

Peripheral blasts are associated with responses to ruxolitinib and outcomes in patients with chronic-phase myelofibrosis

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BACKGROUND: The presence of peripheral blasts (PB) is a negative prognostic factor in patients with primary and secondary myelofibrosis (MF) and PB $\geq 4\%$ was associated with a particularly unfavorable prognosis. Ruxolitinib (RUX) is the JAK1/2 inhibitor most used for treatment of MF-related splenomegaly and symptoms. Its role has not been assessed in correlation with PB. **METHODS:** In 794 chronic-phase MF patients treated with RUX, we evaluated the impact of baseline percentage of PB on response (spleen and symptoms responses) and outcome (RUX discontinuation-free, leukemia-free, and overall survival). Three subgroups were compared: PB-O (no PB, 61.3%), PB-4 (PB 1%-4%, 33.5%), and PB-9 (PB 5%-9%, 5.2%). **RESULTS:** At 3 and 6 months, spleen responses were less frequently achieved by PB-4 ($P = .001$) and PB-9 ($P = .004$) compared to PB-O patients. RUX discontinuation-free, leukemia-free, and overall survival were also worse for PB-4 and PB-9 patients ($P = .001$, $P = .002$, and $P < .001$, respectively). **CONCLUSIONS:** Personalized approaches beyond RUX monotherapy may be useful in PB-4 and particularly in PB-9 patients. **Cancer 2022;0:1-6.** © 2022 The Authors. *Cancer* published by Wiley Periodicals LLC on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

KEYWORDS: myelofibrosis, outcome, peripheral blasts, response, ruxolitinib.

INTRODUCTION

Myelofibrosis (MF) is the most severe among the chronic Philadelphia-negative myeloproliferative neoplasms characterized by progressive splenomegaly and symptoms, cytopenia, and marrow fibrosis. Patients with chronic phase MF show a blast count below 10% both in the peripheral blood and in the bone marrow and they may have a variable survival, ranging from months to decades.^{1,2} The presence of peripheral blasts (PB) is a laboratory feature associated with worse prognosis in all prognostic models that have been developed over the years, both in primary myelofibrosis (PMF) and secondary myelofibrosis.³⁻⁶ Their predictive role has remained substantial even after the inclusion of molecular and histological parameters in disease risk assessment.^{7,8} Moreover, presence of PB has been associated with increased risk of leukemic transformation (LT) ($\geq 20\%$ blasts) in several retrospective studies.^{2,4,9}

Recently, PB $\geq 4\%$ was associated with a particularly unfavorable prognosis in a large MF cohort, including patients in accelerated (blasts, 10%-19%) and blast (blasts, $\geq 20\%$) phase. This analysis also showed that ruxolitinib (RUX), the

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JAK1/2 inhibitor most used for treatment of MF-related splenomegaly and symptoms, provided a survival benefit to chronic phase patients.^{10,11}

However, there is no specific information yet regarding the impact of the percentage of PB in chronic phase MF patients treated with RUX. In this multicenter retrospective study, we aimed to evaluate the clinical characteristics and survival outcomes, as well as the efficacy of RUX therapy, in patients with chronic phase MF who received RUX in a real-life context, as it relates to different percentages of peripheral blasts.

MATERIALS AND METHODS

Patients and Study Design

After institutional review board approval, the “RUX-MF” retrospective study collected 804 chronic phase MF patients who received RUX outside clinical trials in 26 hematology centers. In 794 patients, the percentage of PB was evaluated by morphology at RUX start. Patients were grouped in 3 subcohorts: PB-0 (no peripheral blasts observed at the day of RUX start), PB-4 (peripheral blasts between 1% and 4%), and PB-9 (peripheral blasts between 5% and 9%). To increase data reliability, in PB-0 patients, the absence of blasts during evaluations before RUX start was also established.

Definitions

Diagnoses of PMF and post-polycythemia vera/post-essential thrombocythemia MF were made according to 2016 World Health Organization criteria or International Working Group on Myelofibrosis Research and Treatment (IWG-MRT) criteria, respectively.^{2,12} All patients who received treatment with RUX in the current analysis were in chronic phase (peripheral and marrow blast cells <10%). Risk category was assessed according to the dynamic prognostic score system (DIPSS).⁴ High molecular risk (HMR) mutations were evaluated by next-generation sequencing (NGS) with the myeloid panel SOPHiA Genetics (Sophia Genetics, Saint Sulpice, Switzerland) at RUX start and included *ASXL1*, *IDH1/2*, *EZH2*, and *SRSF2* according to standard definition.¹³ Leukemic transformation was diagnosed according to standard criteria.² Spleen and symptom responses were assessed using IWG-MRT criteria.¹⁴

Statistical Analysis

Comparisons of quantitative variables between groups were performed by Kruskal-Wallis and Dunn’s tests whereas association between categorical variables was tested by the χ^2 test. Variables significantly associated

with RUX discontinuation/leukemic transformation/overall survival in univariate analysis (log-rank test) were considered for multivariable analyses (MVA), performed using the Cox regression model, with adjustment for delayed entry and evaluation of the model’s performance in terms of goodness of fit. 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, Texas).

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. The promoter of this study was the L. and A. Seràgnoli Institute of Hematology (Azienda Ospedaliera S. Orsola-Malpighi, Bologna, Italy), which obtained the approval (protocol code MF-2014-01, approval date 10/06/2014, approval file number 068/2014/U) from the Area Vasta Emilia Centro Ethics Committee (Bologna, Italy; cometico@aosp.bo.it). The study was also approved by the local ethics committee of all participating centers and has no commercial support.

RESULTS

Study Cohort

Patients were categorized according to PB at RUX start: PB-0 (no PB; *n* = 487, 61.3%), PB-4 (PB 1%-4%; *n* = 266, 33.5%), and PB-9 (PB 5%-9%; *n* = 41, 5.2%) (Table 1). DIPSS distribution was intermediate-1 (54.1%), intermediate-2 (38.3%), and high (7.6%); 47.8% had a large splenomegaly (palpable at ≥ 10 cm below costal margin) and 60.6% were highly symptomatic (total symptom score [TSS], ≥ 20). At least 1 HMR mutation was detected in 41.3% of the 167 evaluable patients (≥ 2 mutations in 10.8%). Among baseline characteristics, higher percentage of PB was associated with high DIPSS risk (*P* < .001), platelet count $< 100 \times 10^9/L$ (*P* < .001), fibrosis grade ≥ 2 (*P* < .001), and spleen length ≥ 10 cm (*P* = .003).

Impact of PB on Response to RUX

At 3 and 6 months, 26.9% and 30.4% of 672 and 619 evaluable patients achieved a spleen response, whereas 59.7% and 68.1% were in symptom response, respectively. At 3 months, spleen response (PB-0, 31.8%; PB-4, 20.6%; PB-9, 11%; *P* = .001) and symptom response (PB-0, 62.9%; PB-4, 55.5%; PB-9, 42%; *P* = .02) were less frequently achieved by PB-4 and PB-9 patients compared to PB-0 patients. This association

TABLE 1. Patients Characteristics at RUX Start, Overall, and According to Percentage of PB

Characteristics at RUX Start	Overall Cohort	PB-0 (no PB)	PB-4 (PB: 1%-4%)	PB-9 (PB: 5%-9%)
No. (%)	794 (100)	487 (61.3)	266 (33.5)	41 (5.2)
Median age (range, y)	68.1 (24-89)	67.9 (26.5-89)	68.4 (24-88.5)	68.4 (42.1-82.2)
Male sex, %	58.1	57.7	58.3	61
Primary MF, %	52.5	53	53.4	41.5
Mutational status, JAK2/CALR/MPL/TN, %	80.5/13.1/2/4.4	85.6/8/1.9/4.5	73.7/19.9/1.6/4.8	64.1/30.8/0/5.1
High DIPSS, %	7.6	1.9	16.5	17.1
Platelet <100 × 10 ⁹ /L, %	10.8	7.6	15	21.9
Leukocytes >25 × 10 ⁹ /L, %	16.4	13.6	19.6	29.3
Spleen ≥10 cm below costal margin by palpation, %	47.8	43	54.3	62.5
TSS ≥20	60.6	61.7	59.5	54.3
≥1/≥2 High risk mutations (% 167 evaluable)	41.3/10.8	41.7/11.1	39.6/9.4	50/16.7
Marrow fibrosis grade ≥2	77.9	73.3	84.7	90
Median time from MF diagnosis to RUX (range, y)	1.31 (0-32.8)	1 (0-22)	1.8 (0-32.8)	1.2 (0.2-14.8)
Starting/cumulative RUX dose ≥15 mg bid, %	61.4/52.6	61.4/51.6	62.4/56.3	55.6/42.9

Abbreviations: DIPSS, dynamic prognostic score system; MF, myelofibrosis; PB, peripheral blast; RUX, ruxolitinib; TSS, total symptom score.

remained significant for spleen response at 6 months (PB-0, 35%; PB-4, 25%; PB-9, 13%; $P = .004$) and for both spleen response ($P = .003$) and symptom response ($P = .01$) at any time.

Impact of PB on Outcome

After a median RUX exposure of 1.5 years (0.1-8.9), 491 (61.8%) patients discontinued RUX, 110 patients (13.9%) had a leukemic transformation and 365 patients (46%) died.

Median time to RUX discontinuation was 18.3 months (range, 0.37-107), and main reasons for discontinuation were hematological toxicity (17.5%), lack of spleen response (16.7%), and leukemic transformation (14.9%). Overall, the incidence rate of discontinuation and death during therapy was 48.4 per 100 patient-years. Notably, PB-0 patients discontinued less frequently because of lack/loss of spleen response (13% vs 20% at 3 years, $P = .01$) than PB-9 patients. In univariate analysis, discontinuation-free survival at 2 years was 70.8% versus 59% versus 18.1% in PB-0, PB-4, and PB-9 patients, respectively (log-rank $P < .001$) (Fig. 1A). In MVA, PB-4, TSS ≥20, and ≥2 HMR mutations remained significantly associated with higher probability of RUX discontinuation (Fig. 1B).

At 2 years, leukemia-free survival (LFS) was 94% versus 88% versus 75% in PB-0, PB-4, and PB-9 patients, respectively (log-rank $P = .004$) (Fig. 1C). In MVA, PB-4 and ≥2 HMR mutations remained significantly associated with higher probability of LT (Fig. 1D).

After a median RUX exposure of 1.5 years (0.1-8.9), 365 (46%) patients died. Median overall survival (OS) was 6.4, 5.7, and 2.5 years in PB-0, PB-4, and PB-9 patients, respectively (log-rank $P = .001$) (Fig. 1E). In MVA, PB-4 age ≥65 years and ≥2 HMR mutations remained significantly associated with a lower survival (Fig. 1F). The use of RUX dose >10 mg twice daily at RUX start ($P = .001$), at 3 months ($P < .001$), and overall ($P < .001$) were associated with a higher survival in univariate analysis, but not in MVA (data not shown). Causes of death included MF progression (24.7%), infection (20%), leukemic transformation (18.4%), bleeding (7.4%), second neoplasia (7.4%), heart disease (5.5%), thrombosis (3%), allogeneic stem cell transplantation (2.2%), and other unrelated causes (11.4%). Notably, PB-9 patients more frequently died due to infections ($P = .004$) and leukemic transformation ($P < .001$) compared to PB-0 patients.

Unfavorable association with LFS ($P = .02$) and OS ($P = .05$) was also confirmed in patients with HMR ≥1.

DISCUSSION

Refining the prognosis of chronic phase MF patients treated with RUX and identifying the subcategories that are most at risk of therapeutic failure is of extreme relevance in the current clinical setting, which has been enriched with new therapeutic possibilities, including the recently approved JAK2-inhibitor fedratinib and other agents that are on clinical investigation for second-line use after or in combination with RUX.^{15,16}

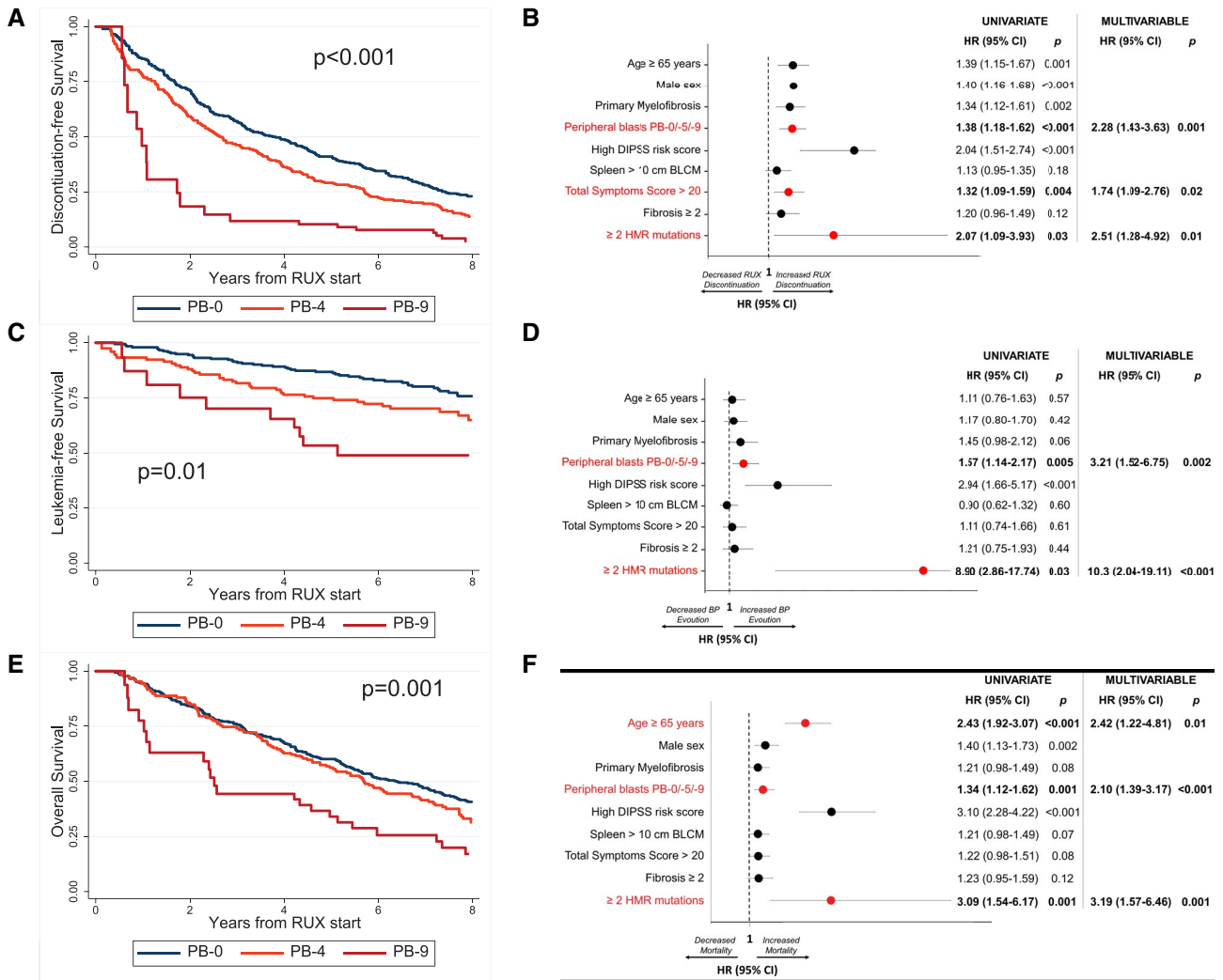


FIGURE 1. Ruxolitinib discontinuation-free survival (A), leukemia-free survival (C), and overall survival (E). Multivariable analysis showing factors associated with ruxolitinib discontinuation (B), leukemic transformation (D), and survival (F).

Here, we analyzed whether further subclassification of PB count, an easily detectable variable, was relevant for treatment response and outcome in chronic phase patients. Overall, RUX monotherapy confirmed its efficacy in this population, with significant response rates and most patients still on therapy at 3 years. However, a higher percentage of PB was significantly associated with significantly lower response rates to RUX at 3 and 6 months. This finding is partly due to the correlation of PB with other factors that were found to be associated with worse clinical response, specifically high DIPSS risk, massive splenomegaly, and thrombocytopenia.¹⁷ Accordingly, patients with PB between 5% and 9% had significantly higher rates

of RUX discontinuation, mainly due to lack/loss of spleen response. Moreover, where PB between 5% and 9% seem to be less impactful, the small number of patients of the PB-9 subgroup, which reduces its statistical power, must be taken into account.

The prognostic role of HMR, which was found here to be correlated with all outcome parameters, has been previously described and is certainly relevant.¹³ However, NGS evaluation is costly and sometimes unavailable. The association between higher PB percentages and higher risk of leukemic transformation and death in MVA, together with HMR mutations, confirms how much this simple laboratory finding reflects a biologically more aggressive disease and makes a strong argument for PB

evaluation at start of RUX. Further studies might also clarify the relevance of prospective PB monitoring during RUX treatment.

The main constraint of this study is its retrospective nature. Particularly, inaccurate count of PBs, that were assessed by the treating hematologists without a centralized re-evaluation, or failure to recognize significant fluctuations in PB count before RUX start, cannot be entirely ruled out. The count of marrow blasts was not available because most patients had a dry tap and it could not be used to integrate and extend data on circulating blasts. Nonetheless, the substantial number of included patients and the use of 3 macro-subcategories, each of which included patients with a wide range of PB counts, may partially compensate these intrinsic shortcomings.

Overall, this study highlights how a lower response rate and a shorter duration of RUX benefit in PB-4, and particularly in PB-9 patients, strongly support the need for clinical trials investigating novel and/or combinatorial approaches in these patients.

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CONFLICT OF INTEREST DISCLOSURES

Francesca Palandri received consultancy fees and/or honoraria from Novartis, Celgene, AOP, Sierra Oncology and CTI. Massimo Breccia received honoraria from Novartis, BMS, Pfizer, and Incyte. Elisabetta Abruzzese received honoraria from Novartis, BMS, Pfizer, and Incyte. Massimiliano Bonifacio received honoraria from Novartis, BMS, Pfizer, and Incyte. Mario Tiribelli received consultancy fees and honoraria from Novartis. Malgorzata M. Trawinska received consultancy fees and honoraria from Novartis. Giuseppe A. Palumbo received honoraria and/or consultancy fees from AbbVie, AOP, AstraZeneca, BMS-Celgene, Novartis, Incyte, Janssen, and Takeda. Giulia Benevolo received honoraria from Novartis, Janssen, Amgen, Takeda, and BMS. Gianni Binotto received honoraria from Novartis, Incyte, BMS-Celgene, and Pfizer. Francesco Cavazzini received honoraria from Novartis, Incyte, and Pfizer. Monica Crugnola received honoraria from Novartis and Amgen. Florian H. Heidel received consultancy fees from Novartis, CTI, and Celgene and research funding from Novartis. Monica Bocchia received honoraria from Incyte, Janssen, Jazz, and Novartis. Fabrizio Pane received honoraria from Incyte, Novartis, Jazz, BMS-Celgene, AMGEN, and Gilead. Michele Cavo received consultancy fees and honoraria from Janssen, BMS-Celgene, SanoFI, GlaxoSmithKline, Takeda, Amgen, Oncopeptides, AbbVie, Karyopharm, Adaptive, and Novartis. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Francesca Palandri: Conceptualization, data curation, investigation, methodology, project administration, resources, supervision, validation, visualization, writing—original draft, and writing—review and editing. **Daniela Bartoletti:** Data curation, formal analysis, investigation, methodology, project administration, resources, validation, visualization, writing—original draft, and writing—review and editing. **Giuseppe A. Palumbo:** Conceptualization, validation, investigation, resources, and writing—review

and editing. **Massimo Breccia:** Conceptualization, validation, investigation, resources, and writing—original draft. **Alessandra Iurlo:** Investigation, resources, and writing—review and editing. **Massimiliano Bonifacio:** Investigation, resources, and writing—review and editing. **Elisabetta Abruzzese:** Investigation, resources, and writing—review and editing. **Giovanni Caocci:** Investigation, resources, and writing—review and editing. **Elena M. Elli:** Investigation, resources, and writing—review and editing. **Giuseppe Auteri:** Investigation, resources, and writing—review and editing. **Mario Tiribelli:** Investigation, resources, and writing—review and editing. **Nicola Polverelli:** Investigation, resources, and writing—review and editing. **Maurizio Miglino:** Investigation, resources, and writing—review and editing. **Florian H. Heidel:** Investigation, resources, and writing—review and editing. **Alessia Tieghi:** Investigation, resources, and writing—review and editing. **Giulia Benevolo:** Investigation, resources, and writing—review and editing. **Eloise Beggiato:** Investigation, resources, and writing—review and editing. **Carmen Fava:** Investigation, resources, and writing—review and editing. **Francesco Cavazzini:** Investigation, resources, and writing—review and editing. **Novella Pugliese:** Investigation, resources, and writing—review and editing. **Gianni Binotto:** Investigation, resources, and writing—review and editing. **Costanza Bosi:** Investigation, resources, and writing—review and editing. **Bruno Martino:** Investigation, resources, and writing—review and editing. **Monica Crugnola:** Investigation, resources, and writing—review and editing. **Emanuela Ottaviani:** Investigation, resources, and writing—review and editing. **Giorgia Micucci:** Investigation, resources, and writing—review and editing. **Malgorzata M. Trawinska:** Investigation, resources, and writing—review and editing. **Antonio Cuneo:** Investigation, resources, and writing—review and editing. **Monica Bocchia:** Investigation, resources, and writing—review and editing. **Mauro Krampera:** Investigation, resources, and writing—review and editing. **Fabrizio Pane:** Investigation, resources, and writing—review and editing. **Roberto M. Lemoli:** Investigation, resources, and writing—review and editing. **Daniela Cilloni:** Investigation, resources, and writing—review and editing. **Nicola Vianelli:** Investigation, resources, and writing—review and editing. **Michele Cavo:** Investigation, resources, and writing—review and editing.

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