COMMENTARY

blood advances

TO THE EDITOR:

Guidance on changing therapy choice in myelofibrosis

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Myelofibrosis (MF) is a heterogeneous disease and presents many treatment challenges. After descriptions of deregulated Janus kinase (JAK) signaling in myeloproliferative neoplasms (MPNs) in 2005, therapeutic advances were rapid, and the JAK1/JAK2 inhibitor ruxolitinib (Novartis, Basel, Switzerland; Incyte, Wilmington, DE) was the first agent to gain a specific license in MF from both the US Food and Drug Administration (FDA) and European Medicines Agency after the success of 2 phase 2 multicenter studies.[1-6] More recently, in September 2019, the FDA approved the use of fedratinib (Inrebic; Celgene) for MF.[7] This approval led to an update of the National Comprehensive Cancer Network guideline on MF to include fedratinib as an initial therapy option for intermediate-2 and high-risk MF in patients with a platelet count $\geq 50 \times 10^9$/L. Additionally, fedratinib was included as a second-line therapeutic option. Globally, clinical trial portfolios for MF are expanding rapidly, with a concentrated focus on the potential benefits of alternative JAK inhibitors, agents directed at those with anemia with or without transfusion dependency, and other approaches, such as antifibrinolytic agents, telomerase inhibitors, BET inhibitors, and numerous combinatorial strategies being explored.[8] As this expansion occurs, especially with the focus on agents next in line after ruxolitinib, practical challenges arise in accurately recognizing patients intolerant to ruxolitinib or for whom ruxolitinib fails and successfully switching patients between therapies. Currently, patients with either stable or slowly progressing disease may continue to receive first-line ruxolitinib to avoid early exhaustion of available potential therapeutic options. Moreover, the optimal timing of allogeneic stem cell transplantation (alloSCT) for patients receiving therapy with JAK inhibitors remains unclear, although such a topical discussion will not be the focus of this commentary. Here we provide practical considerations when addressing the successful transition of MF patients across an increasingly complex therapeutic spectrum.

Situations will arise when it is required to switch from ruxolitinib to fedratinib and, over time, vice versa. Here concerns relate to the potential occurrence of marked proinflammatory states and systemic deterioration resulting from JAK inhibitor withdrawal, which can occur after patients substantially reduce dosages of ruxolitinib or stop (it remains unclear if this occurs with fedratinib). However, in clinical practice, unlike clinical trials, most patients will switch directly from 1 drug to the other without a washing-out period from the first agent. Overall, the prognosis of MF patients discontinuing ruxolitinib is generally poor.[9,10] It is unclear if a similar situation exists when first-line fedratinib fails. This is likely due to advancing disease prompting a switch of therapy; however, there are also important safety considerations within this context. Lastly, some patients may switch from first-line JAK inhibitor therapy directly to alloSCT, and at present, practice varies with regard to the weaning (or not) from first-line JAK inhibitors before alloSCT. An unaddressed question is whether a switch to the other licensed JAK inhibitor agent during the lead-in time to transplantation is helpful.

Consideration must be given to duration of therapy, dosage, and time to response regarding the first-line agent to define whether the patient should continue. Objective monitoring with a validated symptom questionnaires, such as the MPN Symptom Assessment Form or MPN10, should be mandated, coupled with accurate spleen size determination.[11] Potential confounding factors affecting assumed JAK inhibitor efficacy, such as depression, drug-drug interactions, and whether anemia or thrombocytopenia require intervention, should be reviewed regularly. Accumulated data confirm the clinical efficacy of ruxolitinib in addressing disease symptoms and splenomegaly and its association with a survival advantage in responders; however, discontinuation rates from JAK inhibitors are not inconsiderable.[12-14] In 5-year data cutoff analyses, 72% of those randomized to ruxolitinib in COMFORT-1 had discontinued, with a similar rate in COMFORT-2 (73%).[12,15] Furthermore, in a report by Palandri et al[10] of 442 patients receiving ruxolitinib, at a median follow-up of 30.5 months (range, 1.7-84.3 months), 43 (20%) died had while receiving therapy, and almost half (214; 48%) had discontinued ruxolitinib therapy.[10] Median survival of the evaluable discontinuation cohort (n = 171) was 22.6 months. For patients discontinuing

Table 1. Potential clinical considerations when switching therapies

Potential clinical scenario	Options and considerations
Patient 1: 72-y-old woman with high-risk primary MF initially responded to ruxolitinib but now has a spleen 18 cm below the left costal margin and a total symptom score of 45 and is on 20 mg of ruxolitinib twice daily. On attempted ruxolitinib wean, painful splenomegaly, fever, sweats, and debilitating bone pain ensue.	Difficult clinical scenario with a high risk of rebound systemic inflammatory response during wean and potential compromise. Options may include a direct overlap of both ruxolitinib and fedratinib with wean off ruxolitinib once the patient is established on fedratinib and stable or steroid cover during ruxolitinib wean before establishment on fedratinib once wean is complete.
Patient 2: 46-y-old man with intermediate-2 risk after polycythemia vera MF on stable dose of ruxolitinib for 4 y but meets criteria for failure at last review. Spleen has returned to baseline, and symptom score is 22. Currently on 10 mg twice daily.	Before switch, consider whether this patient just needs a dose increment of ruxolitnib. If switch is planned, consider tapering tuxolitinib dose over 10-14 d and monitor. Could then start standard recommended dose fedratinib. There is not much experience of the reverse switch (ie, moving from fedratinib to ruxolitinib), and whether weaning of fedratinib in that situation is required remains unknown but seems likely. Consideration of other clinical trial options and role of alloSCT. Assess for clonal evolution.
Patient 3: 56-y-old man with intermediate-2 risk primary MF with gradual splenic enlargement and rising symptom score despite dose optimization of ruxolitinib. Successful gradual taper of ruxolitinib with no flare. Patient has been on no therapy for 4 wk with stable spleen and symptoms.	Could start recommended dose of fedratinib[21] or consideration of other clinical trials or transplantation if suitable.
Patient 4: 82-y-old man develops blastic-phase disease after clonal evolution while on fedratinib first-line therapy.	Dismal prognosis, and therefore, options include best supportive care, investigational agents for acute leukemia in clinical trials, low-intensity chemotherapy, or hypomethylating agents.[22] To date, in contrast to ruxolitinib,[23,24] there is no published experience of combining fedratinib with either low- or high-intensity chemotherapy regimens.
Patient 5: 65-y-old woman with high-risk primary MF on a stable dose of fedratinib has an optimal spleen volume reduction and complete resolution of symptoms; transplantation is planned.	No formal recommendations exist on how to manage fedratinib before transplantation. As with ruxolitinib, we would recommend a gradual taper over a 10- to 14-d period, aiming to stop the drug on the day before conditioning. Theoretical potential exists for peritransplantation continuation of the agent, but effects on engraftment kinetics and posttransplantation modulation/immune reconstitution are unknown.

because of intolerance or resistance in chronic phase, survival seemed improved in those subsequently receiving another JAK inhibitor or investigational agent compared with the more historical therapies danazol or hydroxycarbamide, highlighting the importance of appropriate therapy sequencing, but also perhaps reflecting eligibility for clinical trials. In a phase 1/2 study of 107 MF patients, 86 had discontinued ruxolitinib after a median follow-up of 79 months (30 of whom had died during therapy), and median survival after discontinuation was 14 months.[16] Those with emergent, worsening thrombocytopenia (platelets $<100 \times 10^9$/L) at discontinuation and or those with clonal evolution had a dismal prognosis.

Proactive surveillance for loss of response, disease progression, and unacceptable treatment-emergent adverse events is therefore warranted. Criteria used in defining ruxolitinib failure across trials remain variable (some studies permitted as few as 14 days of exposure) and highly dependent on investigator discretion. Definitions of JAK inhibitor failure have recently been developed and are gaining recognition within the clinical arena. Practically, duration of optimized therapeutic exposure is pivotal before ascertaining efficacy or lack thereof; physicians/nurses need to ensure each individual patient receives the optimal maximum tolerated dose based on the clinical scenario before abandoning a therapy and switching agents. We agree that loss of response or refractoriness to ruxolitinib can be practically defined by the criteria used in the recent JAKARTA-2 reanalyses: ruxolitinib therapy ≥3 months with initial response followed by either spleen regrowth or a suboptimal response (defined as <10% splenic volume reduction [SVR] or <30% decrease in spleen size from baseline).[17] Intolerance was defined in this analysis as ruxolitinib treatment for ≥28 days complicated by the development of transfusion requirement (≥2 units per month for 2 months) or grade ≥3 thrombocytopenia, anemia, hematoma, and/or hemorrhage during ruxolitinib treatment. A practical understanding of these criteria, particularly the inclusion of dose optimization, is critical to enhancing the patient-individualized chance of response.

The patient-specific factors to consider here are risk and tolerance. Both ruxolitinib and fedratinib may cause on-target hematological toxicities, specifically anemia and thrombocytopenia.[5,6,18,19] Cross-trial comparisons remain difficult, not least because of different instructions concerning the management of treatment-emergent adverse events (eg, at what level of thrombocytopenia to reduce dose). There remains an undefined balance between a tolerated low platelet count vs adequate clinical response. Recent analyses of both JAKARTA studies suggest that fedratinib may be of utility in those with baseline platelet counts of $<100 \times 10^9$/L.[20] In JAKARTA, median fedratinib dose density and SVR were similar in those with platelets $<$ or $>100 \times 10^9$/L, and modification of dose or discontinuation because of grade 3 to 4 thrombocytopenia was infrequent. In JAKARTA-2, SVR rates were similar in both platelet groups, and although higher rates of grade 3 to 4 thrombocytopenia occurred in those with platelets $<100 \times 10^9$/L, dose modification or discontinuation remained low. At present, it is unclear if the enhanced JAK2 specificity of fedratinib will alter the rates of nonmelanoma skin cancers and infectious complications potentially observed with ruxolitinib, but the fedratinib profile involves low-grade gastrointestinal toxicity and a black-box warning for thiamine deficiency and encephalopathy. These differences may influence clinician choice of agent to use in the first-line setting and timing of therapeutic switch. To illustrate all of these factors, clinical cases highlighting potential scenarios are listed in Table 1, and factors requiring consideration at time of planned switch are shown in Figure 1.

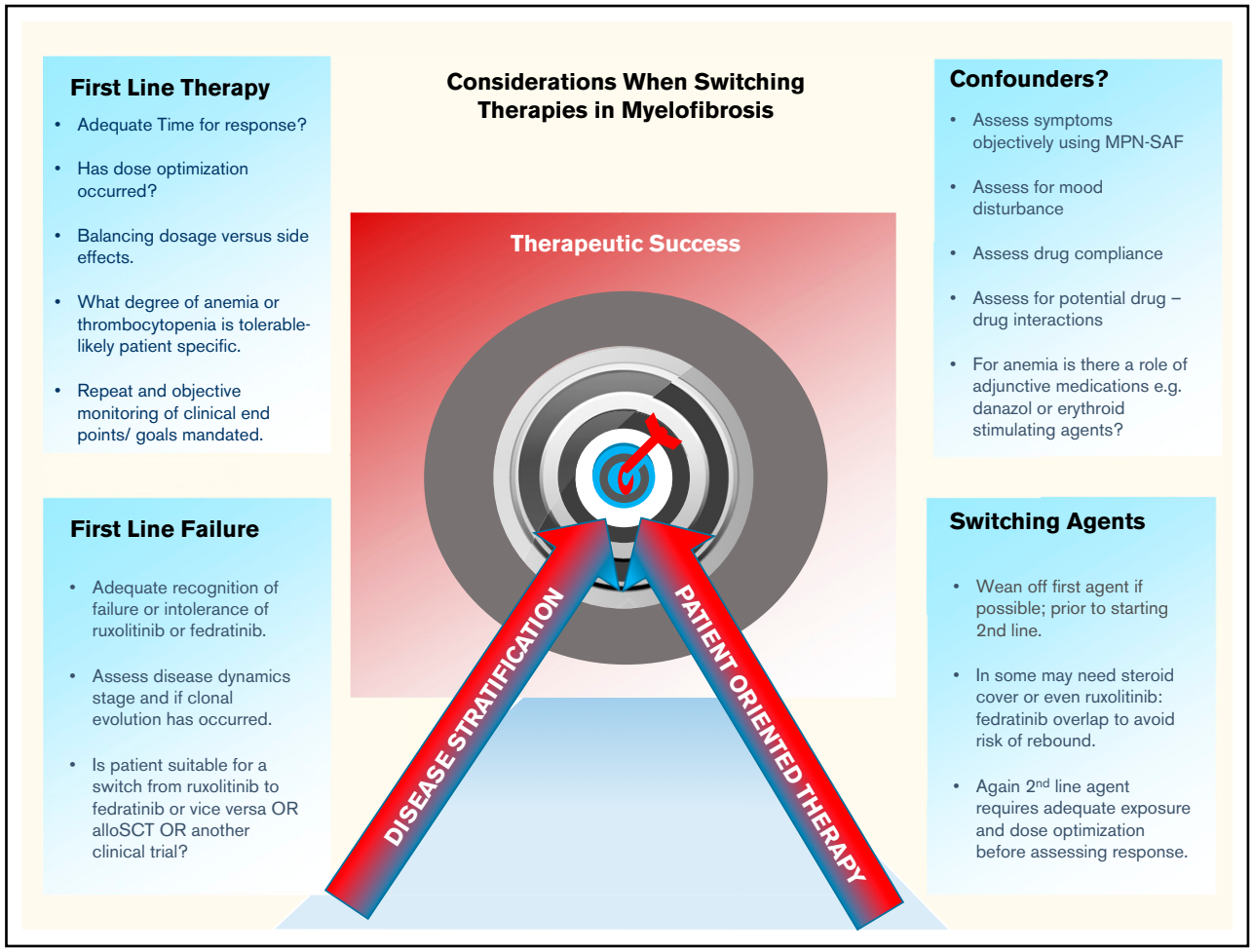

Figure 1. Considerations when switching therapies in MF.

Currently, we have the fortunate situation of having 2 approved JAK inhibitors in MF, and we hope to have additional approved therapies in the future, when switching among agents will become a reality. This area is rarely covered in summaries of product characteristics or practice guidelines. As highlighted through clinical cases, recommendations should be individualized based on clinical status, dose of current drug, disease dynamics, existing toxicities, and predicted half-life of the agents. Cumulative experience in the real-world setting will modify these approaches and lead to personalized, stratified choice of first and second, and indeed beyond, lines of therapy.

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