Ruxolitinib in cytopenic myelofibrosis: Response, toxicity, drug discontinuation, and outcome

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Abstract

Background: Patients with cytopenic myelofibrosis (MF) have more limited therapeutic options and poorer prognoses compared with patients with the myeloproliferative phenotype.

Aims and Methods: Prognostic correlates of cytopenic phenotype were explored in 886 ruxolitinib-treated patients with primary/secondary MF (PMF/SMF) included in the RUX-MF retrospective study. Cytopenia was defined as: leukocyte count <4 × 10⁹/L and/or hemoglobin <11.0/10.0 g/dL (males/females) and/or platelets <100 × 10⁹/L.

Results: Overall, 407 (45.9%) patients had a cytopenic MF, including 249 (52.4%) with PMF. In multivariable analysis, high molecular risk mutations (p = .04), intermediate 2/high Dynamic International Prognostic Score System (p < .001) and intermediate 2/high Myelofibrosis Secondary to Polycythemia Vera and Essential Thrombocytosis Prognostic Model (p < .001) remained associated with cytopenic
INTRODUCTION

Myelofibrosis (MF) is a rare, chronic, Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) that may present as primary disease (PMF) or secondary to essential thrombocythemia or polycythemia vera (SMF).

Cytopenic MF includes patients with thrombocytopenia, leukopenia, and/or anemia. Moderate (platelet counts, 50–100 × 10^9/L) thrombocytopenia frequently pairs with anemia and is present in approximately 25% of patients at diagnosis. The prevalence increases to 45% at 1 year after diagnosis and to more than 70% at any time during follow-up. The prognostic significance of a platelet count <100 × 10^9/L and hemoglobin <10 g/dL is incorporated into the Dynamic International Prognostic Scoring System (DIPSS) and DIPSS-Plus and in the Mutation and Karyotype-Enhanced International Prognostic Scoring System for PMF. Similarly, a platelet count <150 × 10^9/L and hemoglobin <11 g/dL are poor prognostic markers in the Myelofibrosis Secondary to Polycythemia Vera and Essential Thrombocythemia Prognostic Model (MYSEC-PM). The role of leukopenia in the prognosis of MF is less thoroughly validated.

A recent retrospective study showed that the cytopenic phenotype is associated with high-risk clinical and molecular features and correlates with inferior survival in patients with preblastoid and overt PMF. Other, treatment options are limited in patients with cytopenic MF. Ruxolitinib is a JAK1/JAK2 inhibitor that may significantly improve MF-related splenomegaly and symptoms. However, patients with moderate thrombocytopenia are treated with low doses, whereas those with platelet count below 50 × 10^9/L are excluded from treatment. Ruxolitinib is also burdened by on-target hematological toxicity, with many dose reductions and treatment discontinuations caused by anemia and/or thrombocytopenia. New JAK2 inhibitors, namely fedratinib, pacritinib, and momelotinib, are becoming available for the treatment of MF and may have a role in patients with cytopenia.

In the current study, we investigated the prognostic correlates of the cytopenic phenotype in a large cohort of patients with MF requiring ruxolitinib therapy, in terms of response and toxicity rates, drug discontinuations, and outcome.

MATERIAL AND METHODS

Patients and study design

After institutional review board approval, the RUX-MF retrospective study collected 886 patients with chronic-phase MF who received ruxolitinib outside clinical trials in 26 hematology centers dedicated to treating MF. The list of the participating centers is available in the Appendix. All centers were asked to report, in an electronic case report form, their consecutive patients with MF who received ruxolitinib according to standard clinical practice. The total number of medical files was reported by each center by data input into an electronic database developed to record all study data after deidentifying patients with an alphanumeric code to protect personal privacy. Any treatment decision, including starting ruxolitinib doses and dose adjustments over time, was at the physician’s discretion, based on patients’ characteristics and independent from participation to this study. After the first data entry, the follow-up information was validated with revision of clinical data, and specific queries were addressed to the participating center in case of inconsistent data. All...
patients were followed from 2013 until death or to data cutoff (June 28, 2022), with a median follow-up time of 4.4 years.

Definitions

Diagnoses of PMF and SMF were made according to 2016 World Health Organization criteria and International Working Group on Myelofibrosis Research and Treatment criteria, respectively.\(^\text{18}\) Cytopenias at ruxolitinib start were defined as follows: white blood cell <\(4 \times 10^9/L\), hemoglobin <\(11 \text{ g/dL}\) for males and <\(10 \text{ g/dL}\) for females, and platelets (PLTs) <\(100 \times 10^9/L\). Cytopenic phenotype was defined by the presence of at least one cytopenia. Patients not included in the cytopenic group were considered as having a proliferative phenotype.

Risk category was assessed at the time patients started on ruxolitinib according to the DIPSS in PMF and to the DIPSS/MYSEC-PM in SMF.\(^\text{6,9}\) Histologic examination was performed at local institutions; fibrosis was graded according to the European Consensus Grading System.\(^\text{20}\) Unfavorable karyotype was categorized as previously described.\(^\text{7}\) Diagnosis of leukemic transformation was made according to World Health Organization criteria.\(^\text{18}\) MF-related symptoms were assessed using the 10-item Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (TSS).\(^\text{19}\) Spleen and symptom responses were assessed by palpation and by routine MPN-TSS evaluation, respectively, according to 2013 International Working Group on Myelofibrosis Research and Treatment/European LeukemiaNet criteria.\(^\text{20}\)

Anemia and thrombocytopenia were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5.x7.pdf). Drug-induced anemia and thrombocytopenia were defined as an increase in anemia/thrombocytopenia grade with respect to baseline levels. Patients who were transfusion dependent before the start of ruxolitinib therapy were not evaluable for subsequent anemia.

Mutations were evaluated by next-generation sequencing (NGS) with the myeloid panel SOPHIA Genetics (Sophia Genetics, Saint Sulpice, Switzerland) at the start of ruxolitinib or within 6 months before the start of ruxolitinib. High molecular risk (HMR) mutations included ASXL-1, IDH1/2, EZH2, and SRSF2.\(^\text{21}\)

Ethical aspects

The RUX-MF study was performed in accordance with the guidelines of the institutional review boards of the participating centers and the standards of the Helsinki Declaration. All patients provided written informed consent. The promoter of this study was the IRCCS Azienda Ospedaliero-Universitaria S. Orsola-Malpighi, Bologna, which obtained approval from the Area Vasta Emilia Centro Ethics Committee (approval file number: 048/2022/Oss/AOUBo). The study was also approved by the local ethics committee of all participating centers (protocol code: RUX-MF) and has no commercial support.

Statistical analysis

Statistical analysis was performed at the biostatistics laboratory of the MPN Unit at the Institute of Hematology “L. and A. Seràgnoli,” IRCCS Azienda Ospedaliero-Universitaria di Bologna.

Continuous variables have been summarized by their median and range, and categorical variables by count and relative frequency (% of each category. Comparisons of quantitative variables between groups were performed with Wilcoxon–Mann–Whitney rank-sum test, whereas association between categorical variables was tested by the \(\chi^2\) test. Ruxolitinib discontinuation, leukemic transformation, and overall survival (OS) were compared with the log-rank test, considering time from ruxolitinib start to ruxolitinib stop, leukemic transformation, and death or last contact, with adjustment for delayed entry. Patients were censored at the time of allogeneic stem cell transplantation (ASCT) in survival analysis. Comparisons of ruxolitinib discontinuation and leukemic transformation were also performed with the Fine and Gray model, treating death as a competing event, whereas comparison of OS was also performed with the Cox regression model in multivariable analysis with DIPSS risk score.

For all tested hypotheses, two-tailed \(p\) values <.05 were considered significant. Statistical analyses were performed using STATA Software, 15.1 (StataCorp LP, College Station TX, USA).

RESULTS

Baseline characteristics associated with cytopenic phenotype

DIPSS distribution of the entire cohort of 886 patients was intermediate 1 (55.2%), intermediate 2 (37.9%), and high (6.9%). Notably, the percentage of patients who started ruxolitinib at intermediate 1 risk was approximately 50% in the first years of ruxolitinib use (2013–2019) and then increased to 71% and 66.7% in 2020 and 2021, respectively. Overall, 46.6% had a large splenomegaly (palpable at ≥10 cm below costal margin) and 61.8% were highly symptomatic (TSS ≥20). At least 1 HMR mutation was detected in 48.9% of the 184 (20.8%) evaluable patients (≥2 mutations in 13.6%). Notably, NGS evaluation of HMR mutations at ruxolitinib start was performed in a relatively low percentage of patients, mainly (62%) those younger than aged 70 years. However, the number of molecular evaluations tended to increase over time (from 16.9% in the years 2013–2015 to 24.7% in the years 2015–2021), suggesting an increased availability of NGS technique and awareness of the importance of mutational study in MF.

A cytopenic phenotype was present in 407 (45.9%) patients, including 249 (52.4%) PMF and 158 (38.4%) SMF (Table 1). Eighty-four (20.6%) patients had ≥2 cytopenias. At ruxolitinib start, 93 (10.5%) patients had platelet counts between 50 and 99 \(\times 10^9/L\) (PLT-50), 236 (26.6%) had platelet between 100 and 199 \(\times 10^9/L\) (PLT-100), and 557 (62.9%) had platelet ≥200 \(\times 10^9/L\) (PLT-200).
## Table 1

Patients characteristics at ruxolitinib start according to proliferative or cytopenic phenotype in PMF or SMF myelofibrosis.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PMF (n = 475)</th>
<th>SMF (n = 411)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proliferative (n = 226, 47.6%)</td>
<td>Proliferative (n = 253, 61.6%)</td>
<td>Cytopenic (n = 249, 52.4%)</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>66.4 (26.5–86.8)</td>
<td>69.3 (39.4–88.9)</td>
<td>.003</td>
</tr>
<tr>
<td>Age ≥ 65, n (%), years</td>
<td>130 (57.5%)</td>
<td>170 (68.3%)</td>
<td>.02</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>137 (60.6%)</td>
<td>153 (61.5%)</td>
<td>.85</td>
</tr>
<tr>
<td>DIPSS, n (%)</td>
<td>Intermediate 1 190 (84.1%)</td>
<td>51 (20.5%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Intermediate 2 36 (15.9%)</td>
<td>168 (67.5%)</td>
<td>.65</td>
</tr>
<tr>
<td></td>
<td>High 0</td>
<td>30 (12.1%)</td>
<td>.65</td>
</tr>
<tr>
<td>MYSEC, n (%)</td>
<td>Low -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Intermediate 1 137 (54.8%)</td>
<td>33 (20.9%)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Intermediate 2 58 (23.2%)</td>
<td>68 (43.0%)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>High 19 (7.6%)</td>
<td>50 (31.7%)</td>
<td>.02</td>
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<tr>
<td>Blasts, median (range)</td>
<td>0.8 (0–9)</td>
<td>0.9 (0–9)</td>
<td>.66</td>
</tr>
<tr>
<td>Blasts ≥1%, n (%)</td>
<td>81/223 (36.3%)</td>
<td>84/245 (34.3%)</td>
<td>.65</td>
</tr>
<tr>
<td>Mutational status, n (%)</td>
<td>n = 218</td>
<td>n = 230</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>JAK2 173 (79.4%)</td>
<td>168 (73.0%)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>CALR 33 (15.1%)</td>
<td>34 (14.8%)</td>
<td>.02</td>
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<tr>
<td></td>
<td>MPL 2 (0.9%)</td>
<td>15 (6.5%)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>TN 10 (4.6%)</td>
<td>13 (5.7%)</td>
<td>.02</td>
</tr>
<tr>
<td>Unfavorable karyotype, n (%)</td>
<td>10/154 (6.5%)</td>
<td>23/150 (15.3%)</td>
<td>.01</td>
</tr>
<tr>
<td>HMR, n (%)</td>
<td>n = 57</td>
<td>n = 42</td>
<td>.33</td>
</tr>
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<td></td>
<td>SRSF2 8 (14.0%)</td>
<td>7 (16.7%)</td>
<td>.71</td>
</tr>
<tr>
<td></td>
<td>IDH1 2 (3.5%)</td>
<td>0</td>
<td>.22</td>
</tr>
<tr>
<td></td>
<td>IDH2 5 (8.8%)</td>
<td>0</td>
<td>.05</td>
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<tr>
<td></td>
<td>EZH2 8 (14.0%)</td>
<td>4 (9.5%)</td>
<td>.50</td>
</tr>
<tr>
<td></td>
<td>ASXL1 22 (38.6%)</td>
<td>22 (52.4%)</td>
<td>.17</td>
</tr>
<tr>
<td></td>
<td>HMR ≥1, n (%)</td>
<td>28 (49.1%)</td>
<td>27 (64.2%)</td>
</tr>
<tr>
<td></td>
<td>HMR ≥2 12 (21.1%)</td>
<td>2 (7.4%)</td>
<td>.10</td>
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<tr>
<td></td>
<td>U2AF1, n (%)</td>
<td>1 (1.5%)</td>
<td>.03</td>
</tr>
<tr>
<td>Fibrosis ≥2, n (%) on 425 evaluable patients with PMF</td>
<td>136/207 (65.7%)</td>
<td>176/218 (80.7%)</td>
<td>.001</td>
</tr>
<tr>
<td>Palpable spleen, median (range)</td>
<td>10.8 (0–35)</td>
<td>11.4 (0–31)</td>
<td>.38</td>
</tr>
<tr>
<td>Spleen ≥10 cm, n (%)</td>
<td>94/225 (41.8%)</td>
<td>116/247 (46.9%)</td>
<td>.26</td>
</tr>
<tr>
<td>TSS, median (range)</td>
<td>25.4 (0–100)</td>
<td>28.7 (0–100)</td>
<td>.05</td>
</tr>
<tr>
<td>TSS ≥20, n (%)</td>
<td>119/210 (56.7%)</td>
<td>165/235 (70.2%)</td>
<td>.003</td>
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</tbody>
</table>

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; HMR, high molecular risk; MYSEC, Myelofibrosis Secondary to Polycythemia Vera and Essential Thrombocythemia; PMF, primary myelofibrosis; SMF, secondary myelofibrosis; TSS, Total Symptom Score.
In multivariable analysis, only HMR mutations (odds ratio [OR] [95% CI], 4.31 [1.42–13.0]; p = .01) and only unfavorable karyotype (OR [95% CI], 2.53 [1.12–5.73]; p = .04) confirmed their significant association with the cytopenic group and with the presence of ≥2 cytopenias, respectively.

Among patients with PMF, cytopenic status was due to leukopenia, thrombocytopenia, and sex-adjusted anemia in 20.9%, 22.9%, and 82.0% of patients, respectively. In SMF, leukopenia, thrombocytopenia, and sex-adjusted anemia occurred in 13.9%, 22.8%, and 83.0% of patients, respectively (Figure 1). Two or more cytopenias were found in 22.1% and 18.3% of patients with PMF and SMF, respectively. In multivariable analysis, intermediate 2/high DIPSS [OR [95% CI], 17.62 [6.08–31.05]; p < .001] and intermediate 2/high MYSEC–PM [OR [95% CI], 3.07 [2.33–4.05]; p < .001] remained significantly associated with the cytopenic phenotype in PMF and SMF, respectively.

**Ruxolitinib dose according to cytopenic phenotype**

Ruxolitinib starting dose was 5 mg twice daily, 10 mg twice daily, 15 mg twice daily, and 20 mg twice daily in 158 (17.8%), 193 (21.8%), 205 (23.1%), and 330 (37.2%) patients, respectively. Median ruxolitinib doses at 3 months and overall were 20.6% and 19.6% (5 mg twice daily), 26.1% and 29.6% (10 mg twice daily), 27.1% and 26.6% (15 mg twice daily), 26.1% and 24.1% (20 mg twice daily) of patients, respectively.

Average ruxolitinib doses were significantly lower in cytopenic versus evaluable patients both at therapy start (25.2 mg/day vs. 30.2 mg/day, p < .001), during the first 3 months (23.8 mg/day vs. 27.6 mg/day, p < .001), and overall (23.6 mg/day vs. 26.8 mg/day, p < .001). Accordingly, the percentage of patients receiving low (5–10 mg twice daily) ruxolitinib doses was significantly higher in the cytopenic group both at start, at 3 months, and overall (Figures 2A–C). This was also confirmed in PMF and SMF patients separately.

Notably, ruxolitinib starting dose was 5 or 10 mg twice daily in 85% of PLT-50, 15 mg twice daily in 43.8% of PLT-100, and 20 mg twice daily in 53.9% of PLT-200 patients. A substantial portion of PLT-100 and PLT-200 patients (45.5% and 46.1%, respectively) started with lower doses than expected, mainly 10 mg twice daily (Figure 2D). In PLT-50 patients, median dose tended to be stable over time, whereas in PLT-100 and in PLT-200 patients, median dose tended to decrease with respect to starting dose (Figure 2E,F).

Notably, among the 365 (41.2%) patients who started with lower-than-expected ruxolitinib dose, 177 (48.5%) had anemia and/or leukopenia.

**Response to ruxolitinib and hematological toxicity according to cytopenic phenotype**

At 6 months, 30.6% of 666 evaluable patients achieved a spleen response, whereas 65.1% of 642 evaluable patients achieved symptom response. The rate of spleen response was significantly lower in patients with cytopenia (26.5% vs. 34.1% at 6 months, respectively; p = .04) and in patients with ≥2 cytopenias compared with patients with only one cytopenia (28.7% vs. 17.2%; p = .05).

The rate of symptom response at 6 months was significantly lower in patients with cytopenic MF, being 59.8% versus 68.8% (p = .008). Particularly, sex-adjusted anemia was significantly associated with lower symptom response (59.6% vs. 68.5% in non-anemic patients; p = .02).

Rates of 6-month responses were lower in patients with cytopenia and SMF (spleen: 19.1% vs. 37.5%, p = .001; symptoms: 54.7% vs. 69.4%, p = .01) but comparable across the two groups in PMF (spleen, p = .82; symptoms, p = .16).

At 3 and 6 months, the percentage of patients with any grade anemia was higher in proliferative compared with cytopenic patients (3-month anemia: 65.2% vs. 55.4%, p = .01; 6-month anemia: 56.6% vs. 28.7%, p < .001). Conversely, patients with cytopenia had higher rates of thrombocytopenia (3-month thrombocytopenia: 31.1% vs. 18.8%, p < .001; 6-month thrombocytopenia: 35.7% vs. 30.7%, p = .14). Among the 14 PLT-50 patients who started with a ruxolitinib dose higher than 10 mg twice daily, 3- and 6-month anemia and thrombocytopenia rates were comparable to those observed in PLT-50 patients starting with lower doses.

**Impact of cytopenic phenotype on outcome**

After a median ruxolitinib exposure of 2.3 years (range, 0.1–12.4), 538 (60.7%) patients discontinued ruxolitinib permanently, 117

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**Figure 1** Bar graph reporting the distribution of peripheral blood cell counts in PMF (top) and SMF (bottom). PMF indicates primary myelofibrosis; SMF, secondary myelofibrosis.
(13.2%) had a leukemic transformation, and 414 (46.8%) died, with an incidence rate of 9.6, 1.9, and 6.8 per 100 patient-years, respectively.

Main reasons for discontinuation were hematological toxicity (17.9%), lack/loss of spleen response (23.3%), and leukemic transformation (13.8%). Among patients who discontinued ruxolitinib, 6.3% underwent ASCT and 6.7% were later enrolled in an investigational clinical trial. Reasons for discontinuation, including ASCT, were comparable among cytopenic and proliferative patients, except for hematological toxicity, which was higher in patients with cytopenia (21.8% vs. 12.5%, p = .005). After competing risk analysis, the cumulative incidence of ruxolitinib discontinuation at 5 years was 57% and 38% in cytopenic and proliferative patients (p < .001), with a median time to discontinuation of 1.8 versus 2.9 years, respectively (Figure 3A). Incidence of ruxolitinib discontinuation was significantly higher in patients with ≥2 cytopenias compared with one cytopenia (median discontinuation time, 1.1 vs. 2.0 years, respectively; p < .001). Analyzing PMF and SMF separately, cytopenic phenotype remained significantly associated with higher incidence of ruxolitinib discontinuation in both settings (p = .03 in PMF and p < .001 in SMF) (Figure S1A–C).

After competing risk analysis, the cumulative incidence of leukemic transformation was not different between cytopenic and proliferative phenotypes (19% vs. 14% at 5 years, respectively; p = .06) (Figure 3B). This was also confirmed in the separate analysis of PMF (p = .37) and SMF (p = .16). Considering prefibrotic PMF only, the cumulative incidence of leukemic transformation was significantly higher in patients with a cytopenic phenotype (16% vs. 26% in proliferative patients; p = .05) (Figure S1D). No differences were observed between cytopenic and proliferative patients with overt PMF (20% vs. 22%; p = .41).

Median OS was 4.1 and 7.6 years in cytopenic and proliferative patients, respectively (log-rank p < .001). OS was also different between cytopenic patients with one (median, 5.9 years) and ≥2 (median, 2.6 years) cytopenias (p = .006). In Cox regression analysis adjusted for DIPSS score, OS was significantly shorter in patients with cytopenic versus proliferative MF (p < .001) (Figure 3C). This was confirmed also in patients with PMF (p = .002) and SMF (p = .003) (Figure S1E,F). Patients with prefibrotic PMF and cytopenic phenotype had a remarkably inferior OS compared with proliferative patients (p = .004) (Figure S1G). Accordingly, OS was significantly lower in cytopenic overt PMF patients compared with proliferative overt PMF patients (p = .02) (Figure S1H).

**DISCUSSION**

The efficacy of ruxolitinib in cytopenic MF, and the prognostic impact of these hematological features in a homogeneously treated cohort, is unknown.

Here, we observed that most (45.9%) patients presented at least one (mainly, anemia) cytopenia and 20.6% more than one cytopenias at treatment start. A cytopenic phenotype was associated with prognostically detrimental genetic markers (HMR mutations and unfavorable karyotype) and with higher DIPSS/MYSEC-PM risk category. These results are in line with those observed in a cohort of patients with prefibrotic and overtly fibrotic PMF at diagnosis. Notably, the percentage of patients who started ruxolitinib at intermediate 1 risk was high overall (55.2%) and increased over the years up to 70%. Early real-life use of ruxolitinib was likely related to
the demonstration that early treatment could improve the likelihood of responses, without worsening the toxicity profile at least in the short to medium term, and possibly improving survival.\textsuperscript{22–26}

The presence of cytopenias resulted in using lower doses of ruxolitinib, both at the beginning of therapy and on average during the first 3 months and throughout the observation period. This was partially expected because the dose of ruxolitinib is determined by platelet count. However, a substantial number of patients ($n = 365$; 41.2\% of the total cohort) started ruxolitinib at lower doses than expected based on platelet count. Of these, 48.5\% had other cytopenia (mostly, anemia) that might warrant reduced initial dosing. Indeed, the prospective Realise phase 2 study recently showed that ruxolitinib start at the dose of 10 mg twice daily may be beneficial in patients with baseline anemia.\textsuperscript{27} In the remaining 188 patients (21.2\% of the total cohort), ruxolitinib was started at low doses by clinical decision only.

A significantly lower rate of spleen and symptoms response at 6 months was observed in cytopenic MF. This adverse result may be primarily related to the use of lower ruxolitinib doses. Indeed, a correlation between dose and response has been observed in the prospective phase 1/2 trial and in real-world studies.\textsuperscript{28–30} Because dose also correlates with hematological toxicity, we accordingly observed a lower rate of drug-induced anemia in patients with cytopenia.

The probability of ruxolitinib discontinuation was significantly higher in patients with cytopenic MF. Also, survival was worse in patients with cytopenic PMF and SMF and in those with more than one cytopenia. The substantial overlap between this outcome result and that observed in a retrospective cohort of patients with PMF undergoing heterogeneous therapeutic strategies\textsuperscript{12} suggests that the cytopenic phenotype has a key prognostic value, likely because of its association with high-risk biological features, which ruxolitinib does not significantly alter. Additionally, both absence of spleen response and ruxolitinib discontinuation are associated with worse\textsuperscript{23,31} outcome. Finally, after competing risk analysis, the cumulative incidence of leukemic transformation was not statistically different among cytopenic and proliferative patients. However, we confirmed a significant association between cytopenic phenotype and worse outcome in patients pre-PMF, as already showed by Coltro et al.\textsuperscript{12}

Overall, this study shows that cytopenic MF has a lower probability of therapeutic success with ruxolitinib as monotherapy and suggests that these patients should be considered for alternative therapeutic strategies. Unlike ruxolitinib, fedratinib seems effective and tolerable with standard dosing in patients with moderate thrombocytopenia without the need for titration during treatment course\textsuperscript{32–35} Pacritinib, a JAK2, FLT3, and IRAK1 inhibitor, is characterized by less myelosuppression compared with ruxolitinib and fedratinib and seems to be most promising in patients with MF and severe thrombocytopenia.\textsuperscript{36–38} Momelotinib is an oral JAK1/2, ACVR1 inhibitor that reduces expression of hepcidin, with increased iron availability for erythropoiesis and significant rates of anemia response.\textsuperscript{39,40}

The implementation of new drugs specifically tailored to this patient population represents an important focus of future clinical research and practice.
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Francesca Palandri reports consultancy and honoraria from Novartis, Celgene, AOP, Sierr Oncology, and CTI. Giulia Benevolo reports honoraria from Novartis, Janssen, Amgen, Takeda, and BMS. Alessandra Iurlo, Massimo Breccia, and Monica Bocchia report honoraria from Novartis, BMS, Pfizer, and Incyte. Monica Crugnola reports honoraria from Novartis and Amgen. Gianpietro Semenzato reports honoraria from AbbVie, Roche, and Takeda. Gianni Binotto reports honoraria from Novartis, Incyte, BMS-Celgene, and Pfizer. Roberto M. Lemoli reports honoraria from Jazz, Pfizer, AbbVie, BMS, Sanofi, and StemLine. Florian H. Heidel reports consultancy for Novartis, CTI, and Celgene and research funding from Novartis. Fabrizio Pane reports honoraria from Incyte, Novartis, Jazz, BMS-Celgene, Amgen, and Gilead. Michele Cavo acted as consultant and received honoraria from Janssen, BMS, Celgene, Sanofi, GlaxoSmithKline, Takeda, Amgen, Oncopendes, AbbVie, Karyopharm, and Adaptive.

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REFERENCES
SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.