CASE REPORT

Efficacy of ruxolitinib retreatment in a patient with high-risk myelofibrosis using the international prognostic scoring system

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Introduction

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm in which clonal proliferation of hematopoietic stem cells and bone marrow fibrosis coexist.[1] Patients may eventually die due to leukemic progression, which occurs in up to 20% of cases, or because of cardiovascular comorbidities or cytopenia, which causes susceptibility to infections and bleeding.[2]

Myelofibrosis diagnosis relies upon the evaluation of several clinical and laboratory criteria suggested by the World Health Organization (WHO) in 2016.[3] The major mutations leading to myelofibrosis usually occur in the *JAK2*, *CALR*, and *MPL* genes. However, in almost 10% of the cases, none of the above-mentioned mutations can be detected (so-called 'triple-negative patients'). Rarely, a number of several different mutations in genes such as *LNK*, *CBL*, *TET2*, *ASXL1*, *IDH*, *IKZF1*, *EZH2*, *DNMT3A*, *TP53*, *SF3B1*, *SRSF2,* and *U2AF1* may occur.[4,5]

In the phase III studies, COMFORT-I and COMFORT-II, ruxolitinib, a JAK 1/2 inhibitor, has been demonstrated to reduce both splenomegaly and symptom burden in patients with international prognostic scoring system (IPSS) intermediate-2 and high-risk myelofibrosis, compared with placebo.[6–8] In these trials, therapy discontinuation, for whichever reason (including noncompliance to study procedures), was as high as 55%. Furthermore, in the COMFORT-II trial, ruxolitinib discontinuation was due to adverse events in 24/146 (16.4%) patients in the ruxolitinib arm (R), 5/73 (6.8%) patients in the 'best-available treatment' arm, and 6/45 (13.3%) patients in the ruxolitinib after best-available treatment arm. In particular, hematologic toxicity in the ruxolitinib arm was 4.6%

(1% anemia and 3.6% thrombocytopenia). Other reasons for therapy discontinuation were consent withdrawn, protocol deviation, noncompliance with either study medication or study procedures, unsatisfactory therapeutic effect, stem cell transplant, meeting protocol-defined imaging discontinuation criteria, investigator decision, important comorbidities/lung cancer), unspecified safety event, and modest spleen response.

Recently, ruxolitinib has also been suggested for the treatment of patients who have polycythemia vera, which is resistant to or intolerant of hydroxyurea.[9]

We report our initial experience with a patient affected by PMF, retreated with ruxolitinib after a 3-month suspension of therapy due to clinical decision.

Case description

The local Ethical Committee (A.O.U.P. Palermo, Palermo, Italy) approved the submission of this paper. The patient provided consent to the publication of his case, which has been described according to the CARE guidelines.

A 71-year-old patient presented to our clinic in July 2015 with intense asthenia, diffuse pain, and premature fullness, after losing 10 kg of body weight in 24 months. Clinical splenomegaly was confirmed with echography, revealing a longitudinal spleen diameter of 22 cm. Laboratory tests at baseline revealed normochromic normocytic anemia (hemoglobin [Hb]: 9 g/dL, red blood cells [RBC]: 3,190,000/mm^3), increased platelet count (PLT: 535,000/mm^3), normal white blood cells (WBCs: 9080/mm^3 with the following formula:

neutrophils (N) 73.7%, leucocytes (L) 17%, monocytes (M) 6.4%, eosinophils (E) 0.9%, basophils (B) 1%), and increased levels of LDH (950 U/L). The blasts were 1%. No cardiovascular or thrombotic episodes were reported at baseline.

No mutations in *JAK2*, *CALR,* and *MPL* were found, and the BCR-ABL search was negative. We could not assess the presence of other nondriver mutations.

Bone marrow biopsy suggested grade II PMF, and the subsequent diagnosis of IPSS high-risk PMF was established. Therapy with ruxolitinib 40 mg per day was consequently started. After 1 month, symptoms and splenomegaly improved; however, due to severe reduction of platelet count (down to 110.000/mmc) and worsening anemia (Hb: 8.6 g/dL) requiring two transfusions per month, the therapy was reduced to ruxolitinib 30 mg/day.

In December 2016, ruxolitinib was stopped due to a marked increase in spleen dimensions and concomitant severe Herpes Zoster infection, treated with valaciclovir. The patient was classified as a nonresponder to ruxolitinib due to persistent splenomegaly. In fact, at baseline, the spleen measured 22 cm in its longest diameter, which initially decreased to 18 cm after 1 month of treatment. However, at the time of the ruxolitinib suspension, the spleen measured 23 cm, thus justifying treatment discontinuation for persistent splenomegaly. In addition, at this time, the peripheral blood sample was as follows: RBC: 2,620,000/mm^3, Hb: 7.8 g/dL; PLT: 165,000/mm^3, WBC: 10,100/mm^3 (N: 71%, L: 18%, M: 8%, E: 1% B: 1%) with blasts stable at 1%. Of note, during ruxolitinib discontinuation, the patient was treated only with antithrombotic medication and transfusions, without any additional treatments.

After approximately 3 months of suspension, ruxolitinib 30 mg/day was reintroduced to control the worsening splenomegaly. Secondary prevention for Herpes Zoster was also introduced. The following course was successful, as systemic symptoms improved, and spleen dimensions decreased to 16 cm within 1 month from therapy reinstitution. Peripheral blood sample was also improved, with RBC: 3,670,000/mm^3; Hb: 9.5 g/dL; PLT: 340,000/mm^3; WBC: 9,500/mm^3 (N: 72%, L: 17%, M: 7%, E: 1%, B: 0.5%, and blasts stable at 1.5%)

In addition, a lower need for transfusions was noted, only two within a year compared with the previous period, and by now the patient tolerated the treatment well with ruxolitinib.

Discussion

Myelofibrosis is a myeloproliferative neoplasm characterized by debilitating symptoms and splenomegaly, related to elevation of circulating proinflammatory cytokines.[10] Splenectomy has limited efficacy in controlling disease progression, and new therapies are focusing on the pathway of JAK2 activation, either directly or indirectly through other related pathways converging on JAK2.[11,12] The upregulation of JAK–STAT (Janus kinase/signal transducer and activator of transcription) signaling may cause the abnormal accumulation of oncoproteins, which may initiate the disease or favor blastic transformation.

The diagnosis of PMF may be challenging sometimes, due to the fact that in almost 10% of cases patients may be 'triple negative' owing to common mutations for PMF (*JAK2*, *CALR,* and *MPL*). On the contrary, patients may present several different mutations in genes, such as *LNK*, *CBL*, *TET2*, *ASXL1*, *IDH*, *IKZF1*, *EZH2*, *DNMT3A*, *TP53*, *SF3B1*, *SRSF2,* and *U2AF1*.[4,5]

Ruxolitinib is a JAK inhibitor that inhibits both JAK1 and JAK2 independently from the presence of any *JAK2* mutations. Its effects have been analyzed in the COMFORT-I and COMFORT-II trials in patients with IPSS intermediate-2 or high-risk myelofibrosis, where ruxolitinib has shown significant levels of spleen size reduction and symptom improvements.[6–8] However, several patients may discontinue ruxolitinib treatment over time, either because of ruxolitinib resistance or ruxolitinib intolerance.[13,14]

Moreover, hematologic toxicity of ruxolitinib has also been reported in various trials,[8,13,14] as well as the diminished efficacy over time that may lead to treatment failure. Our patient experienced an increase of the spleen size, leading to ruxolitinib discontinuation; however, after a few months, treatment with ruxolitinib was reinitiated at a lower dosage due to disease progression with marked splenomegaly. After reintroduction of ruxolitinib, we noted a significant increase of therapy efficacy in our patient. Garcia et al. present similar results in patients from the JAKARTA-2 study, who were switched to ruxolitinib following a period on fedratinib treatment.[15] Conversely from the JAKARTA-2 study, which investigated the efficacy of fedratinib in ruxolitinib-resistant or ruxolitinib-intolerant patients,[16] Garcia et al. report the opposite experience – that is, the retreatment with ruxolitinib after a period of fedratinib therapy. Gupta et al. and Al-Ali et al. also reported on the regained efficacy of ruxolitinib after an interruption in the JUMP trial.[17,18]

We describe the case of a patient who became resistant to ruxolitinib, but after a 3-month suspension, the therapy regained efficacy, allowing for a marked improvement both on systemic symptoms and on splenomegaly. Moreover, retreatment was associated with a lower hematologic toxicity compared with the previous cycle, with a markedly reduced need for transfusional support. Other authors reported similar findings of reduced toxicity after discontinuation and reinitiation of ruxolitinib treatment.[17,19]

However, strong data on the optimal duration of therapy suspension are lacking, and it is unknown whether all patients may benefit from a period of ruxolitinib suspension or not. Thus, our hypothesis-generating case report on ruxolitinib retreatment underlines the importance of well-designed clinical trials aimed to answer these relevant clinical questions.

It is important to underline that the International Working Group on Myelofibrosis has not yet established specific criteria to define ruxolitinib resistance or failure, and thus we based our classification of the patient as a nonresponder based on the persistence of splenomegaly.

In line with similar case reports published on this topic, we found a reduced hematologic toxicity of ruxolitinib at reintroduction after a short discontinuation period. This is, at present, another report to be added in the 'real-life-registry' on myelofibrosis, which should be available among the current literature. In fact, the available literature lacks randomized trials in this subgroup of patients, and only isolated reports of ruxolitinib suspension and reintroduction exist. We believe that it is important to collect all the available information regarding clinical possibilities from the literature, to form a 'real-life' database easily accessible to clinicians who may face the same challenges in the future.

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