Ruxolitinib as a primary treatment for multiple myeloma in a patient with primary myelofibrosis? A case report and the review of the literature

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ABSTRACT

An 80-year-old female with a history of primary myelofibrosis was admitted to the hospital due to worsening symptoms of the primary disease. A secondary tumor — multiple myeloma (MM) — was revealed during the diagnostic process. Monotherapy with a JAK inhibitor (ruxolitinib) was administered, and the severity of both malignancies was alleviated. This article includes a short review of secondary malignancies correlated with PMF and the state of knowledge on using JAK inhibitors, mainly ruxolitinib, in treating MM.

Key words: primary myelofibrosis, multiple myeloma, ruxolitinib, inhibitor

INTRODUCTION

Primary myelofibrosis (PMF) is one of the myeloproliferative neoplasms (MPNs). Apart from PMF, this group consists of polycythemia vera (PV), essential thrombocythemia (ET), chronic myelogenous leukemia (CML), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia (CEL) [1]. The constant activity of the Janus Kinase-signal transducer and activator of transcription (JAK-STAT) pathway is one of the main characteristics of MPNs. *JAK2* V617F and *JAK2* exon 12 mutations are the most frequent drivers found in PMF, PV, and ET and are present in 60% of PMF patients, 98% of PV patients, and 60% of ET patients [2, 3]. Other common mutations include those of calreticulin (CALR) and of myeloproliferative leukemia virus oncogene (MPL) which make up 25% and 7% of PMF cases, respectively [4]. These mutations are believed to start clonal myeloproliferation, leading to clinical presentation including anemia, hepatosplenomegaly, and systemic symptoms like fatigue, night sweats, and low-grade fever [5].

To this day, several treatment methods are used in PMF, ranging from allogeneic hematopoietic stem cell transplantation (allo-HSCT) in higher-risk patients to pharmacological means of treatment, which mainly alleviate the symptoms of the disease. Pharmacological treatment options include JAK inhibitors (JAKi), cytoreductive therapy with hydroxyurea, corticosteroids, and immunomodulatory agents such as thalidomide and lenalidomide [4, 6–8].

Out of the agents used, the group of JAKi seems to be of great interest, also in other diseases, due to inhibition of downstream signaling of STAT3/5, phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinase (MAPK) [9]. For example, the treatment with ruxolitinib stimulates the increased cytotoxic activity when co-administered with anti-programmed cell death protein-1 (anti-PD-1) immunotherapy in pancreatic cancer [10, 11]. Additionally, immunosuppressive qualities of ruxolitinib are being assessed in coronavirus disease 2019 (COVID-19) and hemophagocytic lymphohistiocytosis (HLH) [12, 13]. In the case of PMF, ruxolitinib, a selective inhibitor of JAK1 and 2, has clinically significant activity in PMF. In a phase 3 randomized trial ruxolitinib provided significant clinical benefits in patients with PMF by reducing spleen size, ameliorating debilitating myelofibrosis-related symptoms, and improving

overall survival [14]. A later pooled analysis from randomized phase III trials COMFORT-I and COMFORT-II indicated that ruxolitinib improved patients' overall survival compared to conventional therapies [15]. In addition, besides myelofibrosis, ruxolitinib is also approved for the treatment of PV and graft-versus-host disease (GvHD) [16–18].

Herein, a case of a female patient with PMF and multiple myeloma (MM) successfully treated with ruxolitinib monotherapy is presented.

CASE REPORT

At the age of 69, a diagnosis of primary myelofibrosis was made in 2012. Since March 2018, the progression of splenomegaly and weight loss (5 kg over six months) was observed. The laboratory tests revealed normocytic anemia, vitamin B12 deficiency, increased lactate dehydrogenase (LDH), and direct bilirubin levels with negative direct antiglobulin test result. Further diagnostic excluded hemolysis. An increased level of the monoclonal protein was also detected. The patient was treated with B12 supplementation and blood transfusion. Testing for the *JAK2* V617F mutation was negative.

In January 2019, the patient was referred to the regional hospital to reassess her clinical condition. The laboratory findings showed leukopenia [white blood count (WBC) 2.60 G/L], neutropenia [absolute neutrophil count (ANC) 1. 43 G/L], anemia [hemoglobin (Hb) 7.1 g/dL], and increased beta$_2$-microglobulin (4.62 mg/L). The platelet (PLT) count was within the normal range (330 G/L). The serum analysis revealed abnormalities in the free light chain (FLC) concentration kappa 10.9 mg/L, lambda 181.0 mg/L (ratio kappa: lambda 0.06) while the levels of these in urine were as follows: FLC kappa 9.65 mg/L, FLC lambda 2,66 mg/L (ratio kappa/lambda 3.63). Trephine biopsy revealed the characteristic image of myelofibrosis with a reticulin fiber score of 3 (MF3), and the infiltration of bone marrow by plasmatic cells was estimated to be 20% (CD138+, CD38–). Testing for the *CALR* mutation was negative. The patient was referred to the Institute of Hematology and Transfusion Medicine to broaden the diagnostic process and access the treatment options.

Upon admission to the Institute in May 2019, the patient's vital signs were stable. Clinical examination revealed massive splenomegaly (15–16 cm below the costal margin, exceeding the median line by 2–3 cm) measuring 250 mm in ultrasound. The laboratory investigation confirmed previous findings (WBC 2.88 G/L, ANC 1.86 G/L, Hb 7.9 g/dL, PLT 291 G/L) with the aggravation of beta$_2$-microglobulin (6.6 mg/L) and serum FLC lambda levels (369 mg/L), FLC kappa levels (0.65 mg/L) — ratio kappa/lambda 0.001. A monoclonal protein of IgA class type lambda was detected in the immunofixation assay of blood serum at the concentration of 0.65 g/dL. The blood smear showed polychromatic (3%) and orthochromatic (2%) erythroblasts. Other than anemia and the light chain criterion, the patient presented no SLiM CRAB signs. The presence of *JAK2* mutation was reassessed, and a polymorphic variant of c.1641+179_1641+183delTCTTA was detected. No *JAK2* V617F, *CARL,* or *MPL* mutations in exon 10 were detected. Cytogenetic testing of isolated bone marrow plasmocytes using fluorescence in situ hybridization (FISH) probes showed an additional copy of the *ATM* gene suggesting chromosome 11 trisomy; no *TP53* gene deletion nor t(4;14), t(14;16), t(11;14) or t(14;20) was noted. The risk assessment of PMF was graded three according to International Prognostic Scoring System (IPSS) and four according to Dynamic International Prognostic Scoring System (DIPSS). Considering all of the aforementioned characteristics, the main complaint being splenomegaly, initial monotherapy with ruxolitinib was chosen with the possible reevaluation of therapy if the symptoms worsened. A concurrent diagnosis of smoldering MM was also made, as no SLiM CRAB criteria were met, and normocytic anemia was probably caused by PMF advancement.

After six months of ruxolitinib treatment, the patient had no disease symptoms. In the first two months required four units of red blood cell transfusion. The final dose of ruxolitinib was estimated at 10mg two times daily. Patient morphology revealed normal WBC and PLT values with stable normocytic anemia with Hb within the 8.2–9.3 g/dL range. Ruxolitinib was continued. The monoclonal protein remained stable and did not increase during ruxolitinib therapy.

Two years later in April 2021, the patient was hospitalized due to a COVID-19 infection. Because of the patient's anemia, a transfusion of 4 units of red cell concentrate was required during the stay. Additionally, a decrease in platelet count down to 90 G/L was observed. Therefore, it was suspected that the treatment was insufficient, and the patient was referred to the Hematology Department. The signs of anemia were detected (Hb 7.8 g/dL); however, the laboratory results unexpectedly showed platelet, white blood cell counts within normal limits, a decrease of monoclonal protein IgA lambda (0.25 g/dL), a significant decrease within FLC lambda 174 mg/L (ratio kappa/lambda 0.07), and a beta$_2$-microglobulin of 5.9 mg/L. Trephine biopsy revealed a small decline of plasma cell infiltration (10–15%), a reticulin fibers deposition (MF3), and the characteristics of dyserythropoiesis. Reduction of splenomegaly was detected in the computed tomography (CT) scan, and no osteolytic lesions were revealed. Thus, the most probable cause of the decompensation of the disease was the COVID-19 infection. Therefore, the patient was discharged after receiving two units of red cell concentrate with the instruction to continue the ruxolitinib treatment, which she now uses for an overall period of 48 months with good tolerability as of May 2023. In that period levels of monoclonal protein were stable and blood transfusion was required.

DISCUSSION

Aside from well-known features characterizing worse survival in MPNs, such as advanced age, the appearance of constitutional symptoms, alterations within complete blood count, the status of needed transfusion, grade of bone marrow fibrosis, and appearance of particular karyotype or mutations, there is more light being shed on second primary malignancies (SPM) as the unfavorable survival risk factor [4]. Indeed, MPNs carry the risk of second non-hematologic cancers with a hazard ratio (HR) of 1.6 [19]. Moreover, hematologic malignancies are also prone to develop with HR ranging from 46.0 in acute myeloid leukemia (AML) to 1.7 in MM [19]. Interestingly, PMF patients are significantly more likely to develop AML (HR = 99.2), lymphoma (HR = 6.0), and MM (HR = 9.0) than patients suffering from other MPNs [19]. Following the study, there is an association between the subsequent appearance of MM in patients previously diagnosed with PMF [20].

PMF is a disease of a well-characterized genetic landscape that constitutes both "driver" and "other" mutations. The former group consists of three mutations *JAK2*, *CALR*, and *MPL* which are detected in most patients and are a part of the major International Consensus Criteria (ICC) [1, 21]. These alterations lead to a consistently active JAK2, which enhances intracellular signaling *via* STAT3/5, and independently from STAT particles *via* PI3K and MAPK/ERK pathways (Figure 1) [21, 22]. Although 8–10% of PMF cases present without the aforementioned mutations, therefore are described as triple-negative PMF [23]. Other mutations, such as *ASXL1*, *SRSF2*, *EZH2*, *IDH1*, and *IDH2* are frequently seen alongside "drivers" and are of significance concerning the decrease in overall survival (OS) and leukemia-free survival [24].

Intriguingly, the intracellular signals apparent in MM cells are not much different from those in PMF. The activation of JAK/STAT, PI3K, and MAPK routes is crucial to MM survival and progression (Figure 1) [25, 26]. The stimulus that drives the induction of these pathways is likely different from the one in PMF. There is evidence of isolated cases of plasma cells being *JAK2* V617F positive when coexisting

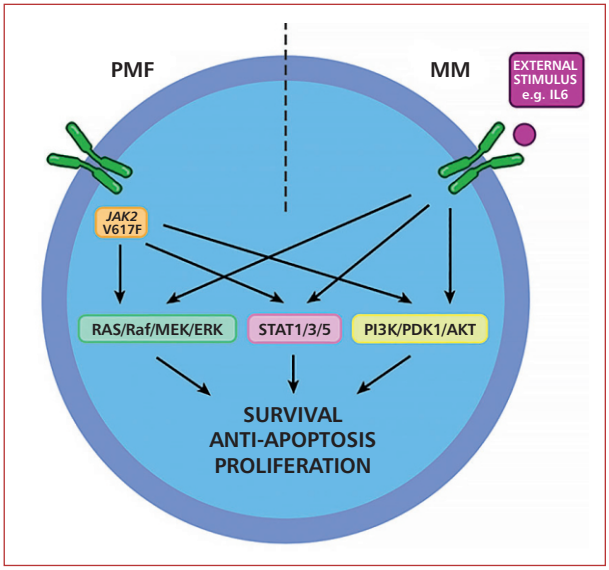

Figure 1. The molecular pathways of primary myelofibrosis (PMF) and multiple myeloma (MM). Molecular signaling in a malignant cell is a complex process involving multiple protein cascades. In PMF the starting point is mostly *JAK2* V617F mutation which activates STAT, RAS/Raf, and phosphatidylinositol 3-kinase (PI3K) routes. On the contrary, MM cells often use external stimuli that through cellular receptors activate the same molecular pathways. As a result, malignant cells gain neoplastic qualities such as increased survival, proliferation, and decreased apoptosis; IL6 — interleukin-6; PDK1 — pyruvate dehydrogenase kinase 1

with MPNs [27]. However, on screening 93 MM patients not associated with MPNs, none presented with *JAK2* V617F mutation [28]. It appears that the increased signaling is rather an effect of other cellular alterations such as interleukin-6 (IL6) signaling and commonly described myeloma mutations (e.g., *KRAS, NRAS, BRAF*) (Figure 1) [26, 29]. Taking it into account, despite the different stimuli, the intracellular signaling is similar in both malignancies. It includes JAK/STAT, PI3K, and MAPK pathways which induce cellular survival, proliferation, and growth.

Introducing ruxolitinib was a great achievement in PMFsymptom control [30–33]. Additionally, the pooled

Table 1. Current studies investigating the use of ruxolitinib in multiple myeloma (MM) patients

Trial number	Status	Drug	Associated therapy	Study phase	Additional features
NCT03110822	Recruiting	Ruxolitinib	Lenalidomide, methylprednisolone	I	Refractory or relapsed MM
NCT00639002	Recruitment completed	Ruxolitinib	Dexamethasone	II	Refractory or relapsed MM
NCT03773107	Active, not recruiting	Ruxolitinib	Carfilzomib, dexamethasone	I/II	Carfilzomib-refractory MM
NCT03017820	Recruiting	Ruxolitinib	Recombinant vesicular stomatitis virus-expressing human interferon beta and sodium--iodide symporter	I	Relapsed or refractory MM
NCT03878524	Recruiting	Ruxolitinib	Various pharmacological agents	Ib	In this study, samples from patients' cancers are to be tested to find combinations of drugs that provide clinical benefits for the kind of cancer the patient has. Then the treatment will be administered to patients for up to 6 cycles and assessed

analysis of the COMFORT I and II study revealed prolonged overall survival (OS) among intermediate-2 or high-risk PMF symptom control patients; therefore, it became one of the best therapeutic options among symptomatic PMF patients [32]. Ruxolitinib works in both *JAK2* V617F positive and negative cells because its molecular target is the adenosine triphosphate (ATP) binding site of JAK2, which remains unchanged when the mutation occurs [34]. Ergo, it inhibits up-regulated JAK2 and its downstream signaling, including STAT3/5, PI3K, and RAS, corresponding with decreased proliferation and increased apoptosis of malignant cells [21, 34, 35]. The convergence of cellular pathways involved in the progression of PMF and MM suggests that ruxolitinib may also inhibit the expansion of myeloma cells. Indeed, there is a growing body of evidence justifying the usage of JAK inhibitors in MM patients (Table 1).

The overexpression of *JAK2* and *JAK1* is seen in 57% and 27% of MM patients, respectively [36]. When combined with bortezomib, ruxolitinib leads to increased MM cell death compared to monotherapy and concurrently decreases in expression of antiapoptotic proteins BCL-2 and BCL-XL *in vitro* [36]. Moreover, studies are introducing ruxolitinib to combine well-known anti-myeloma drugs to increase their anti-tumoral activity [36, 37]. Interestingly, the combination of ruxolitinib and methylprednisolone has an overall response rate of 31% when used in relapsed/refractory MM patients [38]. Few are describing the potential additional benefits of introducing ruxolitinib into the MM regimen. Ruxolitinib may encourage an interruption of MM-mediated immunosuppression by increased T-cell activity due to the downregulation of PD-L1, PD-L2, and CD44 expression by MM cells; and decreased M2 polarization of macrophages [39–41]. Additionally, the downregulation of STAT3 activity in MM cells enhances CD38 expression, which might be used to increase daratumumab activity [42].

CONCLUSION

With prolonged OS in hematological malignancies, there is an increased hazard ratio of SPMs. MPNs are a great example of this phenomenon, with a high risk of developing a broad spectrum of solid and hematologic tumors. The convergence of the molecular pathways of different hematological neoplasms creates an opportunity to use established treatments in new indications. That was the case with ruxolitinib, which may provide additional benefits of MM control aside from its primary anti-PMF action. This discovery is an interest in novel clinical trials, and hopefully, some of them will ensure better treatment options in both MM and PMF.

Article information

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