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ORIGINAL ARTICLE

Efficacy and safety of ruxolitinib and hydroxyurea combination in patients with hyperproliferative myelofibrosis

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Abstract

Ruxolitinib is the only commercially available *JAK1/2* inhibitor approved for the treatment of myelofibrosis-related splenomegaly and symptoms. During treatment, as rare conditions, leukocytosis and/or thrombocytosis could develop and the management of these situations is not well established. We report here 53 myelofibrosis patients that received a combination of hydroxyurea and ruxolitinib because of uncontrolled myeloproliferation. Both drugs were administered outside clinical trials. At 48 weeks, a significant reduction in leucocyte and platelet counts was observed ($p = 0.02$ and $p = 0.04$, respectively). Additionally, the spleen volume decreased from a median value of 10 cm below the left costal margin (range, 0–10) to 6 cm (range, 0–15). The rate of spleen response increased from 14% at the start of the combination to 45% after 48 weeks. The safety profile of the combination was consistent with that observed with ruxolitinib single agent. These data require further confirmation in large cohorts of patients prospectively assessed.

Keywords Myelofibrosis · Ruxolitinib · Hydroxyurea · Efficacy

Introduction

Myelofibrosis (MF) is the most aggressive among Philadelphia-negative chronic myeloproliferative neoplasms (MPN) and it is burdened by symptomatic splenomegaly, debilitating systemic symptoms, worsening cytopenias and an overall unfavourable survival [1]. In 10–30% of the cases, MF may be characterized by hyperleukocytosis and thrombocytosis [2]. Ruxolitinib (JAKAVI, Novartis; JAKAFI, Incyte Corporation) is the first-in-class *JAK1/2* inhibitor that has demonstrated efficacy in reducing splenomegaly and symptoms in several prospective clinical trials and also in large retrospective studies [3–7]. Ruxolitinib is currently recommended in the International Prognostic Scoring System (IPSS) intermediate-2 and high-risk patients for the front-

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line treatment of symptoms and splenomegaly, and in patients with highly symptomatic intermediate-1 risk disease [8, 9].

Hydroxyurea is a non-alkylating anti-neoplastic agent commonly used for the control of leucocytosis and thrombocytosis but has limited efficacy on splenomegaly and may induce haematological and extra-haematological toxicities [10]. It is recommended as the first-line treatment in low- and intermediate-1 patients with a lower disease burden and/or hypermyeloproliferation [10, 11].

While ruxolitinib often causes anaemia and thrombocytopenia, it has been rarely associated with hyperleukocytosis and/or increased platelet counts during treatment. In such cases, the combination of ruxolitinib with cytoreductive drugs is usually needed but not standardized.

We hereby retrospectively describe a series of patients affected by primary myelofibrosis (PMF) or by post-polycythemia vera/post-essential thrombocythemia myelofibrosis (PPV-MF/PET-MF) who received a combination of ruxolitinib plus hydroxyurea outside of clinical trials, with a particular focus on the safety and efficacy of this treatment strategy.

Patients and methods

A centralized electronic database was established to retrospectively collect clinical and laboratory data on patients with myelofibrosis who received a combined therapy with ruxolitinib and hydroxyurea in 9 Italian haematology centres. All patients that were treated with ruxolitinib and hydroxyurea were included.

Clinical/laboratory data including hematologic parameters, IPSS/Dynamic-IPSS scores [2, 12], comorbidities, spleen/symptoms, and type of driver mutations were collected at ruxolitinib start and over time. Diagnosis of MF and PET/PPV-MF was made according to the 2008 WHO criteria [13]. Ruxolitinib was administered according to prescribing information and hydroxyurea was combined at the treating physician's discretion. Spleen and symptom responses were defined according to the 2013 IWG-MRT/ELN criteria [14, 15]. Haematological and extra-haematological side effects during treatment were registered according to the CTCAE scale. Continuous variables were expressed as median and ranges, and categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the chi-square test and two-sample Student's *t* test for categorical and continuous variables, respectively, and the Wilcoxon signed-rank test.

Results

Data from a total of 53 MF patients treated with the combination of ruxolitinib and hydroxyurea between 2012 and 2017 were collected. Patients' characteristics at the start of ruxolitinib are detailed in Table 1. Hydroxyurea was initiated after a median time of 5.2 months from the start of ruxolitinib (range, 2.4–7.8) with a median daily dose of 1.500 mg/day (range, 500–2.000). At the time of hydroxyurea start, the median ruxolitinib dose was 15 mg BID (range, 5–20 mg BID). The reasons for initiating hydroxyurea were leucocytosis (37 patients), ruxolitinib-resistant splenomegaly (10 patients), thrombocytosis (4 patients), and increase of both leucocyte and platelet counts (2 patients). Table 2 shows the changes in the haematological and clinical parameters during ruxolitinib alone and the combination treatment. Over time, a significant reduction in leucocyte and platelet counts was observed ($p = 0.02$ and $p = 0.04$, respectively). Additionally, the spleen decreased from a median value of 10 cm below the left costal margin (range, 0–10) to 6 cm (range, 0–15). Overall, after the start of the combination therapy, 45% of patients had a reduction of the baseline splenomegaly, and the rate of spleen response increased from 14% at the start of the combination to 28.5%, 37.5%, and 45% after 12, 24, and 48 weeks, respectively. After 48 weeks of the combined

Table 1 Patient's characteristics at the start of ruxolitinib

Features	Patients (*n*, 53)
Male sex, no (%)	33 (62.3%)
Median age, years. (range)	67 (54–82)
Primary MF, no (%)	23
PET-MF, no (%)	12
PPV-MF, no (%)	18
DIPSS category	
Int-1	8
Int-2	25
High	20
Molecular status	
JAK2^{V617F}-positive	37
CALR-positive	6
MPL-positive	2
Triple negative	8
Palpable spleen, no (%)	48 (90%)
Median cm below LCM, no (range)	8 (5–14)
Spleen ≥ 10 cm below LCM, no (%)	35 (73%)
Median time MF-RUX start, months (range)	6 (2–16)
RUX starting dose, no (%)	
5 mg BID	2 (3.7%)
10 mg BID	12 (22.6%)
15 mg BID	20 (37.7%)
20 mg BID	19 (35.8%)

PET-MF, post-essential thrombocythemia myelofibrosis; *PPV-MF*, post-polycythemia vera myelofibrosis; *DIPSS*, Dynamic International Prognostic Score System; *LCM*, left costal margin

Table 2 Haematological parameters and spleen length over time

Features	At the start of ruxolitinib (n, 53)	At the start of combination (n, 53)	+ 12 weeks (n, 50)	+ 24 weeks (n, 40)	+ 48 weeks (n, 33)	p value
Median haemoglobin, g/dL (range)	10.5 (5–15)	10 (6.7–16.4)	9.5 (6.8–14.6)	10.3 (7–13)	11.4 (7.8–14)	0.123
Median leukocytes, $\times 10^9$/L (range)	18.2 (4.2–110)	34.9 (5.7–208)	24.6 (5.9–203)	23.6 (2.4–201)	17.2 (2.3–106)	0.020
Median platelets, $\times 10^9$/L (range)	190 (55–900)	186 (60–1.110)	113 (30–652)	135 (35–545)	158 (78–523)	0.049
Median spleen length, cm below LCM (range)	7 (0–15)	10 (0–20)	9 (0–15)	8 (0–20)	6 (0–15)	0.001

LCM, left costal margin. p values were calculated comparing parameters at the start of the combination of ruxolitinib and hydroxyurea and parameters after 48 weeks

treatment, 55% of patients achieved a symptoms response, starting from only 25% after ruxolitinib single agent. During ruxolitinib therapy alone, 25% and 45% of patients had a thrombocytopenia/anaemia of grade ≥ 2, respectively. In 81% of cases, platelet and leucocyte counts increased over time, finally requiring the combination with hydroxyurea.

After starting the association, 22.6% of patients developed various grades of anaemia and/or thrombocytopenia. Specifically, 7 patients experienced a grade 3 thrombocytopenia and 5 patients a reduction in haemoglobin baseline value limited to the first 12 weeks. During the combination therapy, 6 patients suffered from a grade ≥ 2 infectious event; specifically, pneumonia (5 cases) or recurrent urinary infection (1). At week 48, the median dose of ruxolitinib was 10 mg twice daily (range, 5–50) and 55% of patients required a dose reduction, whereas the median dose of hydroxyurea decreased to 1000 mg/day (range, 500–1500 mg) in 25% of patients. The median time from starting the combined therapy to dose reduction was 3 months and the median time to discontinuation was 2.5 months. Seventeen patients (32%) have died: 4 patients due to a progression into an acute myeloid leukaemia, 4 for cardiovascular complications, 2 for thrombotic disorders, 3 for infections, and the remaining patients for other reasons unrelated to myelofibrosis. At the last follow-up, 3 patients had discontinued both drugs and proceeded to allogeneic stem cell transplant, while 32 patients remain on the combination therapy.

Discussion

Ruxolitinib is a *JAK1/2* inhibitor that has been approved for the treatment of MF based on the results of two studies that tested its efficacy and safety in intermediate-2/high IPSS risk. The results showed its superiority in ameliorating disease-related splenomegaly and symptoms compared with placebo and best available therapy [3, 4, 6]. An expanded access trial and real-life observation have then confirmed the above results [5, 7]. Rare cases of leukocytosis and/or thrombocytosis during ruxolitinib treatment have been described but the correct management of these situations has not been standardized. This retrospective study reported 53 patients treated with ruxolitinib combined with hydroxyurea for hyperproliferative conditions. Overall, this analysis shows that hypermyeloproliferation requiring hydroxyurea combination may comparably occur in primary and PPV/PET-MF and across the Dynamic International Prognostic Score System (DIPSS) risk categories. This combined approach could effectively reduce leucocyte and platelet count with significant improvement of splenomegaly and symptom burden over time in nearly half of patients. In particular, at 48 weeks of observation, a significant reduction in median leucocyte and platelet counts was observed. Additionally, the spleen volume progressively decreased, with a rate of spleen responses growing from 14 to 45% after 48 weeks. In terms of safety, no excess of haematological and extra-haematological toxicity was observed; however, most patients required a ruxolitinib dose reduction. In comparison with the toxicity reported in the COMFORT studies and in the JUMP trial [3–6], the combination did not seem to substantially increase the rate of hematologic toxicity. In fact, 13% of patients experienced grade 3/4 thrombocytopenia, similar to the incidence (11%) observed in intermediate-1 risk patients enrolled in the JUMP study. About 23% of patients experienced some degree of anaemia, again similar to 22% experienced by the same category in the JUMP trial. This is particularly important since the majority of patients included in the present study belonged to the intermediate-2 or high DIPSS categories.

Overall, this series validates the efficacy and safety of the association of ruxolitinib and hydroxyurea previously described only in three single case reports [16–18]. Efficacy and safety data suggest that this combination therapy, which is feasible in real-world practice outside clinical trials, may be a useful option in patients presenting a hyper-proliferative disease, which is not adequately controlled by ruxolitinib monotherapy. This experience requires however further confirmation in large cohorts of patients assessed prospectively.

Authors' contribution MB designed the study, wrote and revised the manuscript; LL, NP, ER, MT, ES, MB, BM, RL, GB, GC, GB, VM,

MC, FP, and VDS followed patients; FP and RF critically revised the paper and approved the final version.

Compliance with ethical standards

Conflict of interest MB received honoraria by Novartis, Pfizer, Incyte, and Celgene. All other authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained for all patients included.

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