ≥0.5x10^9/L) or absence of baseline monocytosis.
- Week 24 efficacy outcomes were analyzed in the intention-to-treat-efficacy population randomized ≥22 weeks prior to study termination and included spleen volume response (SVR), Total Symptom Score (TSS) response, and Patient Global Impression of Change (PGIC).
  - Only patients who completed the Myeloproliferative Neoplasm-Symptom Assessment Form (MPN-SAF) TSS version 2.0 were included.
- Transfusion independence response (TI-R) was assessed among patients requiring RBC transfusion at baseline (assessed within 90 days prior to baseline), with response defined as the absence of RBC transfusions over any 12-week period through 24 weeks (Gale criteria)
- Change in hemoglobin and monocytes over time was determined for those patients with monocytosis
- Data is summarized using descriptive statistics such as mean, median and quartiles for continuous endpoints and count and percent for categorical endpoints.

RESULTS

Baseline characteristics

- At baseline, 35 patients (8%) had monocytosis and 395 patients did not.
- The two groups were similar in age, sex, JAK-inhibitor naïve, and JAK2V617F positive (**Table 1**).
- Median white blood cell count was higher in patients with monocytosis than those without, while median platelet count was lower in patients with monocytosis compared to those without (**Table 1**).

Table 1. Patient Characteristics

Baseline characteristics	Patients with monocytosis N=35	Patients without monocytosis N=395
Age, median years	70	67
Males, n (%)	22 (62.9)	218 (55.2)
DIPSS high risk, n (%)	10 (28.6)	81 (20.5)
Platelet count, x10^9/L, median	64	89
Hemoglobin, g/dL, median	9.7	10.0
WBC, x 10^9/L, (median, IQR)	11.8 (6.0, 32.4)	8.9 (4.8, 20.0)
JAK-inhibitor naïve, n (%)	23 (65.7)	304 (77.0)
JAK2V617F positive, n (%)	26 (74.3)	288 (72.9)
Spleen length, cm, median	13	13
Spleen volume, cm^3, median	2662.9	2167.3

DIPSS, Dynamic International Prognostic Scoring System; WBC, white blood cell; IQR, interquartile range

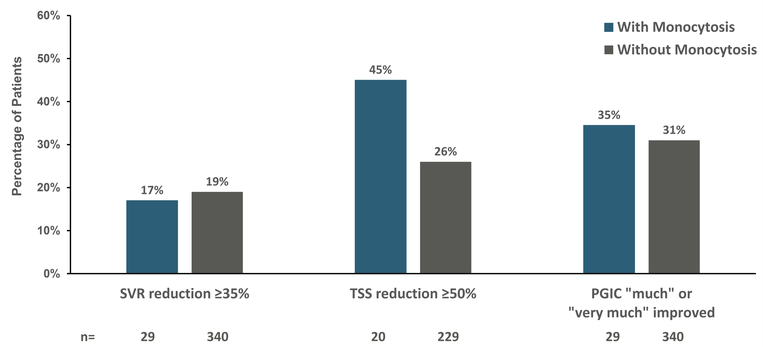
Treatment Duration

- Average treatment duration was 9.75 months for patients with monocytosis compared to 11 months for those without.

Similar Efficacy With and Without Monocytosis

- The percentage of patients achieving SVR ≥35% and PGIC responses of "much" and "very much" improved at week 24 were similar between the groups. (**Figure 1**).
- TSS response rate in patients with monocytosis was higher but did not reach statistical significance (*P*=0.103).

Figure 1. Percentage of Patients Achieving Efficacy Outcomes



SVR, spleen volume response; TSS, total symptom score (version 2.0, excluding tiredness); PGIC, Patient Global Impression of Change

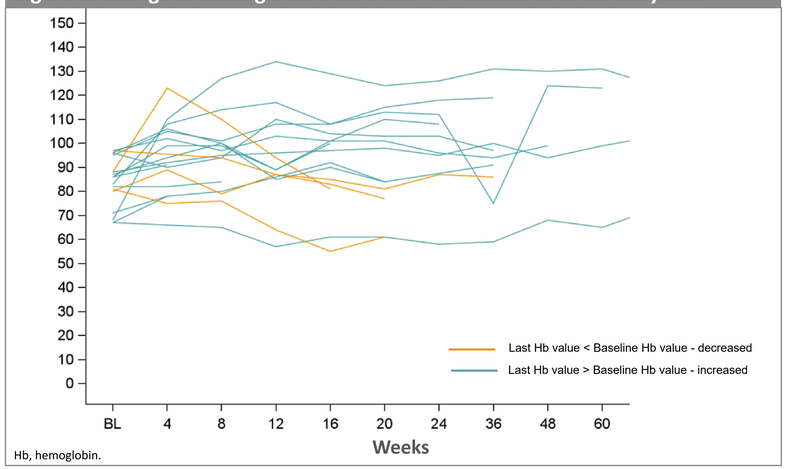
Median Reduction of Spleen Volume and Symptom Burden

- The median reduction in spleen volume was similar in those with monocytosis (19%) and those without monocytosis (23%).
- The response rate for symptom burden in those with monocytosis corresponded to a median 55% reduction in symptom score compared to 35% in those who did not have monocytosis.

Anemia Benefit in Patients with Monocytosis

- Among the 16 patients on pacritinib with monocytosis who received RBC transfusions at baseline, 50% (n=8) of patients achieved TI-R.
- Among the 34 patients on pacritinib with monocytosis and who had hemoglobin <10 g/dL at baseline, 22.2% of patients had an increase of 1.5 g/dL of hemoglobin and 11.1% had ≥2 g/dL increase.
- Many of the patients with monocytosis on pacritinib (14 out of 18) experienced stabilization or an increase in hemoglobin levels over time (**Figure 2**).

Figure 2. Change in Hemoglobin Over Time for Patients with Monocytosis



Hb, hemoglobin.

Reduction of Monocytes with Pacritinib

- Median percent change from baseline to week 24 for absolute monocyte count in the pacritinib-treated patients with monocytosis (n=16) was -72.5 (interquartile range: -87.3, -0.2).

Safety

- The rates of treatment emergent serious adverse events (~50% in each group) and treatment emergent adverse event leading to drug discontinuation (26% in the with monocytosis group vs 20% without) were not significantly different between the groups, suggesting no signal for safety specific to the presence of monocytosis.

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