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Real-World Dosing Patterns of Ruxolitinib in Patients With Polycythemia Vera Who are Resistant to or Intolerant of Hydroxyurea

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Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm affecting >100,000 people in the United States (US) annually[1]
- Patients with PV are at risk for thromboembolic events (TEs), premature death, and high symptom burden[2,3]
- Hydroxyurea (HU) is recommended for high-risk patients with PV[4]; however, up to 40% of patients become resistant and/or intolerant to HU[5]
- Ruxolitinib, a Janus kinase (JAK) 1/JAK2 inhibitor, is currently the only FDA-approved treatment option for patients with PV who are resistant to or intolerant of HU[6]

Objectives

- To characterize the reasons patients with PV were switched from HU to ruxolitinib and to describe real-world dosing patterns of ruxolitinib in these patients

Methods

Study Design and Patients

- This retrospective medical chart review was conducted at US community hematology/oncology practices in the Cardinal Health Oncology Provider Extended Network
- Eligible patients were ≥18 years old, initiated ruxolitinib therapy during the index period (January 1, 2015, to December 31, 2016), were treated with HU for ≥3 months prior to the initiation of ruxolitinib, and had ≥2 follow-up visits during the 6 months following the initiation of ruxolitinib
- Patients who had received any cytoreductive treatment other than HU prior to ruxolitinib, or who had received any cytoreductive treatment in combination with ruxolitinib, were excluded

Data Collection

- Data were collected for the 12 months prior to ruxolitinib initiation, including at the time of HU discontinuation, at the time of ruxolitinib initiation (index), and up to the last provider visit
- Demographic and clinical characteristics were collected, including blood counts, symptoms, TEs, cardiovascular disease risk factors, phlebotomy, and HU and ruxolitinib treatment patterns

Statistical Analyses

- Descriptive statistics were utilized for analysis; frequencies and percentages were reported for categorical variables; mean, SD, median, and interquartile range (IQR) values were calculated for continuous variables

Results

Patient Characteristics

- Providers identified 249 patients for inclusion **(Table 1)**; mean (SD) age was 65.0 (9.9) years, 57% were male, and 80% had high-risk PV (ie, age ≥60 years and/or history of TE)
  - Characteristics for patients in the 10 mg twice daily (BID) dose cohort (US prescribing information [PI]–recommended starting dose for PV treatment) were generally similar to those of all patients and patients who initiated ruxolitinib at any other dose

Table 1. Patient Baseline and Clinical Characteristics

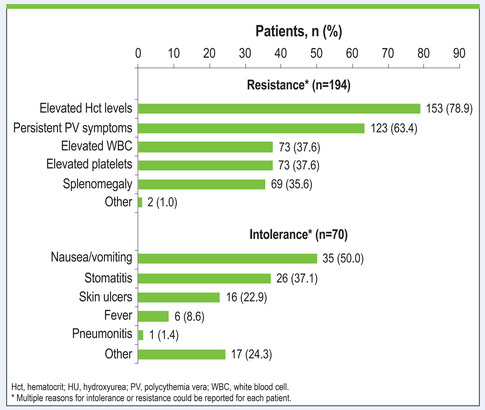
Clinical Characteristics	All Patients (N=249)
Age, y, mean (SD)	65.0 (9.9)
Male, n (%)	142 (57.0)
PV risk, n (%)	
High	200 (80.3)
Low	49 (19.7)
*JAK2*V617F mutation testing, n (%)	
Positive	243 (97.6)
Negative	2 (0.8)
Inconclusive	1 (0.4)
Data not available	3 (1.2)
Cardiovascular risk factors, n (%)	
0	57 (22.9)
1	64 (25.7)
≥2	128 (51.4)
Patients with history of TE prior to ruxolitinib, n (%)	78 (31.3)
Frequency of phlebotomy at ruxolitinib initiation, n (%)	
Once every 2 wk	46 (18.5)
Once every 4 wk	104 (41.8)
Once every 3 mo	38 (15.3)
Other	10 (4.0)
Not receiving phlebotomy	51 (20.5)
Hematologic parameters at ruxolitinib initiation, median (IQR)	
Hct, %*	51.0 (47.0–55.0)
Platelet count, × 10^9/L	450.0 (250.0–620.0)
Hgb, g/dL	16.7 (15.0–18.0)
WBC count, × 10^9/L	12.0 (7.3–15.0)

Hct, hematocrit; Hgb, hemoglobin; IQR, interquartile range; PV, polycythemia vera; TE, thromboembolic event; WBC, white blood cell.
* Hct control is defined as Hct <45%.

HU Treatment Patterns

- At the time of HU discontinuation, 24.9% of patients had reached an HU dose of ≥2 g/day; median (IQR) HU treatment duration was 10.8 (6.0–21.6) months
- Causes of HU discontinuation were resistance (77.9%), intolerance (28.1%), patient choice (22.5%), and other reasons (4.4%; **Figure 1**); 14.1% of patients were reported as both resistant and intolerant
  - Resistance was most frequently due to hematocrit (Hct) ≥45% (78.9%) and/or persistent PV-related symptoms (63.4%)
  - Intolerance was most frequently due to nausea/vomiting (50.0%) and/or stomatitis (37.1%)

Figure 1. Rationale for HU Discontinuation Among Resistant and Intolerant Patients

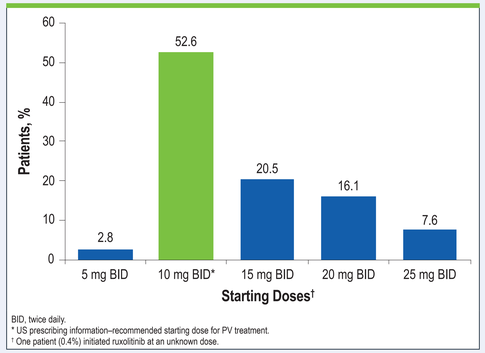


Hct, hematocrit; HU, hydroxyurea; PV, polycythemia vera; WBC, white blood cell.
* Multiple reasons for intolerance or resistance could be reported for each patient.

Ruxolitinib Treatment Patterns

- 131 patients (52.6%) initiated ruxolitinib at the US PI–recommended dose of 10 mg BID **(Figure 2)**

Figure 2. Ruxolitinib Starting Doses



BID, twice daily.
* US prescribing information–recommended starting dose for PV treatment.
† One patient (0.4%) initiated ruxolitinib at an unknown dose.

- During the first 6 months of ruxolitinib treatment, 5 patients (2.0%) had a total of 5 dose interruptions
  - The most common reason for dose interruption was an adverse event
  - There was no dose reduction after an interruption during this period
- 27 patients (10.8%) had 32 dose increases and 31 patients (12.4%) had 37 dose decreases during the first 6 months of ruxolitinib treatment **(Table 2)**; no patient had both a dose increase and decrease during the first 6 months
  - The most common reasons for dose increases were continued need for phlebotomy (4.8%) and/or persistent PV symptoms (3.6%)
  - The most common reasons for dose decreases were low platelet counts (8.4%) and/or low hemoglobin (3.2%)
  - Overall, patients had more dose modifications (increases or decreases) in the first 6 months of ruxolitinib treatment (all patients, 23.3%; 10 mg BID, 26.7%) and fewer dose modifications after 6 months (all patients, 12.9%; 10 mg BID, 11.5%)
    - The opposite was observed for dose interruptions, with fewer interruptions in the first 6 months (all patients, 2.0%; 10 mg BID, 3.1%) and more after 6 months (all patients, 3.2%; 10 mg BID, 4.6%)
- Hct control (Hct <45%) at initiation of ruxolitinib treatment was 18.9%, compared with 63.1% after 6 months of ruxolitinib treatment
- At the time of the last visit, 61.4% of patients were still receiving ruxolitinib
  - The majority of patients (all patients, 66.7%; 10 mg BID, 58.1%) who discontinued ruxolitinib had no dosing changes from the time of initiation to discontinuation

Table 2. Dosing Patterns and Hematocrit Control for Patients Initiated on Ruxolitinib

	10 mg BID* (n=131)	Doses Other Than 10 mg BID (n=118)	All Patients (N=249)
Duration of ruxolitinib treatment, mo, median (IQR)	29.2 (11.2–37.1)	35.3 (19.0–42.9)	31.4 (14.5–40.4)
Patients with dosing modifications during initial 6 mo of ruxolitinib treatment, n (%)	35 (26.7)	23 (19.5)	58 (23.3)
Patients with increase in dose†	24 (18.3)	3 (2.5)	27 (10.8)
Continued need for phlebotomy to maintain Hct <45%	11 (8.4)	1 (0.8)	12 (4.8)
Persistent PV symptoms	9 (6.9)	0	9 (3.6)
Persistent splenomegaly	2 (1.5)	2 (1.7)	4 (1.6)
Maintain Hct <42%	1 (0.8)	0	1 (0.4)
Leukocytosis	1 (0.8)	0	1 (0.4)
Patients with decrease in dose†	11 (8.4)	20 (16.9)	31 (12.4)
Reduced platelet count	6 (4.6)	15 (12.7)	21 (8.4)
Reduced Hgb	3 (2.3)	5 (4.2)	8 (3.2)
Adverse event	0	1 (0.8)	1 (0.4)
Nausea/vomiting	1 (0.8)	1 (0.8)	1 (0.4)
Patient doing well but WBC trending down	1 (0.8)	1 (0.8)	1 (0.4)
Patients with dose interruptions, n (%)	4 (3.1)	1 (0.8)	5 (2.0)
Adverse event	2 (1.5)	1 (0.8)	3 (1.2)
Patient request	1 (0.8)	0	1 (0.4)
Lung cancer	1 (0.8)	0	1 (0.4)
Patients with Hct control, n (%)‡			
At ruxolitinib initiation	19 (14.5)	28 (23.7)	47 (18.9)
After 6 mo of ruxolitinib treatment	82 (62.6)	75 (63.6)	157 (63.1)
At last visit	70 (53.4)	70 (59.3)	140 (56.2)
Discontinuation of ruxolitinib, n (%)	62 (47.3)	34 (28.8)	96 (38.6)
Time to ruxolitinib discontinuation, mo, median (IQR)	10.5 (6.6–17.1)	11.7 (6.1–18.0)	10.9 (6.3–17.4)

BID, twice daily; Hct, hematocrit; Hgb, hemoglobin; IQR, interquartile range; PV, polycythemia vera; WBC, white blood cells.
* US prescribing information–recommended starting dose for PV treatment.
† More than one reason could be cited for dose modification.
‡ Hct control is defined as Hct <45%.

Conclusions

- **HU was discontinued due to resistance in approximately 78% of patients; only a quarter of these patients received a guideline-referenced HU dose of ≥2 g/day, which suggests that this minimum daily dose may not be relevant to the real-world**
- **Of patients who were switched from HU to ruxolitinib, the duration of HU treatment (10.8 mo) was shorter and the proportion of patients treated with HU doses ≥2 g/day (25%) was higher than data reported in a prospective observational study (REVEAL) for all patients discontinuing HU (35.7 mo and 6.5%, respectively)[7]**
- **53% of patients were initiated on ruxolitinib at the recommended dose of 10 mg BID**
  - **29.8% of these patients underwent dose modifications, primarily dose increases, or interruptions during the initial 6 months of treatment**
  - **The majority of patients who discontinued ruxolitinib had no dose modifications during their treatment**
- **The rate of Hct control observed in this 24-week real-world study is similar to the 32-week efficacy reported in the RESPONSE trial (60%)[8]**
- **Proper starting dose and active titration during the first 6 months of ruxolitinib treatment appear to decrease the possibility of early discontinuation**

Disclosures

IA served as a consultant for Amgen, Incyte, Novartis, and Rigel, and served on a speakers bureau for Incyte. AN, SP, DP, and PC are employees and stockholders of Incyte. JK and KL are employees and stockholders of Cardinal Health, which received funding from Incyte.

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