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Clinical use of ruxolitinib in an academic medical center in unselected patients with myeloproliferative neoplasms not on clinical study

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Abstract

Ruxolitinib is the only approved therapy for myelofibrosis (MF). However, its use in patients with myeloproliferative neoplasms (MPN) not participating in clinical studies has been poorly described. We reviewed the medical records of 45 patients (35 MF, 10 others) treated with ruxolitinib at our center, off clinical study, during the year after its approval. Patients had advanced features and were refractory to multiple therapies. Ruxolitinib was effective in reducing splenomegaly (51% response rate) and constitutional symptoms (42% response rate). It controlled blood counts in patients with polycythemia and thrombocythemia but was not effective in patients with non-classic MPNs. Ruxolitinib was an active therapy in patients previously treated with a JAK inhibitor and was safely combined with hypomethylating agents in patients with elevated blasts. Median overall survival was 24 months; 10 patients transformed to acute leukemia. Its use in combination with other active agents should be further explored in clinical studies.

Keywords

myeloproliferative neoplasms; myelofibrosis; splenomegaly; ruxolitinib

Introduction

Classic myeloproliferative neoplasms (MPNs) comprise primary myelofibrosis (PMF), essential thrombocythemia (ET) and polycythemia vera (PV) (1). The latter two can also progress to myelofibrosis, known as post ET MF (PET-MF) or post PV MF (PPV-MF) (2). MF is characterized mainly by bone marrow fibrosis, peripheral blood cytopenias, extra medullary hematopoiesis manifesting as massive splenomegaly or hepatomegaly, as well as constitutional symptoms including fatigue, weight loss, night sweats and bone pain (3). Median age at presentation is 67 years (4) and survival varies between 2–11 years (5). Some patients may present with both features of MPN and dysplasia and are classified as having myelodysplastic/myeloproliferative neoplasm (MDS/MPN), which includes, for example, chronic myelomonocytic leukemia (CMML) (6).

Treatment of MF remains a challenge. While allogeneic stem cell transplantation offers a cure, not many are eligible to undergo this treatment. With the discovery in 2005 of a gain of function mutation in the Janus kinase 2 gene (JAK2V617F) (7) and the underlying hyperactive JAK-STAT pathway as the unifying pathobiological abnormality in MPNs, came a series of trials evaluating the role of different JAK inhibitors in MF. Ruxolitinib is a potent oral JAK1/JAK2 inhibitor that has demonstrated significant improvement in splenomegaly, MF-associated constitutional symptoms, and improved overall survival (OS) in 2 phase III studies comparing ruxolitinib with placebo (COMFORT-I) and best available therapy (COMFORT-II) in patients with MF (8, 9). These studies led to the FDA approval of the drug for the treatment of intermediate- and high-risk MF. Ruxolitinib has also been studied in patients with ET, PV, MDS, and MDS/MPN. However, experience with ruxolitinib therapy in patients with chronic myeloid neoplasms treated outside clinical trial is rather sparse. The first commercial use of ruxolitinib was described by Geyer et al (10) in patients with MF, describing a 64% reduction in spleen size with complete resolution of splenomegaly in 36% as well as significant improvement in fatigue, weight loss, fever, night sweats, etc. Similar results in patients with MF treated off clinical study were reported by other groups from Taiwan and Israel (11, 12). In this study, our aim was to review the use of ruxolitinib in our center during the year following its approval for MF in patients with myeloid neoplasms treated off clinical study. Since our center had and continuously has a number of clinical studies that provide ruxolitinib as therapy for different patients with myeloid neoplasms, we wanted to describe its use outside of a clinical study.

Materials and Methods

We reviewed the medical records of 45 patients with MPN or MDS/MPN who presented to MD Anderson Cancer Center and were treated with ruxolitinib outside of clinical protocols from December 2011 through January 2013 (approximately during the year after ruxolitinib approval; ruxolitinib was approved in November 2011). Diagnosis was confirmed based upon the clinical and bone marrow biopsy evaluation according to the 2008 World Health Organization criteria. In addition to demographic data, that included age and gender, we also collected laboratory data including complete blood counts and differential JAK2 mutation status, previous and concomitant therapies, and leukemic transformation. A spleen size was noted as measured by palpation during physical examination and recorded in medical records. Symptoms were assessed through verbal response, as documented in the medical record. Patients were considered transfusion dependent (per the IWG-MRT and ELN guidelines) if they required at least 6 units of PRBC transfusion in the 12 weeks prior to starting ruxolitinib, for a hemoglobin < 8.5gm/dl, with most recent transfusion episode within 28 days of starting therapy (14).

Decisions to treat patients with ruxolitinib, and not on clinical study, was solely made by the treating physician at the time. We report here a review of clinical practice as it happened at our center, based on a review of medical records. Descriptive statistics of the study population, including means (with corresponding standard deviations), medians (with corresponding ranges), and proportions, together with 95% confidence intervals (CIs) were computed.

Results

Medical records of 45 patients who received ruxolitinib outside of a clinical trial were reviewed (Table 1): 35 with PMF/PPV-MF/PET-MF and 10 with other diseases (2 CMML, 1 ET, 3 PV, 1 MPN-U and 3 MPN/MDS). Median duration on ruxolitinib therapy was 12.2 months (range, 0.9–28.5). Median follow-up duration was 17.1 months (range, 5.4–36.5). Seventy-three percent of patients harbored the JAK2 *V617F* mutation. Twenty-five patients (55.5%) had a diploid karyotype. All MF patients were intermediate and high-risk per the Dynamic International Prognostic Scoring System (DIPSS) (13). Previous treatments included JAK2 inhibitors (n=18), hydroxyurea (n=23), anagrelide (n=7), hypomethylating agents (n=5) and immunomodulators (n=6). The median spleen size prior to starting ruxolitinib was 16.0 cm (4–28 cm) below the left costal margin on palpation, in patients with splenomegaly (n=35). Seven patients did not have a palpable spleen at baseline while 3 patients had undergone splenectomy prior to starting ruxolitinib. Fatigue was the most common presenting symptom reported by 60% of patients.

Ruxolitinib was started at 20 mg twice daily for patients (n=11) with platelet count $> 200 \times 10^9/L$. An additional eleven patients with platelets $> 200 \times 10^9/L$ were started at a reduced dose of ruxolitinib by physician's choice. The remaining patients (n=23) started at reduced doses mainly due to thrombocytopenia. Doses were subsequently adjusted to reduce side effects and enhance efficacy, as judged by the treating physicians. Decisions on how to manage patients with ruxolitinib were not guided by any specific guidelines in existence at our center (they don't exist), but were solely made by treating physicians according to their medical judgement.

Of the 35 patients with palpable symptomatic splenomegaly at baseline, 18 patients (51%) experienced a 50% reduction in palpable spleen size from baseline (if spleen was 10 cm) or complete disappearance of splenomegaly (if spleen was 5–10 cm), at any time during the observation on therapy. Among them, complete resolution of splenomegaly was noted in 11 patients (32% of the total). Median time to best spleen response (as defined by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) (14)) was 3 months (0.4–23.6). Thirteen patients (37%) had no response by IWG-MRT criteria, while 2 patients had progression in splenomegaly associated with transformation to AML; 2 patients were not evaluable.

Improvement in quality of life (QOL) including fatigue, weight gain and resolution of fever and night sweats, was noted in 19 patients (42%). Nineteen patients were PRBC transfusion dependent (by IWG-MRT and ELN guidelines) at initiation of therapy and remained transfusion dependent on ruxolitinib, while 7 patients became transfusion dependent after starting ruxolitinib. Only 1 patient who was transfusion independent at initiation of ruxolitinib was noted to have an improvement in hemoglobin.

At the time of analysis, 19 patients (42%) remained on therapy, while 25 patients had discontinued therapy; one patient was lost to follow-up. While 4 patients discontinued therapy given no response, only 3 patients discontinued treatment due to worsening anemia and thrombocytopenia; 4 patients proceeded to SCT, 6 transformed to AML and 8 stopped

due to other causes (1 insurance issues; 1 subdural bleed; 3 cardiorespiratory failure; 2 death from unknown cause; 1 patient's choice).

Overall, 10 patients (22%) transformed to AML on ruxolitinib; 6 discontinued ruxolitinib at transformation, while 4 continued ruxolitinib treatment after transformation with the addition of decitabine in one 1 and chemotherapy in 3. One patient had extramedullary disease only, presenting as a soft tissue mass involving the T2 spine and right knee, which was treated with XRT. Median time to AML transformation was 9.8 months (3.6–30.1). Median OS for all transformed patients was 24 months (3.2–36.5). Five of the 10 patients had PMF as the original diagnosis, 2 ET, 1 CMML, 1 MDS/MPN, and 1 MPN-U. All 10 had been previously treated (median, 2 [range, 1–5]) and 5 had abnormal cytogenetics. Two of the patients with PMF who eventually transformed had peripheral blood and BM blasts > 10% at the start of ruxolitinib therapy; the other 8 patients who transformed to AML had 0–4% peripheral blood/BM blasts at the start of therapy.

Interestingly, 18 patients were previously treated with a JAK2 inhibitor [8 with SB1518 (pacritinib); 3 with Ly2784544; 3 with NS-018; 2 with CYT387 (mometinib); 2 with BMS911543]. We first analyzed their previous splenomegaly (n=13) response to the initial JAK2 inhibitor (3 patients did not have a palpable spleen at presentation, while 2 patients had undergone splenectomy): 23% (3/13) patients with palpable splenomegaly had a reduction in spleen size of ≥ 50% (2 responded to SB1518 (pacritinib) and 1 responded to Ly2784544), but all 3 relapsed with progressive splenomegaly. With subsequent therapy with ruxolitinib, 7/13 patients achieved a reduction of ≥ 50% in spleen size. The discontinuation rate of ruxolitinib was, however, high in this group of patients (83% versus 37%). Median duration of ruxolitinib for this group was 12.9 months (1.3–28.5). Moreover, 9 patients with prior JAK2 inhibitor therapy underwent repeat bone marrow evaluation before ruxolitinib initiation and 2 were noted to have clonal evolution; both progressed to AML 6 and 2 months into treatment with ruxolitinib and died.

Thirteen patients received concomitant therapy with ruxolitinib that included hydroxyurea, danazol or hypomethylating agents. Danazol was given to 4 patients to improve anemia: 2 patients had stabilization of hemoglobin, though they remained transfusion dependent, and in the other 2 danazol was stopped due to disease progression. Patients with elevated peripheral blood and/or bone marrow blasts were treated with a combination of ruxolitinib and hypomethylating agents (HMA). This consisted of 6 patients in accelerated phase (MPN-AP) and 1 patient in blast phase (MPN-AML). Median follow-up duration was 5.1 months (3.3–13.0). Median OS (from the initiation of HMA) of this sub-group of patients was 7.9 months (1.8–13.2) (Table 2).

Of the 10 patients with other MPNs that were treated with ruxolitinib off protocol per physicians' choice, all 3 with PV and 1 with ET responded to ruxolitinib with resolution of constitutional symptoms, splenomegaly (1/3 PV patients; other 2 PV patients had splenectomy), durable hematocrit control and improvement in platelet count. Patients with MPD-U, MPD/MDS (n=4) and 1 CMML patient showed no response to therapy, while 1 patient with CMML who received ruxolitinib after failing decitabine had resolution of constitutional symptoms with ruxolitinib.

Discussion

In our retrospective study of advanced, heavily pretreated MPN patients, ruxolitinib treatment off clinical trial showed a significant reduction in spleen size (51%) and improvement in quality of life (42%) consistent with the results obtained with ruxolitinib in clinical studies for patients with MF. The main reason for use of ruxolitinib in our patients was, indeed, presence of symptomatic splenomegaly and/or worsening constitutional symptoms, which a treating physician thought might be responsive to ruxolitinib. Ruxolitinib was generally well tolerated; anemia and thrombocytopenia remained the two most common hematological toxicities. Though 19 patients were transfusion dependent prior to starting therapy (anemia is not a contraindication for ruxolitinib use) and 7 more patients became transfusion dependent on ruxolitinib, drug discontinuation due to cytopenias was noted in only 3 patients.

Several findings of our study require discussion. For example, in our experience, retreatment of MF patients with another JAK2 inhibitor (in this case ruxolitinib after exposure to a variety of different other investigational JAK2 inhibitors) provided a benefit to patients, with a meaningful reduction in spleen size and symptoms. Of note is, however, a shorter duration of benefit in such patients, which may be a reflection of more advanced disease that is less responsive to a therapy with an agent in the same class of drugs. This is valuable information since clinical studies with novel JAK2 inhibitors are being currently performed in this setting as a second line therapy.

Of the 10 patients (22%) treated with ruxolitinib who had transformed to AML, the majority were multiply treated and had evidence of clonal evolution. One of those patients was also noted to have extramedullary disease at transformation, manifesting as paraspinal mass and leukemia cutis. All others presented at transformation with generalized malaise, worsening splenomegaly, worsening cytopenias and elevated blood blasts. This is in contrast to other limited experience, for example, by Kremyanskaya and colleagues who reported on four out of 5 patients with MF treated with ruxolitinib that had transformation to AML in form of extramedullary only (15). Our patient with extramedullary disease received palliative XRT to the paraspinal mass in addition to systemic therapy.

Four patients continued therapy with ruxolitinib after transformation to AML, to control splenomegaly and constitutional symptoms that accompanied disease progression (ruxolitinib is not known to decrease blasts in blood or bone marrow, or to prevent AML transformation); 1 in combination with decitabine and 3 in combination with chemotherapy. Results of clinical studies of ruxolitinib as a single agent in patients with AML including post-MPN-AML showed very limited anti-leukemia activity (16) (17). In that regard, of particular interest is a possible role of ruxolitinib in combination with HMA in patients with MPN-AP and MPN-AML. Clinically, use of single agent azacitidine in phase 2 trials in patients with MF has shown modest activity (18–20). However, in a series of 54 patients that had transformed to MDS or AML from MPN and were treated with azacitidine, the overall response rate was 52% and the median overall survival was 11 months (20). The duration of response was 9 months. Similarly, Mascarenhas and colleagues reported improved survival of more than 9 months in a small group of patients with transplant ineligible MPN-AML

treated with single agent decitabine (21). Badar and colleagues recently showed decitabine to be of potential benefit in patients with MPN-AP and MPN-AML, with a significantly prolonged overall survival amongst the responders (22).

Experience with the combination of ruxolitinib and HMA in this patient population remains limited. Tabarrokhi et al (23) studied 3 patients with high-risk MF treated with ruxolitinib and decitabine that showed clinical benefit with reduction in spleen size, decrease in red cell transfusion requirement and a decrease in circulating blasts. Mwirigi and colleagues also reported similar observations in 3 patients with MPN-BP treated with ruxolitinib in combination with either azacitidine or low dose cytarabine (24). In our very limited experience, there appears to be a beneficial effect of combining ruxolitinib and HMA in some patients with advanced MPN. Currently trials are ongoing to evaluate this treatment combination in patients with MPN-AP and MPN-AML ([ClinicalTrials.gov](https://clinicaltrials.gov), NCT01787487, NCT02076191 and NCT002257138).

Several significant limitations exist of our study. First, it relies on the accuracy of written records which may not be complete or fully informative (contrary to clinical study data). Second, because we evaluated patients with MF not treated/eligible for any clinical study, including patients with other MPNs (CMML, MDS-U, etc), and the sole determination of the therapy was physicians' choice, our patient population was highly selective and not devoid of selection bias. Third, our review lacked use of a standard symptom assessment/quality of life scoring system. Lastly the number of patients with other MPNs that were treated per physician choice was too small for any firm conclusions to be made. However, all 3 patients with PV and 1 with ET showed a response to ruxolitinib (all 3 patients with PV started therapy prior to FDA approval of ruxolitinib in PV patients refractory/intolerant to hydrea).

In conclusion, as reported by other colleagues, ruxolitinib provides good benefit in terms of reduction in spleen size and symptom burden in patients with MPNs that are treated off clinical trial. Patients receiving ruxolitinib in a second line setting after previous therapy with a JAK2 inhibitor still respond to ruxolitinib, making it a valuable option. Combination therapies, like ruxolitinib plus HMA, should be explored in clinical studies.

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Table 1

Baseline characteristics

Characteristics		PET-MF (n=4) n(%)	PPV-MF (n=7) n(%)	PMF(n=24) n(%)	Others(n=10) n(%)*
Age	Median(range)	74 (48–81)	70 (56–77)	68 (27–84)	67 (48–81)
Gender	Male	3(75)	5(71)	18(75)	8(80)
	Female	1(25)	2(29)	6(25)	2(20)
DIPSS risk category	Intermediate 1/2	3(75)	6(86)	13(54)	9(90)
	High	1(25)	1(14)	11(46)	1(10)
Jak2 V617F mutation	Median(range)	77 (62.9–90.7)	83(53.4–98.6)	65.8(15.7–97.5)	82(10.2–91.4)
Jak2 V617F mutation	Yes	3(75)	7(100)	16(67)	7(70)
	No	1(25)	0	7(29)	2(20)
Karyotype	ND	0	0	1(4)	1(10)
	Diploid	2(50)	3(43)	13(54)	7(70)
Hgb	Median(range)	10 (8.8–11.3)	12 (7.7–14.4)	10 (6.7–15)	10.5 (7.5–15.9)
WBC	Median(range)	16 (14–22.4)	15 (5.8–84.7)	11 (1.6–74.4)	8.9 (2.4–37.8)
PLT	Median(range)	361 (26–1496)	138 (90–373)	168 (12–1459)	331 (27–1512)
PB BL	Median(range)	0 (0–5)	2 (0–4)	1 (0–10)	0 (0–4)
PB BL	>0	2(50)	6(86)	16(67)	3(30)
	0	2(50)	1(14)	8(33)	7(70)
Splenomegaly	Yes	2(50)	6(86)	22(92)	5(50)
	No	1(25)	0	2(8)	4(40)
Splenectomy	Splenectomy	1(25)	1(14)	0	1(10)
ECOG Performance status	0–1	4(100)	7(100)	19(79)	10(100)

Characteristics	PET-MF (n=4) n(%)	PPV-MF (n=7) n(%)	PMF (n=24) n(%)	Others (n=10) n(%) [*]
2	0	0	5(21)	0
Transformation (AML)	Yes	2(50)	0	5(21)
	No	2(50)	7(100)	19(79)
Previous Therapies	Jak2 inhibitors	2(50)	4(57)	8(33)
	Hydroxyurea	3(75)	6(86)	7(29)
	Anagrelide	3(75)	2(29)	1(4)
	Hypomethylating agents	0	2(29)	1(4)
	Immunomodulators	2(50)	2(29)	2(8)
Start Dose	20mg BID	1(25)	1(14)	5(21)
	<20mg BID	3(75)	6(86)	19(79)
Currently on Jakafi		2(50)	2(29)	9(38)
Median duration of Jakafi (m)	12 (6.2–13.8)	14 (6.7–27.3)	13 (0.9–28.5)	6.4 (1.3–26.4)
Median follow-up (m)	12.9 (11.7–14.1)	27.2 (24.6–36.5)	17.6 (5.4–33.3)	13.7 (6.3–34.6)
Median overall survival (m)	13.7 (8.7–14.1)	Not reached	23.7 (3.2–33.3)	19.6 (5.4–34.6)

PET-MF, post essential thrombocythemia myelofibrosis; PPV-MF, post polycythemia vera myelofibrosis; PMF, primary myelofibrosis; DIPSS, Dynamic International Prognostic Scoring System; Hgb, hemoglobin; WBC, white blood cell; PLT, platelets; PB BL, peripheral blood blast

^{*} Others: chronic myelomonocytic leukemia, MPN/MDS, MPN, polycythemia, essential thrombocythemia

Table 2

Patient characteristics and outcome after treatment

Diagnosis	Age/Gender	Karyotype	Agents	Response	Response Note	OS-m	Outcome
PV --> AP	60/F	Del 20q	Rux+AZA	CR	Splenomegaly completely resolved. BMBL declined from 10% to 0%. Blood counts meet CR. No EMH	13.0	Continue Rux + AZA. CR ongoing
PPV-MF --> AP	63/F	Del 20q	Rux+DAC	inevaluable (DAC $\times$ 1 only)	Splenectomy prior to coming to MDACC	5.0	Haplo SCT ---> Died 3 months after SCT due to renal failure
PMF --> AP	67/M	Del 20q	Rux+DAC	inevaluable (DAC $\times$ 1 only)	PBBL increased from 12% to 26% on day 18 of DAC	1.8	Transformed to AML after 1 cycle of Rux + DAC. Died of multi-organ failure a month later.
PMF --> AP	68/M	ND	Rux+AZA	CI	Splenomegaly completely resolved. Patient remained red cell transfusion dependent	13.2	Transformed to AML after 12 cycles of Rux + AZA. Received cladribine+LDAC alternating with DAC for AML. Died of Sepsis 1.5 months after AML.
PMF --> AP	68/M	Diploid	Rux+AZA	NR	unchanged BMBL after 5 cycles of Rux + AZA	7.9	Received cladribine. Died of unknown cause in 1.5 months
PMF --> AML	55/M	Diploid	Rux+DAC	NR	unchanged BMBL after 3 cycles of Rux + DAC	5.1	Achieved CR with cladribine, idarubicin and cytarabine induction followed by MUD-SCT. Patient remains alive and in CR
MDS/MPD ---> AP	72/M	Del 20q; Del 3q	Rux+DAC	PD(AML)	Transformed to AML after 3 cycles of Rux + DAC	3.3	Treated with intensive chemotherapy for AML

PV, polycythemia vera; PPV-MF, post polycythemia vera myelofibrosis; PMF, primary myelofibrosis; AML, acute myeloid leukemia; AP, accelerated phase; F, female; M, male; Haplo-SCT, haploidentical stem cell transplantation; MUD-SCT, matched unrelated donor stem cell transplantation; Rux, ruxolitinib; AZA, azacitidine; DAC, decitabine; LDAC, low dose ara-C; PBBL, peripheral blood blast; BMBL, bone marrow blast, CR, complete remission, CI, clinical improvement, NR, no response; PD, progressive disease