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ORIGINAL ARTICLE

Between a rux and a hard place: evaluating salvage treatment and outcomes in myelofibrosis after ruxolitinib discontinuation

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Abstract

Ruxolitinib is a JAK1/2 inhibitor that is effective in managing symptoms and splenomegaly related to myelofibrosis (MF). Unfortunately, many patients must discontinue ruxolitinib, at which time treatment options are not well defined. In this study, we investigated salvage treatment options and clinical outcomes among MF patients who received and discontinued ruxolitinib outside the context of a clinical trial. Among 145 patients who received ruxolitinib, 23 died while on treatment, 58 remained on treatment at time of analysis, leaving 64 people available for analysis. Development of cytopenias was the most common reason for discontinuation (38%) after median treatment time of 3.8 months (mo). The majority of patients received some form of salvage therapy after ruxolitinib discontinuation ($n = 42$; 66%), with allogeneic hematopoietic stem cell transplant (alloHSCT) ($n = 17$), being most commonly employed. Lenalidomide, thalidomide, hydroxyurea, interferon, and danazol were used with similar frequency. The response rate to salvage treatment was 26% (8 responses) and responses were most often seen with lenalidomide or thalidomide. Improved outcomes were observed in patients who underwent alloHSCT or received salvage therapy compared to those who did not receive additional therapy. Median overall survival (OS) after ruxolitinib discontinuation was 13 months. These findings show that salvage therapy can provide clinical responses after ruxolitinib discontinuation; however, these responses are rare and outcomes in this patient population are poor. This represents an area of unmet clinical need in MF.

Keywords Ruxolitinib · Myelofibrosis

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Introduction

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) characterized by cytopenias, constitutional symptoms, splenomegaly, and a risk of transformation into acute myeloid leukemia (AML). Historically, the treatment of MF has been directed to specific signs or symptoms, with most treatment options having low response rates and side effect profiles that risk worsening other features of the disease. Ruxolitinib is a Janus-associated-kinase-1 and 2 (JAK1/2) inhibitor approved for the treatment of intermediate and high-risk MF after demonstrating significant efficacy in reducing spleen volume and improving MF-related symptoms in two phase 3 clinical trials [1, 2]. While the ability of ruxolitinib to alter the natural history of MF is still being debated, its effect in this capacity appears modest at best [3]. Mounting evidence suggests a survival benefit associated with ruxolitinib use, though this may be due to its effect on metabolic and nutritional parameters [4–7]. The only curative approach in MF remains allogeneic hematopoietic stem cell transplant (alloHSCT).

Since its approval, ruxolitinib has become the primary treatment option for MF patients; most of whom present with constitutional symptoms and/or splenomegaly [8]. Despite these successes, many patients treated with ruxolitinib must discontinue treatment due to treatment-related side effects or lack or loss of response [1, 2]. Optimal salvage treatment strategies following ruxolitinib discontinuation have not been well-defined. Recent follow-up of patients treated with ruxolitinib in the context of an early phase clinical trial has revealed that outcomes following ruxolitinib discontinuation are poor and that thrombocytopenia and clonal evolution during treatment predict for inferior outcomes [9].

In an effort to assess the impact of salvage treatment in MF after ruxolitinib discontinuation, we retrospectively identified patients who had received and discontinued ruxolitinib outside the context of a clinical trial and analyzed subsequent treatment strategies, responses, and clinical outcomes.

Methods

This was a single-institution retrospective study of patients who presented to our institution with a diagnosis of MF between 1/1/2004 and 1/31/2017. Primary myelofibrosis (PMF) was defined by World Health Organization (WHO) 2008 criteria for patients diagnosed prior to 2016 and by WHO 2016 criteria for those diagnosed in or after 2016. Post-polycythemia vera myelofibrosis (post-PV MF) and post-essential thrombocythemia (post-ET MF) were defined according to the International Working Group for Myeloproliferative Neoplasms, Research and Treatment, respectively (IWG-MRT) [10–12]. Patients receiving ruxolitinib on the basis of a clinical trial were excluded ($n = 3$). Patients were retrospectively assigned to risk categories using the dynamic international prognostic scoring system (DIPSS) based on clinical variables determined at time of presentation to our institution [13]. Target variables including reason for discontinuation, salvage treatment regimens, clinical parameters at the beginning and end of ruxolitinib treatment, and outcomes were attained through detailed chart review. Treatment responses were determined based on IWG-MRT response criteria for MF [14].

Our primary aim was to analyze salvage treatment options and clinical outcome after ruxolitinib discontinuation. Additionally, we wanted to determine the most common reasons for ruxolitinib discontinuation in a real-world setting and determine if any clinical variables correlated with outcomes.

Median follow-up was calculated by reverse Kaplan-Meier method. Overall survival (OS) was determined from time of ruxolitinib discontinuation unless otherwise stated and patients were censored at time of last follow-up or date of alloHSCT. All data was analyzed using GraphPad Prism v6.07 and SPSS 24. P value < 0.05 was considered statistically significant.

Results

In total, 145 patients received ruxolitinib for MF outside the context of a clinical trial. Median follow-up after ruxolitinib discontinuation was 10.3 months (mo). Twenty-three (16%) patients died while receiving ruxolitinib and 58 (40%) were still receiving ruxolitinib at the time of last follow-up, leaving 64 (44%) patients evaluable for outcome after ruxolitinib discontinuation. Patient demographics are shown in Table 1.

Among 64 evaluable patients, ruxolitinib was most commonly discontinued due to the development of cytopenias ($n = 24$; 38%), with anemia ($n = 21$; 33%) more commonly implicated than thrombocytopenia ($n = 9$; 14%), and 6 (9%) patients discontinuing due to two cytopenias. Other reasons for discontinuation included alloHSCT ($n = 10$; 16%), lack of response ($n = 9$; 14%), progression of constitutional symptoms or splenomegaly after an initial response ($n = 7$; 11%), progression to acute myeloid leukemia ($n = 8$; 13%), and treatment intolerance not related to cytopenias ($n = 6$; 10%) (Fig. 1).

Patients who discontinued ruxolitinib due to cytopenias were on treatment for a median of 3.8 months [range 1–45 months]. A hemoglobin less than 10 g/dL ($p = 0.02$) or platelet count less than 100,000/μL ($p = 0.03$) prior to initiation of ruxolitinib predicted for cytopenia-related treatment discontinuation; however, these factors did not predict for lack of benefit. Among 21 patients who discontinued ruxolitinib due to anemia, 3 (5%) had a hemoglobin greater than 10 g/dL prior to initiation of ruxolitinib while 4 (19%) did not have a documented hemoglobin level within 60 days of ruxolitinib

Table 1 Patient demographics. *Abbreviations*: *MF* myelofibrosis, *DIPSS* dynamic international prognostic scoring system, *WBC* white blood cell count, *AML* acute myeloid leukemia

Clinical parameter	Pts discontinuing ruxolitinib
	n = 64 (%)
Median age (year) [range]	65 [40–84]
Male	41 (64)
Primary myelofibrosis	48 (75)
Post-polycythemia vera MF	8 (13)
Post-essential thrombocythemia MF	8 (13)
JAK2 V617F mutant	43 (67)
MPL mutant	3 (5)
CALR mutant	8 (13)
Triple-negative	2 (3)
Driver mutation status unknown	8 (13)
DIPSS	
Low	4 (6)
Intermediate-1	25 (39)
Intermediate-2	24 (38)
High	11 (17)
Prior to ruxolitinib treatment	
WBC > 25×10^9	8 (14)
Monocytes > 1×10^9	11 (22)
Platelets < 100×10^9	13 (22)
Hemoglobin < 10 g/dL	29 (51)
Peripheral blast ≥ 1%	16 (32)
Splenomegaly*	54 (92)
Constitutional symptoms^	40 (63)
Post ruxolitinib treatment	
WBC > 25×10^9	19 (31)
Monocytes > 1×10^9	11 (19)
Platelets < 100×10^9	29 (45)
Hemoglobin < 10 g/dL	45 (70)
Peripheral Blast ≥ 1%	34 (58)
Splenomegaly*	54 (87)
Constitutional symptoms^	27 (42)
Allogeneic hematopoietic stem cell transplant	17 (27)
Conversion to AML	10 (16)

* Defined by palpable spleen on exam or by spleen imaging with ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)

^ Defined by notation of fever, chills, bone pain, drenching night sweats, weight loss > 10% over 6 months, or fatigue impacting ability to perform independent activities of daily living (IADLs)

initiation. Fourteen (48%) patients with a hemoglobin less than 10 g/dL and 8 (62%) patients with a platelet count less than 100,000/μL prior to initiation of ruxolitinib discontinued treatment due to cytopenias. For those patients with pre-treatment hemoglobin less than 10 g/dL, the median duration of ruxolitinib treatment prior to discontinuation was 3.1 months (range 1–35 months). For those with pre-treatment platelet counts less than 100,000/μL, the median duration of ruxolitinib treatment prior to discontinuation was 2.5 months (range 2–45 months).

The median duration of treatment in those patients who discontinued ruxolitinib due to recurrent symptoms or splenomegaly after experiencing an initial response was 21 months (range 4–34 months). In contrast, patients who failed to respond to ruxolitinib were on treatment for a median of 5.2 months (range 1–29 months).

After ruxolitinib discontinuation, 42 (66%) patients received salvage therapy with 11 patients (17%) receiving ≥ 2 lines of therapy. Salvage treatments included alloHSCT (n = 17), lenalidomide (n = 7), thalidomide (n = 6), hydroxyurea (n = 6), interferon (n = 5), danazol (n = 6), hypomethylating agents (n = 4), and investigational agents (n = 3). Among these, 31 treatment regimens used in 19 patients were evaluable for response with an overall response rate (ORR) to salvage therapies of 26% (8/31) (Table 2). Among eight observed responses, four were anemia responses with thalidomide, one spleen response with lenalidomide, one spleen and symptom response with lenalidomide, one anemia response with azacitidine, and one a spleen response to an investigational JAK2/FLT3 inhibitor. No responses were observed with interferon (0/3) or danazol (0/6). In responding patients, the median exposure to salvage treatment was 5.4 months. A response to post-ruxolitinib treatment had no impact on OS (p = 0.72).

Seventeen patients underwent alloHSCT with median age of 62 (range 42–72 years). DIPSS assessment at time of transplant revealed 3 patients (18%) to be high-risk, 11 were intermediate-2 risk (65%), and 3 (18%) were intermediate-1 risk with additional disease features which increased their risk score using other models. Median time from ruxolitinib discontinuation to transplant was 13 days, with 12 of 17 patients undergoing alloHSCT within 6 months of ruxolitinib discontinuation. Among those patients who underwent alloHSCT, 10 (59%) discontinued ruxolitinib in preparation for their transplant, while 3 (18%) discontinued due to cytopenias, 2 (12%) discontinued due to lack of response, 1 discontinued due to treatment intolerance (6%), and 1 discontinued due to progression of disease (6%). Median follow-up for patients undergoing alloHSCT was 11.4 months. Median OS was not reached. Two-year OS in transplanted patients was 67%.

Median OS from ruxolitinib initiation was 35 months. Median OS after ruxolitinib discontinuation was 13 months. Ten patients (16%) progressed to AML, with 8 (80%) progressing while on ruxolitinib. Excluding those who underwent alloHSCT, those receiving salvage treatment had superior OS compared to those who did not, with a median OS of 15.0 months compared to 4.9 months (p = 0.02) (Fig. 2). This difference remained significant after excluding patients

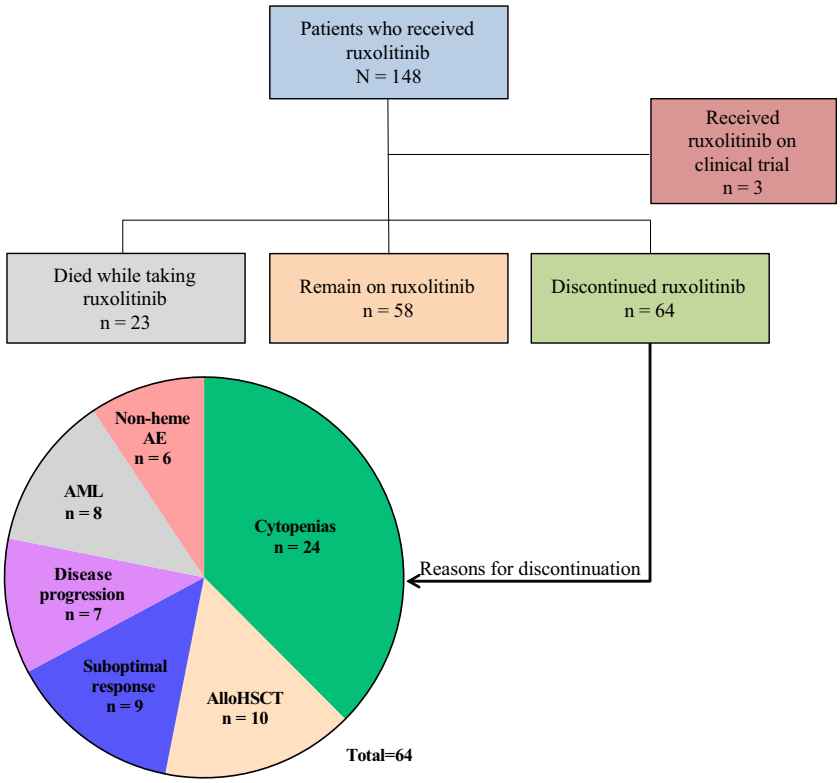

Fig. 1 Disposition of patients receiving ruxolitinib. AML transformation to acute myeloid leukemia. AlloHSCT allogeneic hematopoietic stem cell transplant. Non-heme AE non-hematologic adverse event

who progressed to AML ($p = 0.007$). In multivariate analysis, controlling for hematologic and clinical covariates at the time of ruxolitinib discontinuation, salvage therapy remained a significant covariate ($p = 0.04$).

Discussion

The FDA-approval of ruxolitinib has altered the treatment landscape in MF [8]. Yet, despite its successes, many patients ultimately discontinue ruxolitinib. In our study, we documented the most common reasons for discontinuation in a real-world setting, analyzed salvage treatment options and their efficacy, and confirmed the poor outcomes in MF after ruxolitinib discontinuation.

Ruxolitinib is approved for the treatment of intermediate and high-risk MF based on the COMFORT trials which used the international prognostic scoring system (IPSS) to enroll intermediate-2 and high-risk MF patients [1, 2, 15]. The label for ruxolitinib, however, does not differentiate between intermediate-1 and intermediate-2 risk patients and does not specify the method in which patients are risk stratified. Our study included a significant proportion of intermediate-1 patients; however, it should be noted that the DIPSS was used to risk stratify patients given its ability to evaluate patients at any time during their clinical course [13]. Compared to the IPSS, DIPSS tends to downstage patients without anemia. In our cohort, the use of IPSS modeling would have resulted in an increased percentage of patients being categorized at intermediate-2 or high risk (70 vs 55%). Our cohort was enriched with patients with MF-related symptoms (62%) and/or splenomegaly (92%), suggesting a cohort that would benefit from ruxolitinib.

Follow-up studies of the COMFORT I and COMFORT II trials have shown that approximately 50% of study patients discontinued ruxolitinib by 3 years and only 25% remained on therapy after 5 years. Within the context of these large, phase 3 clinical trials, approximately 20% of patients discontinued due to disease progression, 20–25% discontinued due to adverse events, and another 5–10% discontinued due to unsatisfactory response to treatment [4, 5]. Our analysis, in a real-world scenario, recapitulated these findings. Direct comparison with these analyses is difficult since our study distinguishes between cytopenia-related and non-cytopenia-related adverse events. Additionally, since the focus of our study was on salvage treatment, we did not include those who died on ruxolitinib in our analysis, though death on treatment was considered in analysis of ruxolitinib discontinuation in the COMFORT trials. Nevertheless, we did show that a significant proportion of patients discontinued ruxolitinib due to cytopenias (28% when including the 23 patients who died on ruxolitinib). This is likely attributable to the real-world context of the patients we analyzed; wherein initial dosing strategies and dose modifications were less uniform,

Table 2 Salvage treatment, treatment duration, and response for evaluable patients after ruxolitinib discontinuation. *Abbreviations*: *mo* months, *JAK2* Janus-associated kinase 2, *FLT3* fms-like tyrosine kinase-3

Patient	Salvage treatment	Duration (mo)	Response	Response details
1	Thalidomide	9.14	Yes	Anemia response
	Danazol	6.22	No	
2	Thalidomide	8.98	Yes	Anemia response
3	Thalidomide	5.07	Yes	Anemia response
4	Thalidomide	3.52	Yes	Anemia response
5	Lenalidomide	1.28	No	
	Thalidomide	3.52	No	
	Danazol	3.59	No	
	Pegylated interferon	0.5	No	
6	Lenalidomide	0.56	No	
	Pegylated interferon	3.55	No	
7	Lenalidomide	0.99	No	
8	Lenalidomide	1	No	
	Danazol	1	No	
9	Lenalidomide	6.25	No	
	Cladribine	1	No	
10	Lenalidomide	3.26	Yes	Spleen response
11	Lenalidomide	1.61	Yes	Spleen and symptom response
12	Hydroxyurea	7.27	No	
	Thalidomide	4.11	No	
	Danazol	1.88	No	
13	Hydroxyurea	6.68	No	
14	Hydroxyurea	3.22	No	
15	Danazol	2.01	No	
16	Danazol	0.69	No	
17	Azacitidine	5.75	Yes	Anemia response
18	Investigational agent (JAK2/FLT3 inhibitor)	11.35	Yes	Spleen response
19	Investigational agent (anti-Ephrin A1 antibody)	8.72	No	
	Pegylated interferon	7.99	No	
	Ruxolitinib	1.44	No	
	Investigational agent (imetelstat)	11	No	

and prescribing physicians, who were often community oncologists, had varying levels of comfort with the medication. This is highlighted by the fact that the majority of cytopenia-related discontinuations occurred by the fourth month of therapy, when dose reductions or supportive measures may have been able to bridge the gap to hemoglobin recovery, which typically occurs by week 24 [5]. In terms of non-hematologic adverse events, concurrent infections were suspected or confirmed in 13 patients, but only led to discontinuation in two patients; one of whom had recurrent oral herpetic outbreaks and another who developed recurrent middle ear infections. Most of the reported infections were bacterial urinary tract infections or pneumonias and not necessarily thought to be associated with ruxolitinib use.

After discontinuation of ruxolitinib, we found that alloHSCT and immunomodulatory agents, namely, thalidomide and lenalidomide, were the most often utilized salvage treatment options. Newberry et al., in contrast, found hydroxyurea and investigational agents to be most frequently used, likely reflecting differences in a clinical trial population as well as regional practices. They also reported the relatively frequent used of salvage splenectomy, which was performed infrequently ($n = 3$) in our patient population [9]. Interestingly, we were able to show that salvage therapies can lead to clinical responses, with anemia, spleen, and symptom responses being

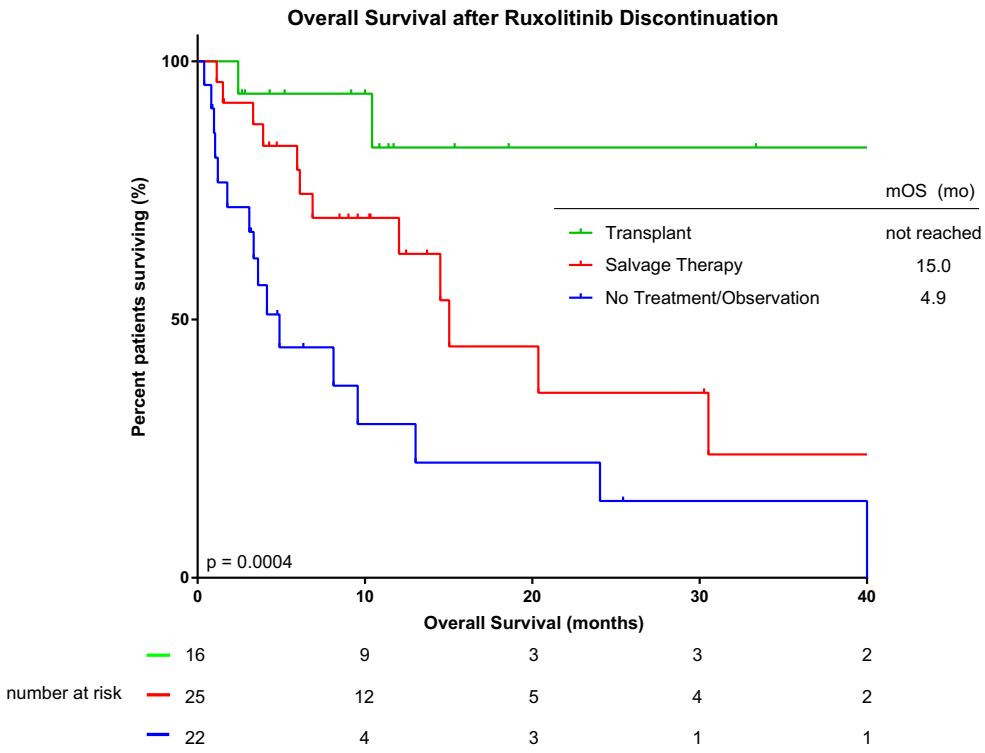

Fig. 2 Overall survival of patients after ruxolitinib discontinuation based on salvage treatment approach

achieved with a variety of agents. Thalidomide and lenalidomide accounted for 75% of the observed responses while interferon and danazol failed to produce any clinical responses.

Lastly, we confirmed that survival after ruxolitinib discontinuation is poor. The median survival seen in our study closely mirrors that which has been previously reported [9]. Patients who can safely undergo alloHSCT should be considered for this option, especially considering the potentially beneficial role of ruxolitinib prior to alloHSCT [16–20]. Those patients that cannot receive alloHSCT should be offered symptom-directed salvage therapy. Even though responses were infrequent and the presence of a response did not correlate with improved survival, we showed that the receipt of salvage therapy correlated with improved survival. This could be attributed to a number of causes. First, patients who received salvage therapy could represent a healthier cohort. Second, salvage therapy could provide therapeutic benefits not captured by current response criteria, such as the ability to prevent worsening of disease. Lastly, this could reflect closer monitoring of patients receiving an active treatment compared to those who are not.

As a retrospective, single-institution study with limited follow-up, our study has several notable limitations. Much of our data was assembled using detailed chart review which if often complicated by missing data and can lead to misinterpretation of clinical scenarios. Specific details regarding initial dosage, dose modifications, and criteria used by prescribing physicians to adjust or discontinue ruxolitinib could not be reliably obtained. While this is certainly a limitation, it also reflects the realities of real-world ruxolitinib treatment, wherein physicians will have varying experience and clinical comfort in managing MF patients. In terms of evaluating salvage therapies, six patients who received a salvage treatment were lost to follow-up and unable to be assessed for response.

Given the poor outcome after ruxolitinib discontinuation and low responses rates observed with existing therapeutic options, treatment of MF after ruxolitinib discontinuation represents an area of unmet clinical need. Further prospective studies utilizing novel agents in ruxolitinib-exposed patients and continued follow-up of prior ruxolitinib-based clinical trials are warranted to provide further guidance in this challenging clinical scenario.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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