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Tips on using ruxolitinib in everyday practice as therapy for myelofibrosis

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Myelofibrosis is the most aggressive of the myeloproliferative neoplasms, both in its effects on the patient's body and in significantly shortening life expectancy.[1] Treating physicians face a challenge in trying to improve 3 main myelofibrosis-related clinical issues: symptomatic organomegaly (the spleen is enlarged in about 80% of patients and liver in about 40%), very poor quality of life due to disease-related constitutional symptoms (with decreased performance status and ability to walk), and anemia.[1] No medication was available as a therapy for myelofibrosis until November 2011, when the US Food and Drug Administration approved ruxolitinib, an inhibitor of the JAK1 and JAK2 tyrosine kinases.[2] Ruxolitinib inhibits the dysregylated, hyperactive JAK-STAT pathway, an underlying biological abnormality in that is present in all patients with myelofibrosis regardless of the presence of the JAK2V617F mutation., Testing for the presence of the JAK2V617F mutation is not necessary, as ruxolitinib is potentially beneficial for any patient with myelofibrosis.[2]

Ruxolitinib significantly improves 2 of the 3 main clinical problems with myelofibrosis: it reduces spleen size and markedly improves quality of life.[3,4] However, in general, it does not improve anemia. So, which patients are proper candidates for therapy with ruxolitinib? Two large, significantly overlapping patient populations exist: 1) Those with symptomatic splenomegaly, and/or 2) those with significant myelofibrosis-related constitutional symptoms.[2] The presence of splenomegaly is not prerequisite for the use of ruxolitinib; it also improves performance status and weight gain and reduces constitutional symptoms in patients without splenomegaly. Ruxolitinib also reduces liver size in patients with an enlarged liver after splenectomy.[5] This is important, in that improvements in organomegaly and constitutional symptoms are not necessarily connected. Indeed, the higher the dose of ruxolitinib (maximum dose is 25 mg twice a day[BID]) the better the spleen reduction.[3] Better spleen reduction means the overall benefits last longer, leading to possibly longer survival times.[6] On the other hand, 10 mg BID is equally as effective in controlling constitutional symptoms as are higher doses.[3] Long-term follow up of patients treated with ruxolitinib for an average of about 2–3 years suggested that patients maintained on the 10 mg BID dose or higher had very good long-term response in terms of splenomegaly and quality of life.[7]

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Many patients with advanced myelofibrosis have not only symptomatic splenomegaly or poor quality of life but also significant anemia requiring transfusion.[1] The presence of anemia, however, is not a contraindication for use of ruxolitinib. As reported by Geyer and colleagues,[8] the addition of another therapeutic agent to improve anemia can be attempted (danazol, erythropoietin, or low-dose thalidomide). Indeed, there is no contraindication to using ruxolitinib. Current recommendations are to use it at a dose of 20 mg BID in patients with platelets above 200×10^9/l, or 15 mg BID in those with platelets between 100×10^9/l and $200 \times 10^{9/l}$.[4] Preliminary results of an ongoing Phase II study in patients with platelets between 50×10^9/l and 100×10^9/l reveal the benefits of therapy starting at a low dose of 5 mg BID and increasing to 10 mg BID if not overly myelosupressive, which was possible in the majority of the patients.[9] A similar approach is possible in patients with significant anemia, as reported by Geyer and colleagues[8]: starting with a lower dose and increasing as possible. A few important points should be mentioned here: 1) ruxolitinib should be used in BID schedule due to its short half-life; single daily dosing was shown to be ineffective.[3]; 2)5mg BID is usually not very effective and the dose should be increased to at least 10 mg BID if it safe to do so[3]; as mentioned above, long-term dosing at 5 mg BID is not very effective[7]; 3) Dose increases should be made monthly, if possible, during first 3 months, as increasing the dose after the initial 3 months of therapy was found to be less effective.[3]

Myelosupression, in particular anemia, is the main side effect of ruxolitinib.[4] As reported by Geyer,[8] close follow-up of patients during the first 2–3 months of therapy is mandatory, and proactive dose adjustments are recommended in order to maintain patients on therapy with an effective dose and without interruptions. While 5 mg BID can be used transiently in a case of significant myelosuppression, 10 mg BID or higher, has been shown to be effective long term.[7] With close attention paid during the first 2–3 months, almost all patients can be maintained on an effective and safe dose regimen. Discontinuations for myelosuppresssion are rare, as reported in previous clinical studies and by Geyer and colleagues as well.[4،8]

The reduction in red blood cell count is usually transient for the first 6 months on treatment, and due in large part to dose adjustments, there is a rebound in hemoglobin levels to near baseline levels in patients on therapy.[2] Importantly, the acquisition of transfusion dependency due to ruxolitinib does not diminish its benefits: patients that acquired anemia requiring transfusions due to ruxolitinib had the same level of improvements in spleen and quality of life as those without therapy-induced anemia.[2] As reported by Geyer and colleagues,[8] despite worsening anemia in some cases leading to periodic transfusions, patients tend to stay on ruxolitinib due to overwhelming improvements in constitutional symptoms and splenomegaly. In the other words, benefits significantly dwarf the risk of the need for transfusions.[2،4]

In general, interruption of ruxolitinib therapy leads to the return of all symptoms to baseline within 7 – 10 days.[4] Regrowth of the spleen also happens, although usually at a slower rate. This return of symptoms may result in some patients (particularly those with excellent results on ruxolitinib) feeling very badly in a short period of time.[1] Therefore, tapering of ruxolitinib or the use of corticosteroids upon discontinuation has been suggested.[1،2] Withdrawal syndrome has been described in 5 patients from one academic center in the

USA, but has not been reported in any other study with ruxolitinib, including some enrolling thousands of patients.[1,2] In the current report by Geyer et al, ruxolitinib was discontinued in some patients without tapering and withdrawal symptoms were not reported.[8]

A recent update of the 2 Phase III randomized studies that led to the approval of ruxolitinib suggested a survival advantage for ruxolitinib-treated patients versus those initially treated with a placebo or best available therapy.[10] Despite the fact that both studies allowed crossover of patients from control arms to the ruxolitinib arm, those patients exposed to ruxolitinib from the beginning had a reduced mortality rate.[10] It is very likely that this is a result of better control of the disease symptoms through the decrease of inflammatory cytokines elicited by ruxolitinib, which has proven to be important for disease biology and patient outcome.[10] These findings suggest that ruxolitinib should not be reserved for only the sickest patients, but should be introduced as therapy for patients with symptomatic splenomegaly or symptomatic disease in general.[2]

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