Received: 7 September 2023 | Revised: 19 October 2023 | Accepted: 14 November 2023

DOI: 10.1002/cncr.35156

ORIGINAL ARTICLE

Incidence of blast phase in myelofibrosis patients according to anemia severity at ruxolitinib start and during therapy

Francesca Palandri MD, PhD[1] | Giuseppe A. Palumbo MD[2] | Giulia Benevolo MD[3] | Alessandra Iurlo MD[4] | Elena M. Elli MD[5] | Elisabetta Abruzzese MD, PhD[6] | Nicola Polverelli MD[7] | Mario Tiribelli MD[8] | Giuseppe Auteri MD, PhD[1,9] | Alessia Tieghi MD[10] | Giovanni Caocci MD[11] | Gianni Binotto MD[12] | Francesco Cavazzini MD[13] | Filippo Branzanti MSc[1] | Eloise Beggiato MD[3] | Maurizio Miglino MD[14,15] | Costanza Bosi MD[16] | Monica Crugnola MD[17] | Monica Bocchia MD[18] | Bruno Martino MD[19] | Novella Pugliese MD[20] | Luigi Scaffidi MD[21] | Marta Venturi MD[1,9] | Andrea Duminuco MD[22] | Alessandro Isidori MD, PhD[23] | Daniele Cattaneo MD[4] | Mauro Krampera MD[21] | Fabrizio Pane MD[20] | Daniela Cilloni MD[24] | Gianpietro Semenzato MD[12] | Roberto M. Lemoli MD[14,15] | Antonio Cuneo MD[13] | Malgorzata M. Trawinska MD[6] | Nicola Vianelli MD[1] | Michele Cavo MD[1,9] | Massimiliano Bonifacio MD[21] | Massimo Breccia MD[25]

Correspondence
Francesca Palandr.
Email: francesca.palandri@unibo.it

Funding information
Ministero della Salute, Grant/Award Number: RC-2023-2778976

Abstract

Background: Anemia is frequently present in patients with myelofibrosis (MF), and it may be exacerbated by treatment with the *JAK2*-inhibitor ruxolitinib (RUX). Recently, a relevant blast phase (BP) incidence has been reported in anemic MF patients unexposed to RUX.

Methods: The authors investigated the incidence of BP in 886 RUX-treated MF patients, included in the "RUX-MF" retrospective study.

Results: The BP incidence rate ratio (IRR) was 3.74 per 100 patient-years (3.74 %p-y). At therapy start, Common Terminology Criteria for Adverse Events grade 3-4 anemia (hemoglobin [Hb] <8 g/dL) and severe sex/severity-adjusted anemia (Hb <8/<9 g/dL in women/men) were present in 22.5% and 25% patients, respectively. IRR of BP was 2.34 in patients with no baseline anemia and reached respectively 4.22, 4.89, and 4.93 %p-y in patients with grade 1, 2, and 3–4 anemia. Considering the sex/severity-adjusted Hb thresholds, IRR of BP was 2.85, 4.97, and 4.89 %p-y in patients with mild/no anemia, moderate, and severe anemia. Transfusion-dependent patients had the highest IRR (5.03 %p-y). Progression-free survival at 5 years was

70%, 52%, 43%, and 27% in patients with no, grade 1, 2, and 3–4 anemia, respectively ($p < .001$). At 6 months, 260 of 289 patients with no baseline anemia were receiving ruxolitinib, and 9.2% had developed a grade 3–4 anemia. By 6-month landmark analysis, BP-free survival was significantly worse in patients acquiring grade 3–4 anemia (69.3% vs. 88.1% at 5 years, $p < .001$).

Conclusions: This study highlights that anemia correlates with an increased risk of evolution into BP, both when present at baseline and when acquired during RUX monotherapy. Innovative anemia therapies and disease-modifying agents are warranted in these patients.

KEYWORDS
anemia, blast phase, myelofibrosis, ruxolitinib

INTRODUCTION

Myelofibrosis (MF) is the most severe among the classical Philadelphia-negative myeloproliferative neoplasm (MPN), which may present de novo (primary myelofibrosis [PMF]) or secondary to essential thrombocythemia/polycythemia vera (PET/PPV-MF, SMF).[1,2] It is clinically characterized by splenomegaly, systemic symptoms, and progressive cytopenias. MF is burdened by severely impaired quality of life, increased risk of progression into blast phase (BP), and overall reduced survival expectation.[3]

Anemia is present at diagnosis in approximately 35%–40% of cases at diagnosis and its prevalence increases over time, affecting virtually all patients along with the natural progression of MF.[4,5] Anemia has a profound impact on quality of life and is one of the major contributors to worse prognosis in all the models that are currently used in PMF and in SMF.[6–10] Anemia has also been listed among factors that are associated with an increased risk of BP progression in patients with PMF.[11]

Very recently, a relevant incidence of BP in anemic MF patients has been observed within a data set of 1752 MF subjects largely unexposed to ruxolitinib (RUX), the first-in-class *JAK2* inhibitor (JAKi) approved for the treatment of MF-related splenomegaly and symptoms.[12]

It is acknowledged that both RUX and fedratinib, which is the second JAKi approved in MF, are burdened by significant hematological toxicity due to on-target inhibition of the *JAK-STAT* signaling, with 30%–45% of patients experiencing grade 3–4 anemia.[13–15]

Although RUX-induced anemia was not found to correlate with reduced survival,[16] information on the role of baseline and acquired anemia on BP progression in patients treated with RUX is currently limited.

In this study, we reported the incidence of BP according to anemia severity in a large real-world cohort of PMF and SMF patients, homogeneously treated with RUX. This could serve as a reference for assessing BP occurrence in populations of MF patients with splenomegaly and symptoms receiving treatments alternative to RUX monotherapy in the front-line setting.

MATERIALS AND METHODS

Patients and study design

After institutional review board approval, the "RUX-MF" retrospective study collected 886 MF patients who received RUX outside clinical trials in 26 hematology centers that are dedicated to the treatment of MF. All patients were in chronic phase at RUX start.

The list of the participating centers is available in Supporting Information S1: Appendix. All centers were asked to report, in an electronic case report form, their consecutive MF patients who received RUX 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 the de-identification of the patients with an alphanumeric code to protect personal privacy. Data collected included patient demographics, comorbidities, medications, clinical/laboratory tests at diagnosis and during follow-up, date of RUX start and stop, type of MF therapies before and after RUX, duration of RUX treatment, and adverse events during the treatment. Any treatment decision, including starting RUX 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).

Definitions

Diagnoses of PMF and SMF were made according to 2016 World Health Organization criteria (WHO) and International Working Group on Myelofibrosis Research and Treatment (IWG-MRT) criteria, respectively.[17,18]

The risk category was assessed at the time patients started on RUX according to the Dynamic International Prognostic Score System (DIPSS).[10] Histologic examination was performed at local institutions; fibrosis was graded according to the European Consensus Grading System.[19] Unfavorable karyotype was categorized as previously described.[20] Triple-negative patients had no mutations in the three driver genes (*JAK2*, *CALR*, and *MPL*). Evolution to BP was defined by leukemic blast cells being at least 20% in peripheral blood or bone marrow according to WHO criteria.[17] MF-related symptoms were assessed using the 10-item Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN10-TSS).[21] Spleen and symptoms responses were routinely assessed by palpation and by periodical TSS evaluation, according to 2013 IWG-MRT criteria.[22]

Anemia was graded according to Common Terminology Criteria for Adverse Events (CTCAE) grading[23]: grade 3–4 anemia corresponded to hemoglobin (Hb) <8 g/dL, grade 2 anemia to Hb 8–10 g/dL, whereas grade 1 (Hb >10 g/dL) anemia was grouped together with normal Hb values. Anemia was graded considering the sex- and severity-adjusted Hb thresholds,[24] including severe anemia (Hb <8 g/dL in women and <9 g/dL in men), moderate anemia (Hb 8–9.9 g/dL in women and 9–10.9 g/dL in men), and mild/no anemia (Hb values higher than those defining moderate anemia). Red blood cell transfusion dependence (RBC-TD) was defined as having received at least four RBC units in the previous 12 weeks.[18] RBC transfusion requirement (RBC-TR) was defined as any RBC transfusion need not meeting the criteria for RBC-TD.

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 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 approved by the local ethics committee of 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 anemia groups were performed by Wilcoxon-Mann-Whitney rank-sum test whereas association between categorical variables was tested by the χ^2 test.

Blast phase free survival (BP-FS) and progression-free survival (PFS) were calculated by Kaplan–Meier curves from the date of RUX start to the date of BP or last contact (BP-FS) or to the date of BP, death, or last contact (PFS), whichever came first.

Patients who underwent allogeneic stem cell transplant (ASCT) were censored at the time of transplant.

To assess factors associated with BP, the following baseline variables selected on the basis of clinical plausibility, have been explored using a logistic regression model: (1) anemia degree by CTCAE e by sex-adjusted anemia level; (2) platelet count (PLT) $<100 \times 10^9$/L; (3) white blood cells (WBC) count $>15 \times 10^9$/L; (4) peripheral blasts >1%; (5) age >70 years; and (6) TSS ≥20. Pearson's correlation test was performed to investigate a relationship between these factors.

A log-rank test was applied to compare survival times among the different anemia-grade classes. By univariate Cox proportional hazards models, we evaluated associations between BP-FS and severity of anemia by CTCAE grade and sex-adjusted anemia level. Comparisons between BP-FS and PFS across anemia categories were also analyzed by univariate Cox proportional hazards models with adjustment for the DIPSS score at RUX start.

To assess factors associated with BP in patients who were not anemic at RUX start, the following variables, evaluated after 6 months of RUX therapy, have been explored using a logistic regression model: (1) acquired grade 3–4 anemia; (2) lack of spleen response; (3) decrease of platelet count to $<100 \times 10^9$/L in patients with $>200 \times 10^9$/L platelet count at baseline; and (4) increase of symptoms burden to TSS ≥20 in patients with TSS <20 at baseline.

A Poisson regression model was applied to calculate the incidence rate ratio (IRR) of BP within 10 years of follow-up, together with 95% confidence interval (CI). The IRR was described as the number of events per 100 patient-years (%p-y).

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).

RESULTS

Patient characteristics

Table 1 reports the main features and follow-up events of the 886 patients included in this study, overall and distinguished by anemia presence and degree at RUX start.

RUX was started after a median of 1.07 years (range, 0–32.9) from MF diagnosis. Median duration of RUX treatment was 2.4 years (range, 0.1–12.4), and median follow-up time was 3.1 years (range, 0.1–12.4).

At RUX start, 597 (67.4%) patients had anemia, which was CTCAE grade 3–4 in 199 (22.5%) patients, grade 2 in 152 (17.2%) patients, and grade 1 in 246 (27.8%) patients. A total of 289 patients had no anemia (32.6%). Considering sex-adjusted anemia, 222 (25%) patients had severe, 206 (23.3%) patients had moderate, and 458

TABLE 1 Main features at RUX start and follow-up events of 886 RUX-treated myelofibrosis patients overall and stratified by anemia degree according to the CTCAE classification.

		CTCAE Hb classification				
	Total	No anemia (Hb >12 g/dL)	Grade 1 anemia (Hb 10–11.9 g/dL)	Grade 2 anemia (Hb 8–9.9 g/dL)	Grade 3–4 anemia (Hb <8 g/dL)	*p*
Patients, No. (%)	886 (100)	289 (32.5)	246 (27.8)	152 (17.2)	199 (22.5)	
PMF diagnosis						<.001
Pre-PMF, No. (% on 425 evaluable)	113 (26.6)	53 (19.0)	22 (9.4)	14 (10.5)	24 (12.6)	
Overt-PMF, No. (% on 425 evaluable)	312 (73.4)	70 (25.1)	94 (40.3)	50 (33.8)	98 (51.3)	
SMF diagnosis						<.001
PET-MF, No. (% on 411 evaluable)	187 (45.5)	39 (14.0)	64 (27.5)	41 (30.8)	43 (22.5)	
PPV-MF, No. (% on 411 evaluable)	224 (54.5)	117 (41.9)	53 (22.8)	28 (21.1)	26 (13.6)	
Driver mutations, No. (%)						.03
JAK2	650 (81)	322 (49.5)	169 (26.0)	116 (17.8)	43 (6.6)	
CALR	100 (12.4)	31 (31.0)	45 (45.0)	19 (19.0)	5 (5.0)	
MPL	19 (2.4)	3 (15.8)	9 (47.4)	6 (31.6)	1 (5.2)	
Triple negative	34 (4.2)	11 (32.4)	7 (20.6)	12 (35.2)	4 (11.8)	
Median age, years (range)	68.4 (24–89)	65.89 (24–88.2)	69.4 (33.5–88)	68.2 (39.4–84.8)	71.1 (41–89)	<.001
Male sex, No. (%)	511 (57.7)	167 (57.8)	146 (59.4)	79 (52)	119 (59.8)	.44
Palpable spleen, No. (% on 878 evaluable)	845 (96.2)	273 (97.1)	238 (97.1)	142 (94.0)	192 (98)	.20
Median cm BLCM (range)	11 (0–35)	10 (0–35)	10 (0–35)	9 (0–27)	11 (0–31)	.13
TSS >20, No. (%)	516 (61.8)	164 (58.2)	125 (56.1)	80 (55.9)	147 (78.6)	<.001
Median % of peripheral blasts (range)	1 (0–0)	0.7 (0–9)	1.1 (0–9)	1.0 (0–9)	1.1 (0–9)	.002
Median WBC count, $\times 10^9$/L (range)	11.32 (1.1–55)	13.8 (1.1–55)	12 (1.46–92.5)	9.02 (1.8–86.27)	8.77 (1.29–92.3)	<.001
Median PLT count, $\times 10^9$/L (range)	257 (14–1887)	301 (36–1345)	279 (32.9–1632)	222.5 (54–1400)	205 (14–1887)	.001
PLT <100 $\times$ 10^9/L, No. (%)	93 (10.5)	17 (5.9)	28 (11.4)	14 (9.2)	34 (17.1)	
DIPSS score, No. (%)						
Low-intermediate 1 risk	456 (51.5)	236 (81.7)	158 (64.2)	30 (19.7)	32 (16.1)	<.001
Intermediate 2- high risk	430 (48.5)	53 (18.3)	88 (35.7)	122 (80.3)	167 (83.9)	.08
Median years from diagnosis to RUX (range)	1.07 (0–32.85)	0.79 (0–24)	1.34 (0–32.9)	1.47 (0–21.3)	1.36 (0–31.7)	
Median RUX duration, years (range)	2.4 (0–12.4)	3.18 (0.04–12.4)	2.49 (0–9.6)	1.92 (0–9.4)	1.73 (0.03–9.8)	<.001
ASCT, No. (%)	74 (8.5%)	24 (8.4%)	20 (8.3%)	13 (8.7%)	17 (8.6%)	.99
Median follow-up from RUX start, years (range)	3.1 (0–12.4)	3.7 (0.06–12.4)	3.3 (0–9.63)	2.9 (0–9.4)	2.3 (0.3–9.8)	<.001
Deaths, No. (%)	414 (46.8)	90 (31.3)	112 (45.5)	81 (53.6)	131 (65.8)	<.001
Median years from RUX start to BP (range)	1.9 (0.1–8.2)	2.06 (0.3–8.2)	2.14 (0.1–6.9)	1.93 (0.3–6.8)	1.59 (0.2–6.5)	.66

Abbreviations: ASCT, allogeneic stem cells transplant; BLCM, below left costal margine; BP, blast phase; CTCAE, Common Terminology Criteria for Adverse Events; DIPSS, Dynamic International Prognostic Score System; Hb, hemoglobin; MF, myelofibrosis; overt-PMF, overt-primary myelofibrosis; PET-MF, post-essential thrombocythemia myelofibrosis; PLT, platelets; PPV-MF, post-polycythemia vera myelofibrosis; pre-PMF, prefibrotic-primary myelofibrosis; RUX, ruxolitinib; TSS, total symptoms score; WBC, white blood cells.

(51.7%) patients had mild/no anemia. Overall, 90 patients (10.2%) were RBC transfusion-dependent and 98 (11.1%) additional patients had RBC transfusion requirement. Anemia was more frequent and severe in overt-PMF patients compared to early-PMF and PPV/PET-MF ($p < .0001$). Patients with grade 3–4 anemia were also older and presented lower leukocyte and platelet count, higher peripheral blast count, and greater symptoms burden. Anemia was also associated with higher DIPSS category at RUX start and to triple negativity.

Overall, ASCT was performed in 74 (8.5%) patients, with no significant differences related to Hb values at baseline. A total of 414 (46.8%) patients died; the percentage of deaths increased along with the severity of baseline anemia ($p < .001$).

Blast phase and PFS per anemia grade at RUX start

Table 2 reports prevalence and incidence of BP transformation by the presence and the degree of anemia at RUX start.

BP evolution was reported in 117 (13.2%) patients, after a median time of 18.5 years (range, 0.13–36.8) from MF diagnosis and of 1.9 years (range, 0.1–8.2) from RUX start.

The global IRR of BP was 3.74 %p-y.

The IRR of BP was 2.34 %p-y in patients with no anemia and reached respectively 4.22, 4.89, and 4.93 %p-y in patients with CTCAE grade 1 (G1), grade 2 (G2), and grade 3–4 (G3–4) anemia. Significant differences in IRR of BP were noted between patients with no anemia and patients with grade 1 (p = .02), grade 2 ($p = .009$), and grade 3–4 ($p = .006$) anemia. No differences were noted between patients belonging to higher anemia grade categories (Table S1).

In patients with RBC-TD, the IRR of BP was the highest (5.03 %p-y). In univariate Cox model, HR for BP-free survival was 1.54 (95% CI, 0.97–2.45; $p = .066$) in case of CTCAE grade 2 and 1.52 (95% CI, 1.32–3.68; $p = .065$) for grade 3–4 anemia, compared to patients with baseline grade 1 or no anemia.

Considering the sex- and severity-adjusted Hb thresholds, BP incidence was 2.85 p-y, 4.97 %p-y, and 4.89 %p-y in patients with mild/no anemia, moderate, and severe anemia, respectively. Comparably to what observed considering CTCAE grades of anemia, only patients with mild/no anemia had significantly lower IRR of BP compared to patients with moderate ($p = .001$) or severe ($p = .02$) anemia, whereas no difference was noted between patients with moderate anemia versus severe anemia ($p = .95$) (Table S1).

In univariate regression model, PLT $<100 \times 10^9$/L (OR, 2.12; 95% CI, 1.25–3.60; $p = .006$) and anemia (OR, 1.63; 95% CI, 1.04–2.56; $p = .033$) were associated with higher probability of BP evolution. PLT $<100 \times 10^9$/L was highly correlated with anemia by using the Pearson test ($p = .006$). Therefore, anemia was retained as the only factor associated with BP-FS.

In univariate Cox model, HR for BP-free survival was 1.70 (95% CI, 1.1–2.63; $p = .016$) for moderate and 1.28 (95% CI, 1.02–1.6; $p = .03$) for severe anemia, compared to patients with baseline mild/no anemia.

Figure 1 shows that BP-FS was significantly associated with the presence and severity of anemia at RUX start, both considering the CTCAE (Figure 1A) and the sex- and severity-adjusted anemia classification (Figure 1B). More specifically, BP-FS at 5 years was 89%, 81%, 82%, and 78% at 5 years in patients with no, grade 1, grade 2, and grade 3–4 anemia, respectively ($p = .02$). BP-FS at 5 years was respectively 86%, 79%, and 78% in patients with no/mild anemia, moderate, and severe anemia considering sex-adjusted anemia thresholds ($p = .02$).

After adjustment for DIPSS score, both CTCAE-defined anemia and sex- and severity-adjusted Hb thresholds remained significantly associated with BP-FS ($p = .002$ and $p = .003$, respectively) (Figure S1A and S1B).

TABLE 2 Blast phase prevalence and incidence of 886 myelofibrosis patients treated with RUX based on anemia degree at treatment start.

Cohort	No. (%)	p-y	IRR %p-y	95% CI
Blast phase overall	117 (13.2)	3128.38	3.74	1.2–5.4
RBC transfusion status				
RBC-TD ($n = 90$)	14 (15.6)	278.14	5.03	0.5–2.7
RBC-TR ($n = 98$)	12 (12.2)	267.63	4.48	0.4–1.9
No RBC-TD ($n = 698$)	91 (13.0)	2582.61	3.52	0.5–1.1
CTCAE Hb classification				
No anemia ($n = 289$)	28 (9.7)	1196.60	2.34	0.3–0.8
Grade 1 anemia ($n = 246$)	36 (14.6)	853.97	4.22	0.8–1.8
Grade 2 anemia ($n = 152$)	25 (16.4)	510.96	4.89	0.9–2.2
Grade 3–4 anemia ($n = 199$)	28 (14.1)	566.85	4.93	0.9–2.2
Sex-and severity-adjusted Hb classification				
Mild/no anemia ($n = 458$)	51 (11.1)	1179.44	2.85	0.4–0.8
Moderate anemia ($n = 206$)	34 (16.5)	683.89	4.97	1.1–2.7
Severe anemia ($n = 222$)	32 (14.4)	654.05	4.89	1.0–2.1

Abbreviations: CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; Hb, hemoglobin; IRR, incidence rate ratio; p-y, patient-year; %p-y, per 100 patient-years; RBC-TD, red blood cells-transfusion dependency; RBC-TR, red blood cells-transfusion requirement; RUX, ruxolitinib.

PFS was 70%, 52%, 43%, and 27% at 5 years in patients with no, grade 1, grade 2, and grade 3–4 anemia, respectively (Figure 2A). Five-year PFS was, respectively, 64%, 44%, and 29% in patients with no/mild anemia, moderate, and severe anemia considering sex- and severity-adjusted anemia thresholds. All three categories were significantly different from the others (no/mild vs. moderate and vs. severe anemia, $p < .001$; moderate vs. severe, $p = .009$) (Figure 2B).

Blast phase incidence according to acquisition of anemia during RUX therapy

In univariate regression analysis that evaluated main clinical/laboratory features available after the first 6 months of RUX therapy, BP was associated with the acquisition of grade 3–4 anemia in patients who were started on RUX with no anemia (OR, 3.14; 95%

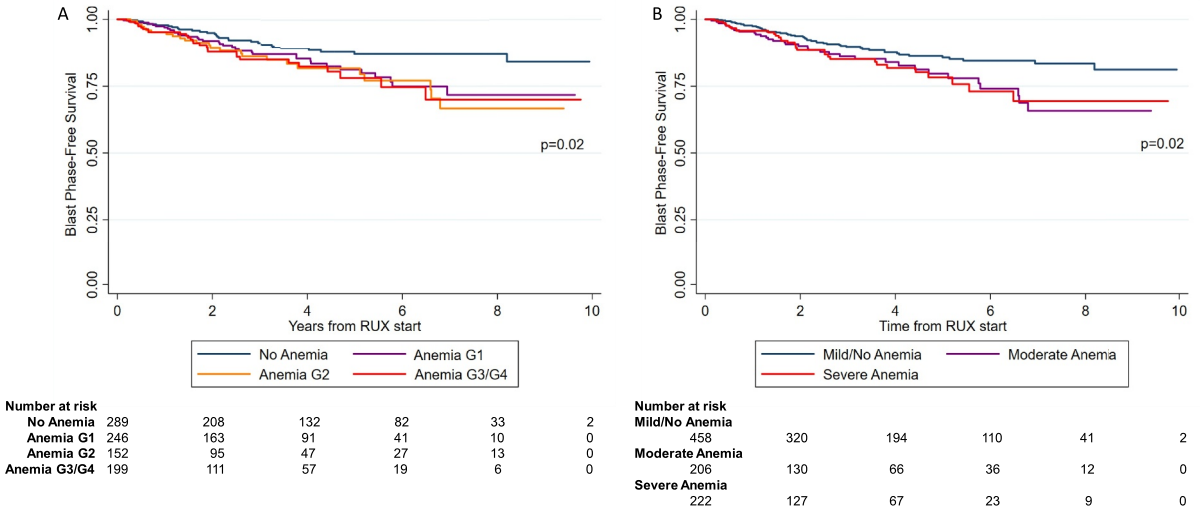

FIGURE 1 Blast phase-free survival (BP-FS) according to anemia degree at treatment start. Significant differences were noted between patients with no anemia and patients with Common Terminology Criteria for Adverse Events grade 1 ($p = .03$), grade 2 ($p = .01$), and grade 3–4 ($p = .01$) anemia. No differences were noted between patients with higher anemia severity (grade 1 vs. grade 2 and vs. grade 3–4 anemia, $p = .57$ and $p = .53$; grade 2 vs. grade 3–4 anemia, $p = .91$). Significant differences were also noted between BP-FS curves of patients with sex and severity-adjusted mild/no anemia versus moderate ($p = .02$) and versus severe ($p = .03$) anemia. No differences were noted between patients with moderate and severe anemia ($p = .99$).

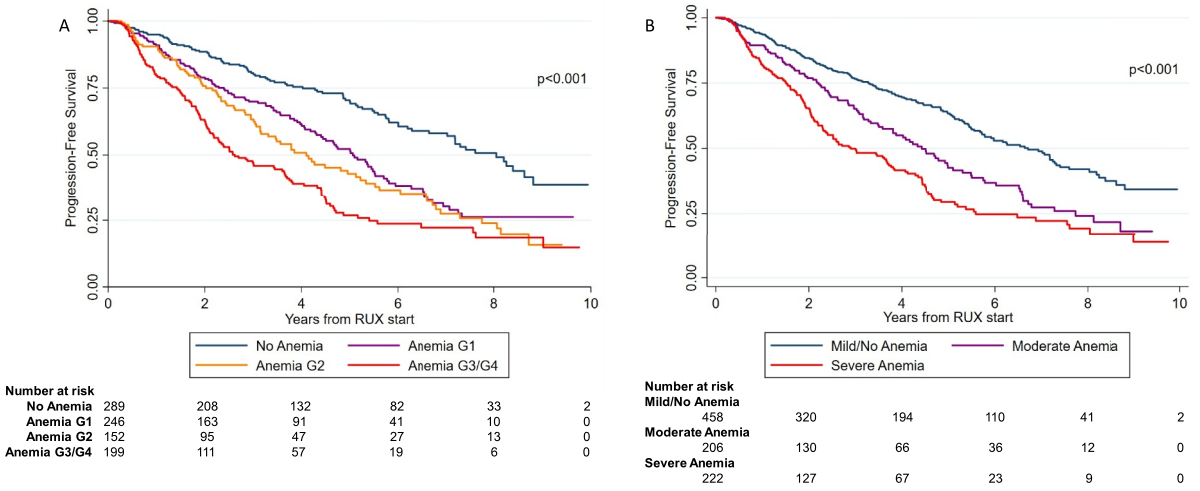

FIGURE 2 Progression-free survival (PFS) according to anemia degree at treatment start. Significant differences were noted between PFS curves of patients with no anemia versus grade 1 ($p < .001$), grade 2 ($p < .001$), and grade 3–4 ($p < .001$) anemia; between patients with grade 3–4 anemia versus grade 1 ($p < .001$) and versus grade 2 ($p = .01$) anemia. No differences were noted between patients with grade 1 and grade 2 anemia ($p = .2$). In addition, significant differences were noted between PFS curves of patients with sex and severity-adjusted mild/no anemia versus moderate ($p < .001$) and versus severe ($p < .001$) anemia and between patients with moderate versus severe anemia ($p = .009$).

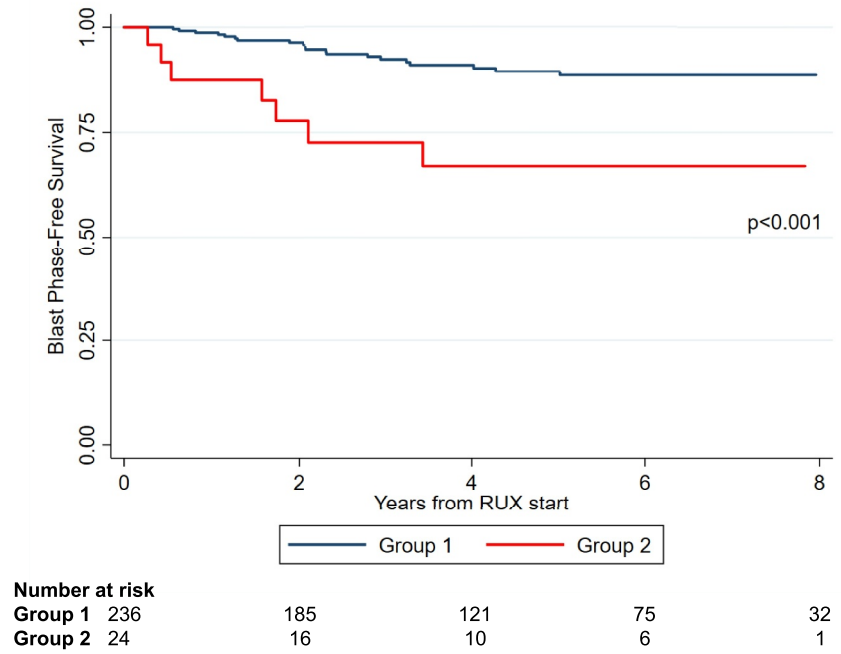

FIGURE 3 Blast phase-free survival according to acquisition of anemia after 6 months of ruxolitinib therapy. Group 1: patients with no anemia at ruxolitinib start and with no or grade 1 and/or 2 anemia at the 6-month time point. Group 2: patients with no anemia at ruxolitinib start and with grade 3–4 anemia at the 6-month time point.

CI, 1.29–7.62; $p = .01$). No significant association was noted between BP and lack of spleen response (OR, 0.91; 95% CI, 0.62–1.35; $p = .65$), occurrence of thrombocytopenia in patients with normal baseline platelet count (OR, 0.91; 95% CI, 0.62–1.35; $p = .65$), or an increase in symptoms burden from baseline (OR, 0.78; 95% CI, 0.44–1.38; $p = .38$).

Among the 289 patients who started RUX without anemia, 260 were still on therapy after 6 months and 24 (9.2%) of these 260 patients developed a CTCAE grade 3–4 anemia during RUX.

Incidence rate of BP was 3.2 %p-y in patients acquiring severe anemia and 1.2 %p-y in patients who did not ($p = .02$). By landmark analysis considering only BP occurring after the 6-month time point, BP-FS was significantly worse in patients acquiring grade 3–4 anemia (69.3% vs. 88.1% at 5 years, $p < .001$) (Figure 3).

A full picture of response status and hematological values of these patients at the 6-month time point is provided in Table 2.

DISCUSSION

Approximately 10%–20% of patients with MF will develop BP. Because of the advanced age of MF patients, the high biological complexity of the disease and the limited therapeutic options, BP is one of the leading causes of death.[25–27]

Despite significant improvements in the survival expectancy of MF patients over the last decades, the incidence of BP has remained unchanged, with no significant impact of RUX monotherapy.[28–31] This finding was very recently confirmed by an international retrospective data collection where the incidence rate of BP was found to be comparable in a large cohort ($n = 1752$) of RUX-untreated patients (2.50 %p-y) and in a smaller cohort ($n = 273$) of RUX-treated patients (2.89 %p-y).[12] In the same study, anemia severity correlated with the incidence of BP, particularly in RUX-unexposed patients, in whom the IRR of BP increased from 1.8 %p-y (anemia grade 0–1) to 4.3 %p-y (anemia grade 3–4). In patients treated with RUX, this trend was not confirmed (the IRR of BP was 4.86 %p-y in patients with grade 2 anemia and 1.61 %p-y in patients with grade 3–4 anemia).

Here, in a large ($n = 886$) cohort of RUX-treated patients, we observed that BP occurred in 13.2% of the cases, for an overall IRR of 3.74 %p-y. These incidences are aligned with previous retrospective observations.[12,31–33]

We also observed a linear correlation between anemia severity and incidence of BP, both considering CTCAE and sex- and severity-adjusted Hb thresholds.

Notably, anemia was present in almost 70% of the patients at baseline and was associated with unfavorable clinical and/or laboratory features, including a cytopenic phenotype, older age, greater symptom burden, higher risk category, and triple molecular negativity. We have previously described how a cytopenic phenotype, including anemia (Hb <10 g/dL), thrombocytopenia (PLT $<100 \times 10^9$/L) and/or leukopenia (WBC$<4 \times 10^9$/L) at the start of RUX is associated with an increased risk of RUX discontinuation and death, but we did not observe a significant effect on leukemic progression.[34]

Particularly, we observed that absence of anemia was associated with the lowest risk of BP transformation, whereas the severity of anemia was not relevant, with IRR of BP only slightly increasing along with the increase of anemia degree. However, transfusion dependency remained the most prominent association with disease progression and its prevention remains a key unmet clinical need.

This finding adds to current knowledge of risk factors for BP transformation, which include advanced age, leukocytosis, exposure to myelosuppressive therapy, cytogenetic abnormalities, higher DIPSS category, peripheral blasts >3%, and platelet count $<100 \times 10^9$/L.[10,32,33,35–38] Notably, anemia remained significantly associated with the incidence of BP even after adjustment for DIPSS category, which is to date the score that best predicts leukemic evolution.

In our cohort, approximately 9% of patients with Hb >10 g/dL at the start of RUX developed grade 3–4 anemia after 6 months of therapy. The acquisition of severe anemia was the only factor significantly associated with subsequent BP evolution, whereas no correlation was observed with other clinical and laboratory features (i.e., lack of spleen response, increase in symptoms burden, thrombocytopenia).

The occurrence of anemia during treatment with RUX is an expected adverse event that can be clinically managed with dose reductions and supportive therapy.[39] Anemia during RUX treatment was not associated with reduced efficacy or survival in a specific subanalysis of patients included in prospective studies.[16,40]

However, need for RBC transfusions during RUX therapy (at months 3 and/or 6; at all time points) has recently been identified as a predictor of reduced survival in the "Response to RUX after 6 Months" (RR6) model,[41] which has been validated in many cohorts.[42,43] The RR6 model highlights how severe anemia during RUX therapy, whether already present at baseline or acquired 3- or 6-months during therapy, has a strong impact on patient prognosis. Together with RUX dose <20 mg twice daily (at baseline, month 3, and month 6) and palpable spleen length reduction from baseline ≤30% (at months 3 and 6), anemia during the early phases of therapy allows the identification of patients with impaired survival.[41]

As in other chronic hematological malignancies, iron overload due to red blood cell transfusions has been associated with reduced survival also in MF.[44] Indeed, in the presence of iron overload, there is an abnormal release of reactive oxygen species in the bone marrow, resulting in impaired marrow function.[45] Additionally, a recent Italian study has shown that use of iron chelation therapy (deferasirox) in combination with RUX in anemic MF patients can increase Hb levels and achieve iron chelation responses that are associated with improved survival.[46]

Here, we show that the acquisition of severe anemia during RUX therapy is a significant predictor of disease transformation into BP. This finding, together with the association between baseline anemia and risk of BP, warrants better consideration and management of anemia in patients requiring *JAK2* inhibition due to splenomegaly and/or symptoms. This is particularly important now that many new agents are being investigated for patients with anemia,[47] alone or combined with RUX. Whether these new agents will be able to significantly target anemia in MF, and mitigate hematological toxicity of *JAK2* inhibitors, remain to be determined. Their impact on BP progression is still unknown.

In conclusion, this study confirms that the rate of BP progression is unaffected by RUX therapy and is strictly related to the degree of anemia at baseline and to the acquisition of severe anemia during therapy. These data strongly suggest the need to rethink the treatment strategy for patients with anemia, also in light of the availability of innovative anti-anemia therapies.

AFFILIATIONS

[1]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Bologna, Italy

[2]Dipartimento di Scienze Mediche, Chirurgiche e Tecnologie Avanzate "G.F. Ingrassia", Università di Catania, Catania, Italy

[3]Division of Hematology, Città della Salute e della Scienza Hospital, Torino, Italy

[4]Hematology Division, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[5]IRCCS San Gerardo dei Tintori, Divisione di Ematologia e Unità Trapianto di Midollo, Monza, Italy

[6]Hematology, S.Eugenio Hospital, Tor Vergata University, Rome, Italy

[7]Unit of Blood Diseases and Stem Cell Transplantation, ASST Spedali Civili di Brescia, Brescia, Italy

[8]Division of Hematology and BMT, Azienda Sanitaria Universitaria Integrata di Udine, Udine, Italy

[9]Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, Bologna, Italy

[10]Department of Hematology, Azienda USL - IRCCS di Reggio Emilia, Reggio Emilia, Italy

[11]Hematology Unit, Department of Medical Sciences, University of Cagliari, Cagliari, Italy

[12]Unit of Hematology and Clinical Immunology, University of Padova, Padova, Italy

[13]Division of Hematology, University of Ferrara, Ferrara, Italy

[14]IRCCS Policlinico San Martino, Genova, Italy

[15]Dipartimento di Medicina Interna e Specialità Mediche, Università di Genova, Genova, Italy

[16]Division of Hematology, AUSL di Piacenza, Piacenza, Italy

[17]Division of Hematology, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy

[18]Hematology Unit, Azienda Ospedaliera Universitaria Senese, University of Siena, Siena, Italy

[19]Division of Hematology, Azienda Ospedaliera 'Bianchi Melacrino Morelli', Reggio Calabria, Italy

[20]Department of Clinical Medicine and Surgery, Hematology Section, University of Naples "Federico II", Naples, Italy

[21]Hematology and Bone Marrow Transplant Unit, Section of Biomedicine of Innovation, Department of Engineering for Innovative Medicine, University of Verona, Verona, Italy

[22]Postgraduate School of Hematology, University of Catania, Catania, Italy

[23]Hematology and Stem Cell Transplant Center, AORMN Hospital, Pesaro, Italy

[24]Haematology Division, Department of Clinical and Biological Sciences, Ospedale San Luigi di Orbassano, University of Turin, Orbassano, Italy

[25]A.O.U. Policlinico Umberto I, Università degli Studi di Roma "La Sapienza", Rome, Italy

AUTHOR CONTRIBUTIONS

Francesca Palandri: Conceptualization, data curation, investigation, visualization, resources, writing–original draft, and writing–review and editing. **Giuseppe A. Palumbo**: Conceptualization, investigation, data curation, visualization, resources, writing–review and editing, and writing–original draft. **Giulia Benevolo**: Conceptualization, investigation, data curation, visualization, resources, writing–original draft, and writing–review and editing. **Alessandra Iurlo**: Conceptualization, investigation resources, visualization, data curation, writing–original draft, and writing–review and editing. **Elena M. Elli**: Conceptualization, investigation, resources, visualization, data curation, writing–original draft, and writing–review and editing. **Elisabetta Abruzzese**: Resources, investigation, and writing–review and editing. **Nicola Polverelli**: Investigation, resources, and writing–review and editing. **Mario Tiribelli**: Investigation, resources, and writing–review and editing. **Giuseppe Auteri**: Investigation and writing–review and editing, Resources. **Alessia Tieghi**: Investigation, resources, and writing–review and editing. **Giovanni Caocci**: Investigation, resources, and writing–review and editing. **Gianni Binotto**: Investigation, resources, and writing–review and editing. **Francesco Cavazzini**: Investigation, resources, and writing–review and editing. **Filippo Branzanti**: Formal analysis, data curation, and writing–review and editing. **Eloise Beggiato**: Investigation, resources, and writing–review and editing. **Maurizio Miglino**: Investigation, resources, and writing–review and editing. **Costanza Bosi**: Investigation, resources, and writing–review and editing. **Monica Crugnola**: Investigation, resources, and writing–review and editing. **Monica Bocchia**: Investigation, resources, and writing–review and editing. **Bruno Martino**: Investigation, resources, and writing–review and editing. **Novella Pugliese**: Investigation, resources, and writing–review and editing. **Luigi Scaffidi**: Investigation, resources, and writing–review and editing. **Marta Venturi**: Investigation, resources, and writing–review and editing. **Andrea Duminuco**: Investigation, resources, and writing–review and editing. **Alessandro Isidori**: Investigation, resources, and writing–review and editing. **Daniele Cattaneo**: 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. **Daniela Cilloni**: Investigation, resources, and writing–review and editing. **Gianpietro Semenzato**: Investigation, resources, and writing–review and editing. **Roberto M. Lemoli**: Investigation, resources, and writing–review and editing. **Antonio Cuneo**: Investigation, resources, and writing–review and editing. **Malgorzata M. Trawinska**: 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. **Massimiliano Bonifacio**: Conceptualization, investigation, resources, visualization, data curation, writing–original draft, and writing–review and editing. **Massimo Breccia**: Conceptualization, investigation, data curation, visualization, resources, writing–original draft, and writing–review and editing.

ACKNOWLEDGMENTS

This work was funded by Italian Ministry of Health (RC-2023-2778976). This work was supported by Ministero della Salute Ricerca corrente and by BolognAIL.

Open access funding provided by BIBLIOSAN.

CONFLICT OF INTEREST STATEMENT

Giulia Benevolo reports honoraria from Novartis, Janssen, Amgen, Takeda, and Bristol-Myers Squibb. Alessandra Iurlo reports honoraria from Novartis, Bristol-Myers Squibb, Pfizer, and Incyte. Massimo Breccia reports honoraria from Novartis, Bristol-Myers Squibb, Pfizer, and Incyte. Massimiliano Bonifacio reports honoraria from Novartis, Bristol-Myers Squibb, 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, Bristol-Myers Squibb, Celgene, and Pfizer. Roberto M. Lemoli reports honoraria from Jazz, Pfizer, AbbVie, Bristol-Myers Squibb, Sanofi, and StemLine. Fabrizio Pane reports honoraria from Incyte, Novartis, Jazz, Bristol-Myers Squibb-Celgene, Amgen, and Gilead. Michele Cavo acted as consultant and received honoraria from Jannsen, Bristol-Myers Squibb Celgene, SanoFI, GlaxoSmithKline, Takeda, Amgen, Oncopeptides, AbbVie, Karyopharm, and Adaptive. Giuseppe A. Palumbo reports consultancy and honoraria from AbbVie, AOP, AstraZeneca, Bristol-Myers Squibb, Incyte, GSK, Morphosys, and Novartis. Elisabetta Abruzzese reports consulting fees from Bristol-Myers Squibb, Incyte, Instituto Científico, Pfizer, and Novartis. Monica Bocchia reports consulting fees from Incyte and Novartis. Filippo Branzanti provided data and safety monitoring for IRCCS Azienda Ospedaliero Universitaria-Policlinico Sant'Orsola. Daniela Cilloni reports fees for Professional Activities from AbbVie and Novartis, and travel fees from Bristol-Myers Squibb. Andrea Duminuco reports consulting fees from A.O.U. Policlinico "G.Rodolico-San Marco" and honoraria from Bristol-Myers Squibb, Celgene, EusaPharma, and Incyte. Francesca Palandri reports consulting fees from AbbVie, Amgen, AOP Health, Celgene, CTI Biopharma, GlaxoSmithKline, Grifols USA, LLC, Karyopharm Therapeutics Inc, MorphoSys, Novartis, Sierra Oncology, and Sobi, Inc. Malgorzata Monika Trawinska reports consulting fees from Novartis. The other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author on reasonable request.

ORCID

Francesca Palandri https://orcid.org/0000-0001-8367-5668
Giulia Benevolo https://orcid.org/0000-0002-3200-9654
Alessandra Iurlo https://orcid.org/0000-0002-4401-0812
Elena M. Elli https://orcid.org/0000-0001-5576-5412
Elisabetta Abruzzese https://orcid.org/0000-0001-5228-6491
Mario Tiribelli https://orcid.org/0000-0001-9449-2621

Novella Pugliese https://orcid.org/0000-0002-2714-5109
Massimiliano Bonifacio https://orcid.org/0000-0003-0716-1686
Massimo Breccia https://orcid.org/0000-0003-1163-6162

REFERENCES

1. Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228. doi:10.1182/BLOOD.2022015850
2. Mesa RA, Verstovsek S, Cervantes F, et al. Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): Consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). *Leuk Res*. 2007;31(6):737-740. doi:10.1016/J.LEUKRES.2006.12.002
3. Passamonti F, Mora B. Myelofibrosis. *Blood*. 2023;141(16):1954-1970. doi:10.1182/BLOOD.2022017423
4. Naymagon L, Mascarenhas J. Myelofibrosis-related anemia: current and emerging therapeutic strategies. *Hemasphere*. 2017;1(1):e1. doi:10.1097/HS9.0000000000000001
5. Tefferi A, Lasho TL, Jimma T, et al. One thousand patients with primary myelofibrosis: the Mayo Clinic experience. *Mayo Clin Proc*. 2012;87(1):25-33. doi:10.1016/J.MAYOCP.2011.11.001
6. Tefferi A, Hudgens S, Mesa R, et al. Use of the functional assessment of cancer therapy--anemia in persons with myeloproliferative neoplasm-associated myelofibrosis and anemia. *Clin Therapeut*. 2014;36(4):560-566. doi:10.1016/J.CLINTHERA.2014.02.016
7. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). *Blood*. 2010;115(9):1703-1708. doi:10.1182/BLOOD-2009-09-245837
8. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31(12):2726-2731. doi:10.1038/LEU.2017.169
9. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood*. 2009;113(13):2895-2901. doi:10.1182/BLOOD-2008-07-170449
10. Passamonti F, Cervantes F, Vannucchi AM, et al. Dynamic International Prognostic Scoring System (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis. *Blood*. 2010;116(15):2857-2858. doi:10.1182/BLOOD-2010-06-293415
11. Vallapureddy RR, Mudireddy M, Penna D, et al. Leukemic transformation among 1306 patients with primary myelofibrosis: risk factors and development of a predictive model. *Blood Cancer J*. 2019;9(2):12. doi:10.1038/S41408-019-0175-Y
12. Mora B, Maffioli M, Rumi E, et al. Incidence of blast phase in myelofibrosis according to anemia severity. *EJHaem*. 2023;4(3):679-689. doi:10.1002/jha2.745
13. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: an updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. *Am J Hematol*. 2020;95(6):594-603. doi:10.1002/AJH.25777
14. Palandri F, Palumbo GA, Bonifacio M, et al. Baseline factors associated with response to ruxolitinib: an independent study on 408 patients with myelofibrosis. *Oncotarget*. 2017;8(45):79073-79086. doi:10.18632/ONCOTARGET.18674
15. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798. doi:10.1056/NEJMOA1110556
16. Gupta V, Harrison C, Hexner EO, et al. The impact of anemia on overall survival in patients with myelofibrosis treated with ruxolitinib in the COMFORT studies. *Haematologica*. 2016;101(12):e482-e484. doi:10.3324/HAEMATOL.2016.151449
17. Barbui T, Thiele J, Gisslinger H, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J*. 2018;8(2):15. doi:10.1038/S41408-018-0054-Y
18. Tefferi A, Barosi G, Mesa RA, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). *Blood*. 2006;108(5):1497-1503. doi:10.1182/BLOOD-2006-03-009746
19. Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica*. 2005;90(8):1128-1132. doi:10.1159/000101708
20. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011;29(4):392-397. doi:10.1200/JCO.2010.32.2446
21. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative Neoplasm (MPN) Symptom Assessment Form Total Symptom Score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. *J Clin Oncol*. 2012;30(33):4098-4103. doi:10.1200/JCO.2012.42.3863
22. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. *Blood*. 2013;122(8):1395-1398. doi:10.1182/BLOOD-2013-03-488098
23. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) v5.0. 2017. Accessed July 20, 2023. https://www.meddra.org/
24. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. *J Clin Oncol*. 2018;36(17):1769-1770. doi:10.1200/JCO.2018.78.9867
25. Iurlo A, Cattaneo D, Gianelli U. Blast transformation in myeloproliferative neoplasms: risk factors, biological findings, and targeted therapeutic options. *Int J Mol Sci* 2019;20(8):1839. doi:10.3390/IJMS20081839
26. Palandri F, Breccia M, Bonifacio M, et al. Life after ruxolitinib: reasons for discontinuation, impact of disease phase, and outcomes in 218 patients with myelofibrosis. *Cancer*. 2020;126(6):1243-1252. doi:10.1002/CNCR.32664
27. Tallarico M, Odenike O. Secondary acute myeloid leukemias arising from Philadelphia chromosome negative myeloproliferative neoplasms: pathogenesis, risk factors, and therapeutic strategies. *Curr Hematol Malig Rep*. 2015;10(2):112-117. doi:10.1007/S11899-015-0259-0/METRICS
28. Tashi T, Yu J, Pandya S, Dieyi C, Scherber R, Parasuraman S. Trends in overall mortality among US veterans with primary myelofibrosis. *BMC Cancer*. 2023;23(1):1-8. doi:10.1186/S12885-022-10495-6/FIGURES/2
29. Verstovsek S, Parasuraman S, Yu J, et al. Real-world survival of US patients with intermediate-to high-risk myelofibrosis: impact of ruxolitinib approval. *Ann Hematol*. 2022;101(1):131-137. doi:10.1007/S00277-021-04682-X
30. Verstovsek S, Gotlib J, Mesa RA, et al. Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses. *J Hematol Oncol*. 2017;10(1):156. doi:10.1186/S13045-017-0527-7
31. Palandri F, Breccia M, Tiribelli M, et al. Risk factors for progression to blast phase and outcome in 589 patients with myelofibrosis treated

with ruxolitinib: real-world data. *Hematol Oncol*. 2020;38(3):372-380. doi:10.1002/HON.2737
32. Passamonti F, Rumi E, Elena C, et al. Incidence of leukaemia in patients with primary myelofibrosis and RBC-transfusion-dependence. *Br J Haematol*. 2010;150(6):719-721. doi:10.1111/J.1365-2141.2010.08275.X
33. Huang J, Li CY, Mesa RA, et al. Risk factors for leukemic transformation in patients with primary myelofibrosis. *Cancer*. 2008;112(12):2726-2732. doi:10.1002/CNCR.23505
34. Palandri F, Breccia M, Mazzoni C, et al. Ruxolitinib in cytopenic myelofibrosis: response, toxicity, drug discontinuation, and outcome. *Cancer*. 2023;129(11):1704-1713. doi:10.1002/CNCR.34722
35. Dupriez B, Morel P, Demory J, et al. Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. *Blood*. 1996;88(3):1013-1018. doi:10.1182/BLOOD.V88.3.1013.1013
36. Vaidya R, Caramazza D, Begna KH, et al. Monosomal karyotype in primary myelofibrosis is detrimental to both overall and leukemia-free survival. *Blood*. 2011;117(21):5612-5615. doi:10.1182/BLOOD-2010-11-320002
37. Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. *Leukemia*. 2013;27(9):1861-1869. doi:10.1038/LEU.2013.119
38. Tefferi A, Guglielmelli P, Lasho TL, et al. CALR and ASXL1 mutations-based molecular prognostication in primary myelofibrosis: an international study of 570 patients. *Leukemia*. 2014;28(7):1494-1500. doi:10.1038/LEU.2014.57
39. Verstovsek S. How I manage anemia related to myelofibrosis and its treatment regimens. *Ann Hematol*. 2023;102(4):689-698. doi:10.1007/S00277-023-05126-4
40. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807. doi:10.1056/NEJMOA1110557/SUPPL_FILE/NEJMOA1110557_DISCLOSURES.PDF
41. Maffioli M, Mora B, Ball S, et al. A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis. *Blood Adv*. 2022;6(6):1855-1864. doi:10.1182/BLOODADVANCES.2021006889
42. Scalzulli E, Ielo C, Luise C, et al. RR6 prognostic model provides information about survival for myelofibrosis treated with ruxolitinib: validation in a real-life cohort. *Blood Adv*. 2022;6(15):4424-4426. doi:10.1182/BLOODADVANCES.2022008158
43. Duminuco A, Nardo A, Garibaldi B, et al. Prediction of survival and prognosis migration from gold-standard scores in myelofibrosis patients treated with ruxolitinib applying the RR6 prognostic model in a monocentric real-life setting. *J Clin Med*. 2022;11(24):7418. doi:10.3390/JCM11247418
44. Palumbo GA, Galimberti S, Barcellini W, et al. From biology to clinical practice: iron chelation therapy with deferasirox. *Front Oncol*. 2021;11. doi:10.3389/FONC.2021.752192
45. Isidori A, Borin L, Elli E, et al. Iron toxicity—its effect on the bone marrow. *Blood Rev*. 2018;32(6):473-479. doi:10.1016/J.BLRE.2018.04.004
46. Elli EM, Di Veroli A, Bartoletti D, et al. Deferasirox in the management of iron overload in patients with myelofibrosis treated with ruxolitinib: the multicentre retrospective RUX-IOL study. *Br J Haematol*. 2022;197(2):190-200. doi:10.1111/BJH.18057
47. Passamonti F, Harrison CN, Mesa RA, Kiladjian JJ, Vannucchi AM, Verstovsek S. Anemia in myelofibrosis: current and emerging treatment options. *Crit Rev Oncol Hematol*. 2022;180:103862. doi:10.1016/J.CRITREVONC.2022.103862

SUPPORTING INFORMATION

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

How to cite this article: Palandri F, Palumbo GA, Benevolo G, et al. Incidence of blast phase in myelofibrosis patients according to anemia severity at ruxolitinib start and during therapy. *Cancer*. 2024;130(8):1270-1280. doi:10.1002/cncr.35156