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Original Study

Ruxolitinib in Myelofibrosis and Baseline Thrombocytopenia in Real Life: Results in Dutch Patients and Review of the Literature

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Abstract

Real-life data on the treatment of myelofibrosis patients with baseline thrombocytopenia with ruxolitinib are limited. We present the outcomes of thrombocytopenic Dutch patients treated within a compassionate-use program. Additionally, we performed a literature review. We conclude that treatment of patients with platelet counts of 50 to 100 × 10^9/L with ruxolitinib is safe.

Background: Ruxolitinib is an approved treatment for myelofibrosis patients, but data regarding patients with baseline thrombocytopenia are limited. The EXPAND study recently suggested tolerability of ruxolitinib, with a maximum starting dose of 10 mg 2 times a day (BID). However, the small sample size and vigorous follow-up in this trial hamper direct translation of these results to routine practice. **Patients and Methods:** We report retrospective data on Dutch ruxolitinib-treated myelofibrosis patients, focusing on those with baseline thrombocytopenia. Additionally, we reviewed current literature regarding ruxolitinib treatment in this subgroup. **Results:** In our cohort, 12 of 119 patients had a baseline platelet count of $< 100 \times 10^9$/L. Spleen responses at a mean treatment duration of 25 weeks were documented in 1 of 6 and 15 of 47 patients with and without baseline thrombocytopenia, respectively. Despite a high rate of grade 3 or higher thrombocytopenia in thrombocytopenic versus nonthrombocytopenic patients (42% vs. 15%), no grade 3 or higher hemorrhage was reported. Median doses in thrombocytopenic patients were 15 and 10 mg BID at the start and after 12 weeks of treatment, respectively. Additionally, 238 thrombocytopenic patients were identified in the available literature, of whom 59 were treated in routine practice. Incidences of severe thrombocytopenia reported separately for patients with baseline thrombocytopenia were 30% to 59% (grade 3 or higher) and 4% to 60% (grade 4). Severe bleeding, pooled across our data and evaluable studies, occurred in 2.4%. **Conclusion:** Ruxolitinib treatment appears to be safe for patients with platelet counts of 50 to 100 × 10^9/L in real-life practice. We did not find any reason to discourage a starting dose of 10 mg BID in this subgroup.

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Introduction

Ruxolitinib, a *JAK2* inhibitor, is an approved treatment for disease-related splenomegaly or symptoms in adult myelofibrosis (MF) patients. Considerable improvement in the outcome of intermediate-2– and high-risk MF patients, regarding spleen size, disease-related symptoms, and overall survival, was demonstrated in

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Table 1 Search Terms and Strategy on PubMed

Search	Query	No. of Items Found
#1	("Primary Myelofibrosis"[Mesh] OR Primary Myelofibros*[tiab] OR Bone Marrow Fibros*[tiab] OR Myelofibros*[tiab] OR Myeloid Metaplasia*[tiab] OR Myelosclerosis*[tiab])	8626
#2	("Thrombocytopenia"[Mesh] OR Thrombopenia*[tiab] OR Thrombocytopenia*[tiab])	71,196
#3	("INCB018424" [Supplementary Concept] OR INCB-018424[tiab] OR INCA24[tiab] OR ruxolitinib[tiab])	1065
#4	((#1) AND #2) AND #3	81

the COMFORT trials.[1-3] Later studies reported similar favorable results in patients with intermediate-1–risk disease.[4,5] However, because cytopenia is the most common adverse effect, patients with a baseline platelet count (BPC) of $< 100 \times 10^9$/L (baseline thrombocytopenia) were excluded from the COMFORT trials, so the safety and toxicity profile of ruxolitinib in this subgroup is less clearly defined. Because approximately one quarter of MF patients have a platelet count of $< 100 \times 10^9$/L,[6] the translation of results to the real-world MF population is hampered. Nevertheless, current dosing recommendations are based on the US Food and Drug Administration (FDA)-approved dose modification schemes derived from these trials. Therein, a low starting dose of 5 mg 2 times a day (BID) is advised for patients with a platelet count of 50 to 100×10^9/L. For those with a platelet count of $< 50 \times 10^9$/L, ruxolitinib is deemed contraindicated.

Two major issues arise with these recommendations. First, although a low starting dose might be optimal for safety, the contrary applies for efficacy. A dose–response relationship regarding spleen response has been demonstrated by multiple groups,[5,6] highlighting the need for the highest tolerable dose in each patient. Second, the recommendations suggest that similar dose modifications are indicated for both drug-induced and disease-related thrombocytopenia, whereas for the latter an increased dose might be even more appropriate in cases where pronounced splenomegaly and an inflammatory state contribute to thrombocytopenia.

To address this issue, 2 recent clinical trials included patients solely with baseline thrombocytopenia: the phase 2 study 258 and the phase 1b EXPAND study.[6,7] Study 258 included 50 patients with a platelet count of $< 100 \times 10^9$/L, of whom 16% required a dose interruption due to grade 4 thrombocytopenia and 2% experienced severe bleeding. The authors proposed a low starting dose of 5 mg BID for this subgroup, with subsequent dose escalation. The EXPAND study included patients with a BPC of 75 to 100×10^9/L (n = 44) and 50 to 75×10^9/L (n = 25). The reported incidences of grade 3 or higher thrombocytopenia in these groups were high: 50% and 76%, respectively. However, this was not deemed clinically significant, as no severe bleeding events were reported. Therefore, the authors suggested that a starting dose of 10 mg BID in these patients

Table 2 Baseline and Treatment Characteristics of Patients Treated in Compassionate-Use Program

Variable	Baseline Platelet Count	
	> 100×10^9/L (N = 107)	< 100×10^9/L (N = 12)
Age at diagnosis (y), median (range)	64 (34-82)	66 (56-77)
Male	68 (64)	5 (42)
Time since diagnosis (mos), median (range)	22 (0-368)	17 (0-109)
MF Subtype		
Primary	48 (45)	7 (58)
Secondary (after ET/PV)	59 (55)	5 (42)
IPSS Score at Baseline[a]		
Low	8 (8)	—
Intermediate-1	20 (19)	—
Intermediate-2	35 (33)	4 (33)
High	43 (40)	8 (67)
Hemoglobin level (mmol/L), median (range)	6.6 (2.9-10.9)	6.2 (4.9-8.4)
Platelet count ($\times 10^9$/L), median (range)	249 (106-1405)	78 (12-95)
Palpable Spleen Length Below Costal Margin		
Not palpable	5 (5)	—
0-5 cm	17 (16)	2 (16.5)
5-10 cm	15 (14)	2 (16.5)
> 10 cm	62 (58)	8 (67)
Not applicable (prior splenectomy)	4 (3.5)	—
Unknown	4 (3.5)	—
Physician-Reported Constitutional Symptoms		
Fever	11 (10)	—
Night sweats	51 (48)	7 (58)
Weight loss	62 (58)	6 (50)
Prior Treatment	87 (81)	10 (83)
Hydroxycarbamide	70 (65)	8 (67)
IMiDs (thalidomide, lenalidomide, pomalidomide)	16 (15)	2 (17)
Interferon	14 (13)	1 (8)
Hematopoietic growth factor (erythropoietin)	12 (11)	1 (8)
Anagrelide	10 (9)	—
JAK2 inhibitor	2 (2)[b]	1 (8)[c]
Allogeneic stem-cell transplantation	1 (1)[d]	—
Other	26 (24)[e]	3 (25)[f]
Ruxolitinib starting dose (mg/d), median/mean,	40/35	30/29
Ruxolitinib dose adjustments during treatment	68 (64)	11 (92)
Treatment duration (mos), median (range)	14 (1-50)	8 (1-35)

Table 2 Continued

Variable	Baseline Platelet Count	
	> 100 × 10^9/L (N = 107)	< 100 × 10^9/L (N = 12)
Reason for Ruxolitinib Discontinuation		
Lack of response	14 (13)	2 (17)
Death	8 (8)	2 (17)
Toxicity	7 (7)	3 (25)
Switch to different therapy	5 (5)	1 (8)

Data are presented as n (%) unless otherwise indicated.
Abbreviations: ET = essential thrombocytosis; IMiD = immunomodulatory imide drug; IPSS = International Prognostic Scoring System; MF = myelofibrosis; PV = polycythemia vera.
[a]IPSS was used in order to be able to compare the results to those of previous trials. IPSS at baseline was unknown in one subject.
[b]A year before inclusion in the CUP, 1 patient received ruxolitinib during 1 month (stopped because of lack of response), followed by pacritinib for 2 months (stopped because of non-hematologic toxicity). One additional patient had received pacritinib for 2 months (stopped because of lack of response).
[c]One patient had received fedratinib until 4 months before inclusion in the CUP (stopped because of nonhematologic toxicity).
[d]Allogeneic stem-cell transplantation had been performed 2 years before the start of ruxolitinib.
[e]Phlebotomy (n = 7), melphalan (n = 8), busulphan (n = 3), 32-phosphorus (n = 3), chlorambucil (n = 1), danazol (n = 2), rituximab (n = 1) and cyclophosphamide (n = 1).
[f]Phlebotomy (n = 1), busulphan (n = 1), danazole (n = 1).

is safe. Although both studies were well conducted, the recommendations are heterogeneous and the sample sizes relatively small. Also, ruxolitinib treatment was performed in the relatively protected setting of clinical trials, thus hampering the translation of results to daily clinical practice.

The current uncertainty and discrepancies in recommendations regarding ruxolitinib dosing in thrombocytopenic patients result in heterogeneous use of the drug in routine practice. This was described in the article by Ellis et al,[8] wherein self-identified "myeloproliferative neoplasm-focused" hematologists varied in their approach and in general were less strict regarding dose reductions in case of worsening thrombocytopenia and mild bleeding compared to current recommendations.

To determine the optimal dose for real-life patients with baseline thrombocytopenia, and in order to prevent suboptimal treatment as well as unacceptable toxicity, we here report our original real-life data from patients treated within a Dutch compassionate-use program (CUP), specifically focusing on the 12 patients with a BPC of < 100 × 10^9/L. Additionally, we provide a review of the currently available literature on MF patients with baseline thrombocytopenia.

Patients and Methods

Original Data

Before the registration of ruxolitinib, Novartis BV provided a CUP for treatment of adult patients with a diagnosis of primary or post–polycythemia vera or essential thrombocytosis MF according to the 2008 World Health Organization criteria.[9] The treating physician was responsible for both the request of participation and treatment in this program. In the current study, we performed a retrospective chart review of patients treated at 6 university hospitals and 3 large teaching hospitals in the Netherlands between June 2011 and July 2015. Central medical ethics committee approval was obtained. Informed consent for use of the data for analysis was obtained if feasible (according to the Code of Conduct for the Use of Data in Health Research).

Spleen response was evaluated by palpation using the International Working Group/European LeukemiaNet criteria: a baseline palpable splenomegaly of 5 to 10 cm below the lower costal margin becomes not palpable, or a baseline palpable splenomegaly > 10 cm below the lower costal margin decreases by ≥ 50%.[10] Patients with baseline palpable splenomegaly < 5 cm below the lower costal margin and/or without documented follow-up measurements were not eligible for spleen response evaluation. Clinical and laboratory parameters were collected before start of treatment (at baseline) and thereafter once every 3 months. For patients with baseline thrombocytopenia, all laboratory results during the first 12 weeks of treatment were collected. Patient histories were checked for the presence of (physician reported) constitutional symptoms (fever, night sweats, and weight loss). A visit was deemed ineligible for evaluation of symptoms in case the complete patient history was left blank. Grade 3 or higher adverse events were documented (graded according to the Common Toxicity Criteria version 3.0). Data collection was discontinued in case of death or treatment discontinuation. Analyses were performed by SPSS 22 (IBM, Armonk, NY).

Literature Review

A literature review was performed for studies describing the use of ruxolitinib in patients with baseline thrombocytopenia, defined as a platelet count of < 100 × 10^9/L. A PubMed search was carried out from inception to February 2019. Search terms are listed in Table 1. Studies were eligible for the review if they met both inclusion criteria: containing primary data (retrospective or prospective) on adult MF patients undergoing ruxolitinib treatment; and including subjects with a documented platelet count of < 100 × 10^9/L before the start of ruxolitinib treatment (baseline thrombocytopenia). Studies were excluded if they were reviews or if results of ruxolitinib treatment were not reported separately (eg, as part of a "best available treatment" arm).

Results

Original Data

Baseline and treatment characteristics of the 119 included patients are shown in Table 2. Twelve patients had a BPC of < 100 × 10^9/L. For the total population, median duration of follow-up was 70 weeks. After a mean treatment duration of 12 weeks, 17 (25%) of 68 evaluable patients had experienced a spleen response, increasing to 16 (30%) of 53 and 11 (34%) of 32 after a mean of 25 weeks and 51 weeks, respectively. Fever, night sweats, and weight loss were documented in 9%, 49%, and 58% of 118 evaluable patients at baseline, decreasing to 2%, 18%, and 2% of 101 evaluable patients after 12 weeks of treatment.

The Kaplan-Meier estimates of overall survival at 48 weeks were 91% for the total population (95% confidence interval, 85-96%) and 89% for the patients with a BPC of < 100 × 10^9/L (95% confidence interval, 68-100). Of note, all patients with a BPC of < 100 × 10^9/L had an intermediate-2– or high-risk score. A total of 16 deaths were reported. Investigator-determined causes of death were progression of MF (n = 6, including the 2 patients with baseline thrombocytopenia),

Table 3 Treatment and Outcome in Patients With Baseline Thrombocytopenia (< 100 × 10^9/L)

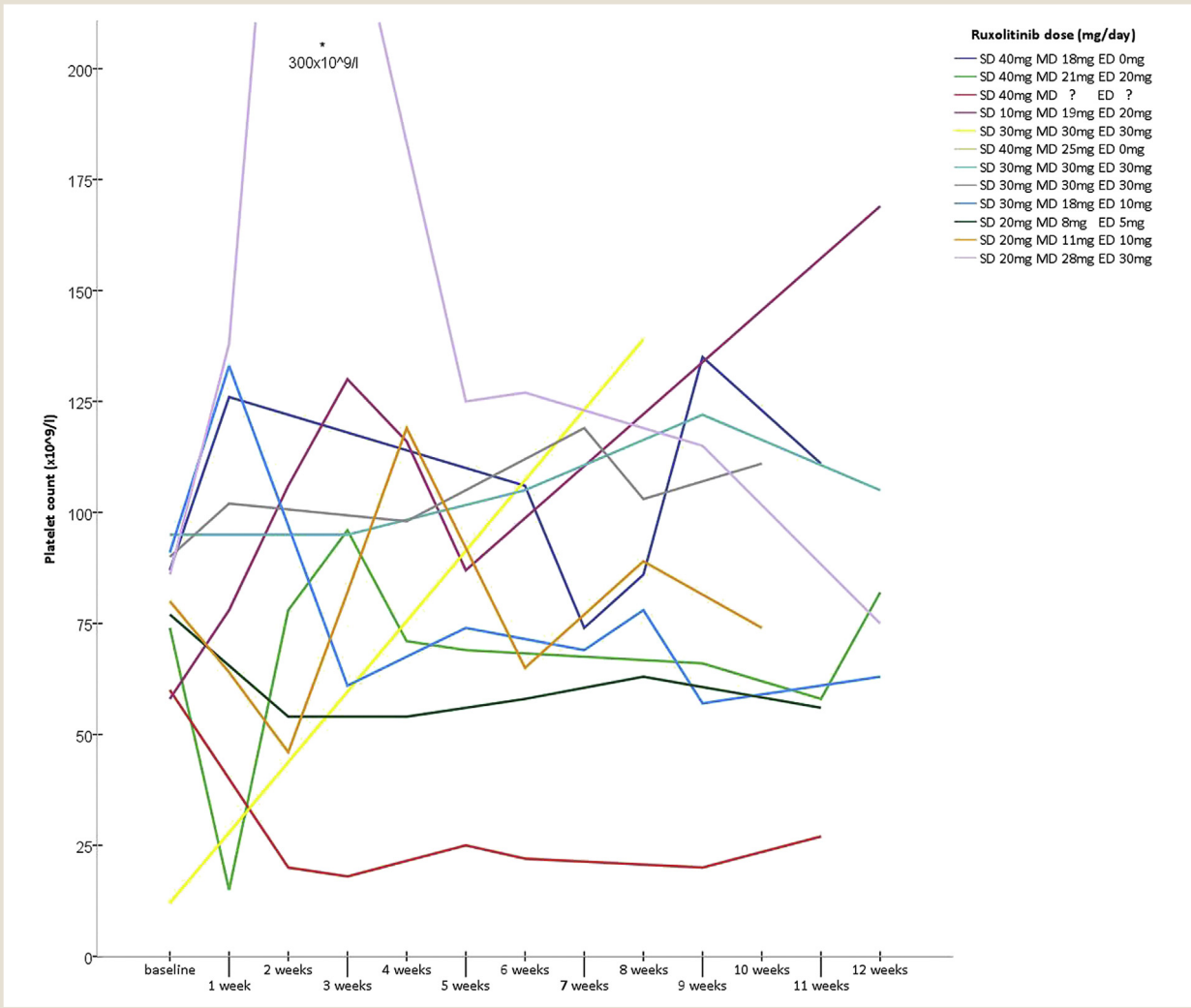
Patient No.	Baseline	BPC (× 10^9/L)	Starting Dose	Treatment Duration (Months)	Dose Adjustments and Reason	Lowest PC (× 10^9/L)	Highest PC (× 10^9/L)	Adverse Events	Response and Outcome
1	• Spleen > 10 cm below LCM. • Night sweats, weight loss.	80	10 mg BID	7	• ↓ 5 mg BID (low PC) • Stop (low PC) • ↑ 5 mg BID • ↑ 10 mg BID • ↓ 10-5 mg (low PC) • ↓ 5 mg BID (low PC)	46 (at 5 mg BID)	119 (at 5 mg BID)	Grade 3 low PC	• Spleen remained > 10 cm below LCM. • No constitutional symptoms reported after 12 weeks. • Treatment discontinued because of hematologic toxicity.
2	• Spleen > 10 cm below LCM. • Night sweats, weight loss.	86	10 mg BID	7	• ↑ 15 mg BID • ↓ 10 mg BID (low PC) • ↑ 15 mg BID • ↑ 20 mg BID • ↓ 15 mg BID	25-50 (at 15 mg BID)	300 (at 10 mg BID)	Grade 3 low PC	• Spleen remained > 10 cm below LCM. • No constitutional symptoms reported after 12 weeks. • Treatment discontinued because of hematologic toxicity.
3	• Spleen • 6-10 cm below LCM. • Weight loss.	87	20 mg BID	1.5	• ↓ 15 mg BID (high WBC) • Stop (high WBC)	106 (at 15 mg BID)	126 (at 20 mg BID)	Grade 3 anemia, extreme high WBC	• No spleen follow-up. • No constitutional symptoms reported after 12 weeks. • Treatment discontinued because of high WBC. Rechallenge after 4.5 months (+ hydroxyurea) until death 1 month later due to PD.
4	• Spleen > 10 cm below LCM. • Night sweats, weight loss.	12	15 mg BID	13	• ↑ 20-15 mg • ↑ 20 mg BID • ↓ 20-15 mg (low PC) • ↓ 15 mg BID (low PC) • ↑ 20 mg BID (PD) • ↓ 15 mg BID (low PC)	85 (at 15 mg BID)	235 (at 15 mg BID)	Grade 3 or higher anemia, low PC	• Spleen remained > 10 cm below LCM. • No constitutional symptoms reported after 12 weeks. • Treatment continued until death due to PD.
5	• Spleen > 10 cm below LCM.	75	20 mg BID	2	• ↓ 15 mg BID (dizziness) • ↓ 10 mg BID (fatigue) • Stop (fatigue)	Unknown	Unknown	Grade 3 or higher anemia, dizziness, fatigue	• No spleen follow-up. • Treatment discontinued because of fatigue.
6	• Spleen > 10 cm below LCM.	74	20 mg BID	22	• ↓ 10 mg BID (pancytopenia) • ↑ 20 mg BID	11 (at 20 mg BID)	109 (at 20 mg BID)	Grade 4 low PC, grade 3 low WBC, rash, diarrhea, dyspnea, edema	• Spleen remained > 10 cm below LCM. • Patient continued to receive treatment.

Table 3 Continued

Patient No.	Baseline	BPC ($\times 10^9$/L)	Starting Dose	Treatment Duration (Months)	Dose Adjustments and Reason	Lowest PC ($\times 10^9$/L)	Highest PC ($\times 10^9$/L)	Adverse Events	Response and Outcome
7	• Spleen 0-3 cm below LCM.	60	20 mg BID	21	• ↓ 15 mg BID (low PC) • ↑ dose unknown (night sweats)	18 (at 15 or 20 mg BID)	61 (at 15 mg BID)	Grade 4 low PC, minor bleeding at PCs 32-61: hematoma, Mallory-Weiss, epistaxis	• Spleen size increased to 6-10 cm below LCM. • Patient continued to receive treatment.
8	• Spleen > 10 cm below LCM. • Night sweats	58	5 mg BID	7	• ↑ 10 mg BID	46 (at 5 mg BID)	227 (at 10 mg BID)	—	• Spleen became not palpable within 24 weeks. • No constitutional symptoms reported after 12 weeks. • Treatment continued until death due to PD.
9	• Spleen > 10 cm below LCM.	77	10 mg BID	4	• ↓ 5 mg OD (low PC)	54 (at 10 mg BID)	66 (at 5 mg QD)	—	• Spleen remained > 10 cm below LCM. • Treatment discontinued due to PD (with low PC as dose-limiting toxicity).
10	• Spleen > 10 cm below LCM.	95	15 mg BID	35	• ↓ 10 mg BID (low PC) • ↑ 15 mg BID • ↓ 10 mg BID (low PC)	59 (at 15 mg BID)	122 (at 15 mg BID)	Painful legs, edema, chronic diarrhea	• Spleen remained > 10 cm below LCM. • Patient continued to receive treatment.
11	• Spleen 0-3 cm below LCM. • Night sweats, weight loss.	90	15 mg BID	25	—	82 (at 15 mg BID)	158 (at 15 mg BID)	Grade 3 or higher anemia, diarrhea, nausea/vomiting, headache	• Spleen became not palpable within 12 weeks. • No constitutional symptoms reported after 12 weeks. • Patient continued to receive treatment.
12	• Spleen > 10 cm below LCM. • Night sweats, weight loss.	91	15 mg BID	9	• ↓ 5 mg BID (low PC) • ↑ 10 mg BID • ↓ 5 mg BID (low PC) • ↑ 10 mg BID • ↓ 5 mg BID (low PC) • ↑ 10 mg BID • ↓ 5 mg BID (low PC) • ↑ 10 mg BID	42 (at 10 mg BID)	133 (at 15 mg BID)	Grade 3 or higher low WBC, erysipelas, fever, cough	• Spleen remained > 10 cm below LCM. • Weight loss and night sweats diminished but were reported at ≥ 1 follow-up visit. • Treatment discontinued, followed by allogeneic stem-cell transplantation.

Abbreviations: BID = 2 times a day; BPC = baseline platelet count; LCM = lower costal margin; PC = platelet count; PD = progressive disease; WBC = white blood cell count.

Figure 1 Course of Platelet Count in Patients With Baseline Thrombocytopenia (< 100 × 10^9/L)

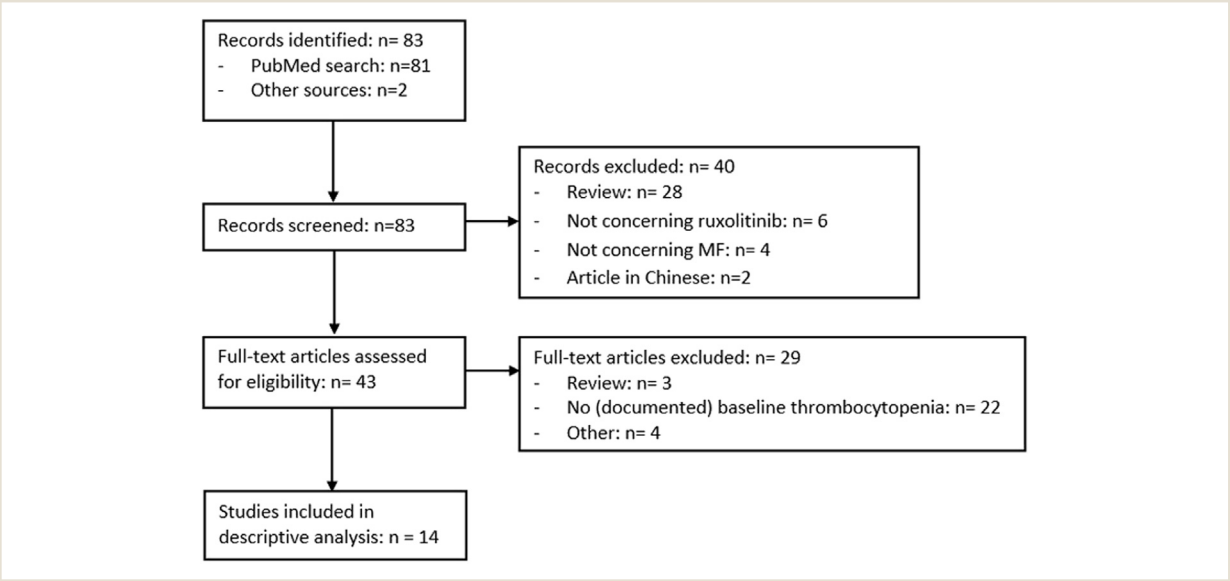


transformation to acute myeloid leukemia (n = 3), complications of prior allogeneic stem-cell transplantation (n = 1), adenocarcinoma (n = 1), thrombosis (n = 1), pneumonia (n = 1), miliary tuberculosis (n = 1), and unknown (n = 2).

In the overall population, the median BPC was 238 × 10^9/L (range, 12-1405 × 10^9/L); this decreased to 173 × 10^9/L in the first 3 months of treatment (range, 27-987 × 10^9/L) and remained relatively stable afterward. Almost half of the patients (48%) received at least one blood transfusion at any time within a year of start of treatment. The incidence of grade 3 or higher thrombocytopenia was 15% in patients with a BPC > 100 × 10^9/L, versus 42% in those with baseline thrombocytopenia (data representing worst grade events during the study).

An overview of treatment and outcome in the 12 patients with baseline thrombocytopenia is provided in Table 3. The FDA-advised starting dose of 5 mg BID was exceeded in 11 (92%) of 12 patients, and subsequent dose modifications were performed in 11 of 12 patients. This included (temporary) dose decreases to below the starting dose in 8 (67%) of 12 patients, including all patients who initiated therapy at 20 mg BID. (Temporary) dose increases to above the starting dose were performed in 25%, including the patient who began treatment with 5 mg BID. In the patients who began therapy with 10 mg BID, (temporary) dose increases and decreases to above and below the starting dose were performed in 1 of 3 and 2 of 3 patients, respectively. The median dose in the entire subgroup after 12 weeks of treatment was 10 mg BID (range, 0-15 mg BID). Figure 1 depicts platelet counts in the patients with baseline thrombocytopenia during the first 12 weeks of treatment. Grade 4 thrombocytopenia occurred in 2 (16.7%) of 12 patients during this period; both began therapy with 20 mg BID. At any time during treatment, an increase in platelet count to > 100 × 10^9/L—with a minimum increase of 27 × 10^9/L—was seen in 9 (75%) of 12 patients. The highest platelet count occurred at a ruxolitinib dose of ≥ 10 mg BID in 8 of these 9 patients (Table 3). Hematologic toxicity led to treatment discontinuation in 3 (25%) of 12 patients. No grade 3 or higher bleeding events were reported with a median follow-up of 43 weeks.

Figure 2 Inclusion and Exclusion Flowchart of Literature Search



Literature Review

Using the search terms listed in Table 1, we identified 81 records through PubMed. Cross-references led to one additional relevant article and one conference abstract. After screening for inclusion and exclusion criteria, we included 13 articles and one conference abstract for a descriptive review (Figure 2). The main findings are summarized in Table 4.

Published data concerned a total number of 238 ruxolitinib-treated patients with a BPC of $< 100 \times 10^9$/L, including only 9 with a documented BPC of $< 50 \times 10^9$/L. We assumed that patients with baseline thrombocytopenia included in the 2016 publication of the JUMP trial were also part of the more detailed subgroup analysis presented at American Society of Hematology in 2014. Therefore, we decided to report results on the latter analysis only. Also, a possible overlap exists between the JUMP trial[5] and the retrospective analysis by Palandri et al[17]; this would concern a maximum of 31 patients. The majority of patients (n = 179) was treated within one of the 5 prospective clinical trials.[5-7,12,13] Four retrospective analyses included a total of 54 unselected patients from cohorts treated in routine practice.[14-17] Finally, information on 5 selected patients was published in 4 separate case reports.[18-21]

Of the 233 patients in whom the ruxolitinib starting dose was known, 68% began therapy with 5 mg BID (range, 5-20 mg BID). Five studies reported on dose reductions or interruptions and/or treatment discontinuation separately for the subgroup with baseline thrombocytopenia.[6,7,11,14,15] In these studies, thrombocytopenia led to dose reductions in 20% to 24%, dose interruptions in 0 to 16%, reductions/interruptions in 33% (average percentage for strata 1 and 2 in the EXPAND study), and discontinuation of treatment in 2% to 20%. Occasionally ruxolitinib doses were maintained or even increased despite persistent or worsening thrombocytopenia. In individual cases, ruxolitinib treatment was continued, and supportive treatment with danazol or platelet transfusions was added.

In most of the publications we assessed, the incidence of adverse events was not reported separately for patients with baseline thrombocytopenia (Table 4). In these studies, in which 1% to 21% of the population had baseline thrombocytopenia, the incidence of grade 3 or higher thrombocytopenia ranged from 4% to 14.3%. The incidence of severe bleeding (defined as a serious adverse event or a grade 3 or higher hemorrhage) ranged from 0 to 7% for the overall population; platelet counts at the time of bleeding were not reported.

@In 3 clinical trials and 1 real-life cohort, including a total of 174 patients, data on thrombocytopenia were reported separately for patients with a BPC of $< 100 \times 10^9$/L.[6,7,11,15] Grade 3 or higher thrombocytopenia occurred in 30% to 59% (59% being the average incidence for strata 1 and 2 in the EXPAND study) and grade 4 thrombocytopenia in 4% to 60%. In the EXPAND study, the incidence of grade 3 or higher thrombocytopenia was highest in patients with BPCs $< 75 \times 10^9$/L (Table 4). Of interest, an increase in platelet counts of $\geq 15 \times 10^9$/L during treatment was observed in 14% of patients in study 258.[6]

Four studies reported the bleeding incidence separately for patients with baseline thrombocytopenia. Grade 3 or higher hemorrhage occurred in 3 of 110 patients treated within these studies, including 10 patients treated in routine practice. This resulted in a pooled severe bleeding incidence of 2.7%. When combined with our own retrospective data, the pooled incidence was 2.4%. Because only bleeding events occurring in $\geq$ 15% to 20% of cases (for maximum safe starting dose and total cohorts, respectively) were specified in the EXPAND study, these patients were not included in the calculation of the pooled bleeding incidence.

The case reports all described patients with an increase in platelet counts during ruxolitinib treatment, sometimes even after an initial drop.[15,18-21] None of the case reports described significant bleeding events at ruxolitinib starting doses of 5 to 15 mg BID.

Table 4 Summary of Literature Regarding Ruxolitinib Treatment in Patients With Baseline Platelet Counts < 100 × 10^9/L

Study	Study Design	Population	Starting Dose in Patients With BPC < 100 × 10^9/L	Main Findings

Talpaz, 2013[6]	Phase 2, open-label, study (study 258)	• n = 50 with BPC 50-100 × 10^9/L
		• (n = 37 available for dosing analysis at week 24)
			• 5 mg BID
			• Dose increases permitted after ≥ 4 weeks in 5 mg QD increments if PC ≥ 40 × 10^9/L (among other criteria)
				• Mean percentage change in PC for study population stable over 24-week treatment period
				• 23/37 (62%) received a dose ≥ 10 mg BID by week 24
				• Dose interruptions due to grade 4 thrombocytopenia in 8/50 (16%)
				• Dose reductions due to PC < 35 × 10^9/L but > 25 × 10^9/L in 12/50 (24%)
				• Treatment discontinuation due to thrombocytopenia in 1/50 (2%)
				• Increase in PC of ≥ 15 × 10^9/L from baseline in 7/50 (14%)
				• Occurrence of hemorrhage:
				  • Grade 1 in 8%
				  • Grade 2 in 6%, at PCs > 35 × 10^9/L
				  • Grade 4 in 2% at PC 71 × 10^9/L

Griesshammer, 2014[11]	Phase 3b single-arm, open label study (subgroup analysis of JUMP trial[5])	• n = 50 with BPC < 100 × 10^9/L • Lowest value 68 × 10^9/L	• 5 mg BID	• Median daily dose in first 6 months of treatment 11.8 mg/d (range, 5.9-40 mg/d) • Grade 3 or higher thrombocytopenia in 30%; grade 4 thrombocytopenia in 4% • Treatment discontinuation due to thrombocytopenia in 3 (6%) • Grade 1/2 hemorrhage in 4 (8%) (1 conjunctival, 1 gastric, 2 epistaxis) • Grade 3 or higher hemorrhage in 2 (4%) (1 intestinal, 1 esophageal varices)

Gowin, 2017[12]	Phase 2 single-arm study	• n = 3 with BPC < 100 × 10^9/L
		• Lowest value 54 × 10^9/L
		• (Total: n = 14)
			• 10 mg BID for BPC 75-100 × 10^9/L
			• 5 mg BID for BPC 50-75 × 10^9/L
			• (All patients received danazol 200 mg TID)
				• None of patients with BPC < 100 × 10^9/L had platelet response (defined as increase of > 50 × 10^9/L)
				• Overall population:
				  • Grade 3 or higher thrombocytopenia in 14.3%
				  • Dose adjustment performed in 57.1%, but unrelated to hematologic toxicity
				  • Grade 3 or higher intracranial hemorrhage in 1 (7%), relation to PC unknown

Komatsu, 2017[13]	Prospective, single-arm, open-label study	• n = 7 with BPC < 100 × 10^9/L • Lowest value unknown • (Total: n = 51)	• 5 mg BID	• Not separately reported for patients with BPC < 100 × 109/L. Overall population: • Grade 3 or higher thrombocytopenia in 7.8% • Dose reductions in 84%, dose interruptions in 43% (reasons not specified) • Thrombocytopenia as cause of treatment discontinuation in 1 (2%) • Two serious bleeding events (4%): GI and esophageal variceal hemorrhage, relation to PC unknown

Vannucchi, 2019[7]	Phase 1b dose-finding study (EXPAND)	• n = 69, including:
		  • n = 44 with BPC 75-99 × 109/L (stratum 1)
		  • n = 25 with BPC 50-74 × 109/L (stratum 2)
		• n = 48 available for analysis at week 48 (MSDD cohort: n = 20 from S1 and n = 18 from S2)
			• Stratum 1 (S1):
			  • 5 mg BID (n = 5)
			  • 5/10 mg (n = 3)
			  • 10 mg BID (n = 20)
			  • 10/15 mg (n = 4)
			  • 15 mg BID (n = 12)
			• Stratum 2 (S2):
			  • 5 mg BID (n = 3)
			  • 5/10 mg (n = 4)
			  • 10 mg BID (n = 18)
				• Overall cohort (n = 69):
				  • Grade 3 or higher thrombocytopenia in 50% (S1) and 76% (S2)
				  • Epistaxis of all grades in 22% (S1) and 4% (S2) Grade 3 or higher epistaxis in 2.3% (S1) and 0% (S2) (only AEs occurring in ≥ 20% were listed)
				• MSSD cohort (n = 48):
				  • Mean dose intensities 17.96 mg/d (S1) and 13.27 mg/d (S2)
				  • Grade 4 thrombocytopenia in 5% (S1) and 39% (S2)
				  • Treatment discontinuation due to thrombocytopenia: 5% (S1), 16.7% (S2)
				  • Dose reductions/-interruptions due to thrombocytopenia: 20% (S1) and 66.7% (S2); most dose reductions < 12 weeks of treatment
				  • Grade 1-2 ecchymosis in 25% (S1) and 11.1% (S2); grade 1-2 epistaxis in 25% (S1) and 0% (S2) (only AEs occurring in ≥ 15% were listed)

Geyer, 2014[14]	Retrospective cohort analysis (routine practice)	• n = 5 with BPC < 100 × 109/L • (Total: n = 28)	• At discretion of providing physician (not specified)	• PCs dropped with an average of 4% by 10 weeks of treatment • Thrombocytopenia was managed with platelet transfusions (n = 1), danazol (n = 1) • Treatment discontinuation due to thrombocytopenia in 1 (20%) • Dose increases performed in 2 • No unexpected serious bleeding events

Table 4 Continued

Study	Study Design	Population	Starting Dose in Patients With BPC < 100 × 10^9/L	Main Findings
Bjørn, 2016[15]	Retrospective cohort analysis (routine practice)	• n = 5 with BPC < 100 × 109/L (including n = 4 with BPC < 50 × 109/L), range 29-72 × 109/L • (Total: n = 12)	• 10-20 mg BID	• Dose reduction due to thrombocytopenia in 1 (20%) • Treatment discontinuation due to thrombocytopenia in 1 (20%) • Grade 4 thrombocytopenia in 3 (60%) • Normalization of PC in 1 (20%) at 10 mg BID • Grade 1 epistaxis in 1 (20%) • No grade 3 or higher hemorrhage
Ellis, 2015[16]	Retrospective cohort analysis (routine practice)	• n = 13 with BPC < 100 × 109/L • Lowest value 50 × 109/L • (Total: n = 93)	• 5 mg BID (n = 9) • 10 mg BID (n = 2) • 15 mg BID (n = 1) • 20 mg BID (n = 1)	• Not separately reported for patients with BPC < 100 × 109/L. Overall population: • Grade 3 or higher thrombocytopenia in 12.9% • Grade 4 thrombocytopenia as cause of treatment discontinuation in 2 (2%) • Bleeding events not reported

Palandri, 2018[17]	Retrospective cohort analysis (treatment both in routine practice + JUMP trial)	• n = 31 with BPC < 100 × 109/L
		• Lowest value 33 × 109/L
		• (Total: n = 291, of which 56.7% had been included in JUMP trial)
			• 5 mg BID	• Not separately reported for patients with BPC < 100 × 109/L. Overall population:
				  • Grade 3 or higher thrombocytopenia in 4-6.4% (equal across age groups)
				  • Dose reductions performed in 34.7% in first 12 weeks (reason unknown)
				  • Bleeding and hematologic toxicity as cause of treatment discontinuation in 3.5% and 9.7%, respectively

Armstrong, 2015[18]	Case report (routine practice)	• n = 1 with BPC < 10 × 109/L (platelet transfusion dependent)	• 5 mg BID	• Ruxolitinib dose increased to 10 mg BID • PC increased to 20-30 × 109/L during 18 months of treatment • Platelet transfusions only required for medical procedures • No bleeding events

Grunwald, 2016[19]	Case report (routine practice)	• n = 2
		• Patient 1: BPC 61 × 109/L
		• Patient 2: BPC 31 × 109/L
			• Patient 1: 15 mg BID + thalidomide 100 mg
			• Patient 2: 15 mg QD
				• Patient 1:
				  • PC decrease to 20 × 10^9/L after 3 months
				  • Initial dose decrease to 15 mg QD, later increase to 10 mg BID
				  • PC thereafter stable around 49 × 10^9/L
				• Patient 2:
				  • PC decrease to 7 × 10^9/L, managed with platelet transfusions.
				  • Nonetheless dose increased: first 15 mg BID, later alternating 15 mg QD/15 mg BID and 10 mg BID
				  • Gradual rise in PC to 106 × 10^9/L after 9 months
				• Both:
				• No bleeding events

Al-Ali, 2017[20]	Case report (treatment setting unknown)	• n = 1 with BPC 50 × 10^9/L	• 10 mg BID	• Dose reduction to 5 mg BID after 2 months due to PC decrease • Lowest PC nadir 36 × 10^9/L • Treatment was continued because of significant spleen response, and PC increased to 67 × 10^9/L after 2 years
Ikeda, 2017[21]	Case report (routine practice)	• n = 1 with BPC 81 × 10^9/L	• 5 mg BID	• Splenomegaly improved and PC normalized during treatment • Ongoing response at 16 months since start of treatment • No significant bleeding events

Abbreviations: AE = adverse event; BID = 2 times day; BPC = baseline platelet count; GI = gastrointestinal; MSSD = maximum safe starting dose; PC = platelet count; QD = once a day.

Discussion

The objective of our study was to determine the safety and the optimal ruxolitinib dose for real-life patients with baseline thrombocytopenia. We systematically searched for published literature and aimed to objectively describe patient outcomes. Furthermore, we report our retrospective results on patients treated in a CUP using uniform outcome measures. To our knowledge, our 12 patients form the largest real-life, unselected cohort in which the outcome was separately described for patients with baseline thrombocytopenia.

Combining our own data with data from the available literature led to a total of 250 known patients with a BPC of $< 100 \times 10^9$/L who were treated with ruxolitinib. Although data are partly subject to selection and publication bias, the absolute number of patients is high, allowing for evaluation of safety in this subgroup. Moreover, because 71 patients were treated outside of clinical trials, the outcome of our analysis can be translated to daily life practice.

The main finding of our study is that although grade 3 or higher thrombocytopenia occurred more often in patients with baseline thrombocytopenia than in those with adequate BPCs (30-59%, vs. 12.9% in the COMFORT-1 trial),[3] the incidence of severe bleeding was not increased (2.4%, vs. 3.9% in COMFORT-1). Understandably, dose reductions or interruptions were frequently indicated, and treatment discontinuation due to thrombocytopenia was more often performed compared to the COMFORT-1 study (2-20% vs. 0.6%). Also, as expected, higher incidences of grade 3 or higher thrombocytopenia were seen in those with the lowest BPCs (eg, $< 75 \times 10^9$/L).

An additional interesting observation was the subset of thrombocytopenic patients in which an increase in platelet counts occurred during ruxolitinib treatment. An association with a decrease in platelet sequestration due to a reduction in splenomegaly was suggested in all case reports. However, many patients in our own cohort experienced an increase in platelet counts without a concurrent spleen response. Another potential mechanism is a ruxolitinib-induced decrease in inflammatory markers, exemplified by transforming growth factor beta, a known inhibitor of thrombopoietin production.[22,23] Because an increase in platelet counts was regularly preceded by an initial decrease, it is difficult to determine which patients are most likely to experience a paradoxical response. In study 258, the patients who showed this response more often had primary MF, younger age, shorter time since diagnosis, lower Dynamic International Prognostic Scoring System score, and lower neutrophil count compared to in those in whom platelet counts were stable or decreased during treatment. For future research, it would be interesting to measure transforming growth factor beta levels throughout treatment, especially in those with baseline thrombocytopenia.

The main limitation of our study is its retrospective nature. For example, the reasons for dose modifications were not always specified in patient charts, and the approach to worsening thrombocytopenia was physician dependent. The incidence of constitutional symptoms and bleeding events could be an underestimation in case not all events were noted by the treating physician. Regarding the literature review, the main objection is that many studies including patients with a BPC of $< 100 \times 10^9$/L did not report the outcome separately for this subgroup, making direct comparisons difficult. For example, the pooled incidence of grade 3 or higher hemorrhage could be based on 110 of 238 patients only. However, because hemorrhage is a feared complication when treating patients with baseline thrombocytopenia, we would expect that severe bleeding incidents would have been specifically mentioned. Therefore, we expect our pooled incidence to be an accurate estimate of reality. Last, because only 10 of 250 patients had a documented platelet count of $< 50 \times 10^9$/L, no conclusions regarding this subgroup could be drawn.

Conclusion

The incidence of grade 3 or higher thrombocytopenia during ruxolitinib treatment in patients with a BPC of $< 100 \times 10^9$/L is increased compared to the general population. Dose modifications were frequently needed, and worsening thrombocytopenia led to treatment discontinuation in 2% to 20%. However, the incidence of severe bleeding in this subgroup was low (pooled incidence of 2.4% across 122 patients, including 22 patients treated in routine practice). On the basis of the above results, we conclude that ruxolitinib treatment in patients with baseline thrombocytopenia is safe, and is also safe in daily clinical practice.

Because many studies found that a higher starting dose was associated with a higher spleen response rate,[5-7,24] the highest tolerable dose in each patient should be sought under strict and frequent monitoring of platelet counts, especially in the first 12 weeks of treatment. The EXPAND trial suggested a starting dose of 10 mg BID for patients with platelet counts of 50 to 100×10^9/L. We did not find any arguments to refute this suggestion. Treatment in patients with a platelet count of $< 50 \times 10^9$/L can be considered in individual cases; however, it is supported by very little evidence.

Clinical Practice Points

- Ruxolitinib treatment of MF patients with baseline thrombocytopenia is challenging because data on safety and toxicity in this subgroup are limited. The current FDA-approved dosing schedules recommend a starting dose of 5 mg BID in patients with a BPC of 50 to 100×10^9/L. More recently, the EXPAND study suggested tolerability of a starting dose of 10 mg BID in this subgroup. However, these results are based on a limited number of patients treated within the protected setting of a clinical trial.
- In combining our retrospective analysis of Dutch patients with a review of current literature, we found a relatively low incidence of severe hemorrhage in an evaluable subset of patients with baseline thrombocytopenia (2.4%), despite a high incidence of grade 3 or higher thrombocytopenia. Therefore, we conclude that ruxolitinib treatment is safe in patients with BPCs of 50 to 100×10^9/L, also in real-life practice. Nevertheless, a thorough screening of other risk factors and a medical history of bleeding should be performed in each patient.
- Data on the optimal starting dose are limited. A dose decrease was performed in our patients who initiated therapy with 20 mg BID, and a dose increase was performed in the patient who began therapy with 5 mg BID. An increase in platelet counts occurred in several patients during treatment with ruxolitinib doses of $\geq$ 10 mg BID, and no grade 3 or higher bleeding

occurred. Therefore, we did not find any arguments to discourage a starting dose of 10 mg BID in patients with a BPC of 50 to 100 $\times$ 10^9/L.

- The question remains how to handle worsening thrombocytopenia. Because decreases in platelet counts occurred mainly in the first 12 weeks of treatment, frequent monitoring in this period is important. Dose reductions and/or interruptions are more often necessary compared to in nonthrombocytopenic patients. However, because an increase in platelet counts was observed in a subset of patients, also after longer treatment periods, permanent treatment discontinuation in case of worsening thrombocytopenia is not always indicated.

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