Retrospective Real-World Analysis of Baseline Characteristics, Treatment Patterns, and Survival in Patients With Myelofibrosis and Anemia Receiving Ruxolitinib

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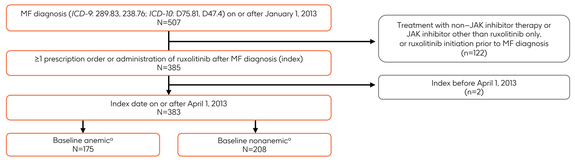
Introduction

- Anemia is a prevalent and progressive clinical manifestation of myelofibrosis (MF) and is present in nearly 40% of patients at diagnosis, with incidence and severity increasing as the disease advances over time[1,2]
- While Janus kinase (JAK) inhibitors such as ruxolitinib are a mainstay of treatment in MF because of their ability to provide spleen and symptom-related benefits, some do not address and may worsen anemia[2,3]
- A previous retrospective analysis of patients treated with ruxolitinib in the US Flatiron Health electronic health record–derived deidentified database found that median times to anemia and thrombocytopenia were <1 year in patients without these cytopenias at baseline; 24% of patients who were not red blood cell (RBC) transfusion dependent at baseline became so after 3 months of ruxolitinib[4]
- Although dose modification of ruxolitinib may mitigate its myelosuppressive effects,[5] characterization of the prevalence and patterns of this strategy and the associated effects on outcomes in real-world patients with anemia has been limited
- This study describes real-world baseline characteristics, treatment patterns, and survival outcomes in patients with MF who did or did not have anemia at baseline and were treated with ruxolitinib

Methods

- This was a retrospective analysis of adult patients in the US Flatiron Health electronic health record–derived deidentified database, comprising patient-level data originated from approximately 280 US cancer clinics (approximately 800 sites of care, primarily community oncology settings) and curated via technology-enabled abstraction[6,7]
- Eligible patients were ≥18 years of age at initial MF diagnosis (*ICD-9/10* diagnosis codes 289.83, 238.76/D75.81, D47.4) on or after January 1, 2013, and had ≥1 prescription order or administration of ruxolitinib after diagnosis (**Figure 1**)
  - Ruxolitinib initiation date was defined as the index date for analysis, and only patients with index dates after April 2013 were included to allow for a pretreatment baseline period of ≥3 months; follow-up was from index date to death or end of data availability (**Figure 2**)
  - The analysis focused on patients treated with ruxolitinib as there were few patients treated with other JAK inhibitors included in the database
- The analysis was stratified by anemia status at index (anemic vs nonanemic); patients were defined as anemic based on hemoglobin (Hb) levels of <10 g/dL from laboratory assessment or *ICD-9/10* diagnosis codes for anemia during the baseline period (**QR code**)
- Baseline characteristics and initial ruxolitinib dose were summarized descriptively; overall survival (OS) and times to first dose reduction, discontinuation, and RBC transfusion were assessed by Kaplan-Meier analyses

Figure 1: **Patient Selection**



Hb, hemoglobin; ICD, International Classification of Diseases; JAK, Janus kinase; MF, myelofibrosis.
[a]Anemia status was evaluated using a combined approach based on the presence of Hb levels of <10 g/dL from laboratory assessments or the presence of ICD-9/10 diagnosis codes for anemia.

Figure 2: **Study Design**



MF, myelofibrosis.

Results

- A total of 383 patients met criteria for analysis, including 175 (46%) with anemia and 208 (54%) without anemia at baseline
  - While most demographic and clinical characteristics were comparable between anemic and nonanemic patients at baseline, anemic patients had numerically higher mean Charlson Comorbidity Index scores, RBC transfusion burden, and incidence of thrombocytopenia (**Table 1**)

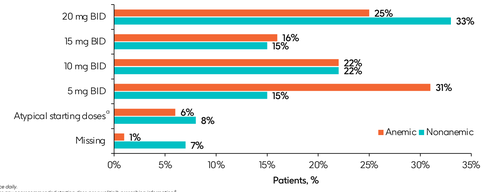
Table 1: **Baseline Characteristics**

	Anemic (n=175)	Nonanemic (n=208)
Age, mean (SD), years	72.8 (9.4)	71.4 (9.7)
Male, n (%)	107 (61)	106 (51)
White, n (%)	117 (67)	143 (69)
Time from MF diagnosis to index, mean (SD), months	8.5 (18.3)	8.8 (17.0)
MF subtype		
Primary	109 (62)	114 (55)
Secondary	66 (38)	94 (45)
Hb level, mean (SD), g/dL[a]	8.7 (1.2)	12.1 (1.8)
RBC transfusion status, n (%)[b]		
Transfusion dependent	71 (41)	9 (4)[c]
Transfusion requiring	6 (3)	3 (1)
Transfusion independent	98 (56)	196 (94)
RBC transfusion units per person per month, mean (SD)	0.3 (0.7)	0 (0.2)
Thrombocytopenia, n (%)[d]	61 (35)	33 (16)
Platelet count, mean (SD), ×10⁹/L[a]	307.7 (302.1)	359.7 (271.3)
CCI score, mean (SD)[e]	1.5 (1.8)	1.1 (1.9)
Any CCI component, n (%)	116 (66)	92 (44)
Renal disease, n (%)	59 (34)	45 (22)
Any malignancy, n (%)	45 (26)	32 (15)
Congestive heart failure, n (%)	25 (14)	19 (9)

CCI, Charlson Comorbidity Index; Hb, hemoglobin; ICD, International Classification of Diseases; MF, myelofibrosis; RBC, red blood cell.
*[a]Per the closest available measurement to the index date within the baseline period. The baseline period was defined as the time window ranging from 3 months before and including the index date. [b]Transfusion independent was defined as no transfusions or Hb levels of <8 g/dL in the previous 12 weeks; transfusion dependent was defined as ≥4 RBC transfusions or an Hb level of <8 g/dL in any 8-week period in the previous 12 weeks; and transfusion requiring was defined as not meeting either of the previous criteria. [c]Patients may have been classified as nonanemic despite having transfusions if (1) their last Hb assessment in the baseline period was conducted after an RBC transfusion and indicated Hb ≥10 g/dL or (2) they did not meet the study-defined anemia criteria but had recorded transfusions during the baseline period. [d]Defined by platelet counts of <150×10⁹/L from laboratory assessment or ICD-9/10 diagnostic codes (**QR code**) [e]Shown are CCI components reported in ≥10% of patients. The CCI score did not include diagnosis codes for MF.*

- Starting dose of ruxolitinib is described in **Figure 3**; anemic patients received ruxolitinib 5 mg twice daily (BID) more often and 20 mg BID less often than nonanemic patients
  - During the entire 3-month period post baseline, 25% of anemic vs 16% of nonanemic patients who remained on treatment received a dose of <20 mg daily (P=.09); 20% vs 13% received <20 mg daily for the entire 6 months post baseline (P=.21)

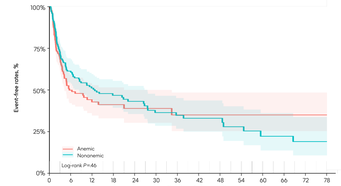
Figure 3: **Ruxolitinib Starting Dose**



BID, twice daily.
[a]Includes any nonrecommended starting dose per ruxolitinib prescribing information.[8]

- Median time to first dose reduction was 5.6 months in anemic patients vs 12.8 months in nonanemic patients (log-rank P=.46) (**Figure 4**)
- Median duration of ruxolitinib treatment was 16.7 months in anemic patients vs 24.8 months in nonanemic patients (log-rank P=.26) (**Figure 5**)
  - The most common reasons for ruxolitinib discontinuation were toxicity (35%), insufficient response (13%), and progression (11%)
- Anemic patients receiving ruxolitinib had significantly shorter (log-rank P<.001) time to RBC transfusion compared with nonanemic patients: median, 2.8 months (95% CI, 2.1-3.8 months) vs 48.8 months (95% CI, 29.0-73.0 months)

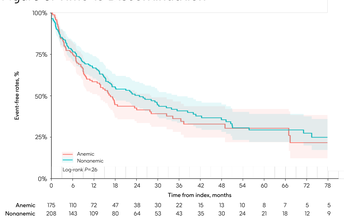
Figure 4: **Time to First Dose Reduction[a]**



	Anemic (n=173)[b]	Nonanemic (n=201)[b]
Events, n (%)	81 (47)	104 (52)
Median time to event (95% CI), months	5.6 (4.2-34.4)	12.8 (8.3-27.6)
Event-free rates, %		
3-month	69	72
6-month	50	61
12-month	43	51

[a]Dose reduction was defined as a decrease in ruxolitinib daily dose relative to the ruxolitinib daily dose in the prior ruxolitinib episode. Ruxolitinib episodes with available dosage information were used to determine ruxolitinib reductions. Ruxolitinib episodes with missing dosage information were removed from this analysis. A patient's first ruxolitinib reduction was defined as the earliest ruxolitinib reduction that occurred before their first ruxolitinib discontinuation date. Patients with no ruxolitinib reductions during follow-up or who had their earliest ruxolitinib reduction after their first ruxolitinib discontinuation date were censored using their first ruxolitinib discontinuation date. [b]9 patients were removed from this analysis due to missing ruxolitinib daily dosage and undetermined ruxolitinib dose change.

Figure 5: **Time to Discontinuation[a]**

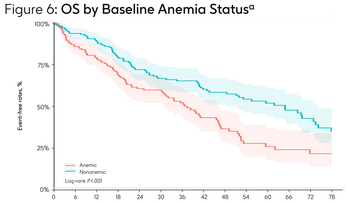


	Anemic (n=175)	Nonanemic (n=208)
Events, n (%)	91 (52)	112 (54)
Median time to event (95% CI), months	16.7 (13.6-28.2)	24.8 (16.9-35.5)
Event-free rates, %		
3-month	84	85
6-month	75	77
12-month	59	67

[a]Ruxolitinib episodes with missing dosage information were removed from this analysis. Discontinuation was defined as the earliest of 3 criteria: (1) ruxolitinib episode where discontinuation was the end reason, (2) ≥60-day gap between ruxolitinib episodes or between the last ruxolitinib episode and the end of follow-up, and (3) the patient died while using ruxolitinib. If none of the criteria occurred before the end of follow-up, patients were censored using the end of follow-up date.

- Median OS was significantly shorter (log-rank P<.001) in anemic vs nonanemic patients receiving ruxolitinib (**Figure 6**)
  - Anemia severity had an incremental negative impact on survival, with median OS of 21.8, 40.7, and 42.9 months in patients with baseline Hb levels of <8 g/dL, ≥8 to <10 g/dL, and ≥10 to <12 g/dL, respectively (**Figure 7**)
- In an exploratory analysis, median OS was also significantly shorter (log-rank P<.05) in patients receiving <20 vs ≥20 mg of ruxolitinib daily in the first 3 months post baseline (**Figure 8**)

Figure 6: **OS by Baseline Anemia Status[a]**



	Anemic (n=175)	Nonanemic (n=208)
Events, n (%)	91 (52)	88 (42)
Median time to event (95% CI), months	37.4 (31.0-46.3)	64.9 (51.2-74.2)
Event-free rates, %		
3-month	93	97
6-month	86	94
12-month	79	89
24-month	61	72

OS, overall survival.
[a]OS was defined as the time from the index date to the date of death. Patients without a date of death were censored at their last known activity (eg, the last clinical note date) or the end of the follow-up period, whichever occurred first.

Conclusions

- This retrospective cohort study identified that a substantial population (46%) of patients with MF who began treatment with ruxolitinib were anemic at the time of treatment initiation
- Patients with anemia initiated ruxolitinib at lower doses than nonanemic patients, perhaps due in part to the risk of worsening anemia or co-occurring thrombocytopenia at baseline[8]
- Baseline anemia, even mild anemia, and lower ruxolitinib dosing were significantly associated with worse OS; patients receiving <20 mg ruxolitinib daily had a comparable median OS to patients with baseline anemia, suggesting that alternative JAK inhibitors that can be fully dosed may be beneficial in this patient population
- Taken together, these findings highlight the substantial burden of baseline anemia in JAK inhibitor–naive patients with MF and the need for alternative first-line treatments to ruxolitinib for those with anemia

Limitations/Future Directions

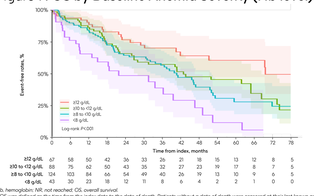
Limitations

- Assessments of anemia and thrombocytopenia using *ICD* codes are based on physician evaluations; as the anemia thresholds used by different physicians may vary, this may have led to misclassification of some patients in this analysis
  - Twelve patients in the nonanemic subgroup had some transfusion burden at baseline, which may be due to a last Hb assessment that occurred after an RBC transfusion or due to not meeting the study-defined criteria for anemia but having documented transfusions
- Differences between the anemic and nonanemic subgroups were not adjusted for potential baseline confounders, and should be interpreted accordingly

Future Directions

- Ruxolitinib dose reduction combined with anemia supportive therapy is a common approach to anemia management in practice; comparative analyses of outcomes with this strategy vs other treatments for anemia will be helpful for therapeutic decision-making
- Clinical outcomes in patients treated with ruxolitinib vs other JAK inhibitors will also be important to further contextualize these findings, as real-world data for these treatment options continue to accrue

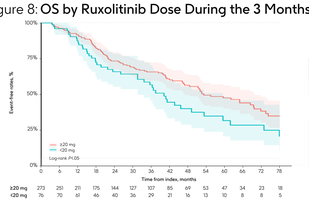
Figure 7: **OS by Baseline Anemia Severity (Hb level)[a]**



Hb, g/dL:	≥12 (n=67)	≥10 to <12 (n=88)	≥8 to <10 g (n=124)	<8 (n=43)
Events, n (%)	24 (36)	43 (49)	58 (47)	27 (63)
Median time to event (95% CI), months	69.6 (51.2-NR)	42.9 (27.9-68.3)	40.7 (33.7-52.0)	21.8 (13.0-46.6)
Event-free rates, %				
3-month	94	95	94	91
6-month	94	93	90	76
12-month	90	86	84	66
24-month	77	66	65	49

Hb, hemoglobin; NR, not reached; OS, overall survival.
[a]OS was defined as the time from the index date to the date of death. Patients without a date of death were censored at their last known activity (eg, the last clinical note date) or the end of the follow-up period, whichever occurred first. 61 patients were excluded from this analysis because they did not have a baseline laboratory value to deduce anemia severity.

Figure 8: **OS by Ruxolitinib Dose During the 3 Months Post Index[a]**



	<20 mg (n=76)	≥20 mg (n=273)
Events, n (%)	43 (57)	111 (41)
Median time to event (95% CI), months	40.1 (31.5-59.4)	53.1 (46.9-69.6)
Event-free rates, %		
3-month	100	100
6-month	96	96
12-month	88	92
24-month	66	73

OS, overall survival.
[a]OS was defined as the time from the index date to the date of death. Patients without a date of death were censored at their last known activity (eg, the last clinical note date) or the end of the follow-up period, whichever occurred first. The analysis includes patients with ≥3 months of follow-up post ruxolitinib initiation regardless of treatment discontinuation by month 3. Patients were stratified by whether or not they received ≥20 mg at any point during the first 3 months post ruxolitinib initiation as determined using available daily dosage data.

Abbreviations

BID, twice daily; CCI, Charlson Comorbidity Index; Hb, hemoglobin; *ICD, International Classification of Diseases*; JAK, Janus kinase; MF, myelofibrosis; NR, not reached; OS, overall survival; RBC, red blood cell.

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