Cancer Therapy & Oncology
International Journal
ISSN: 2473-554X

Juniper Publishers
key to the Researchers

Editorial
Volume 23 Issue 5 - April 2023
DOI: 10.19080/CTOIJ.2023.23.556121

Cancer Ther Oncol Int J

Overview of the Therapeutic Landscape of JAK Inhibitors in Myelofibrosis

Nahla A M Hamed*

Professor of Hematology, Department of Hematology, Faculty of Medicine, Alexandria University, Egypt

Submission: April 17, 2023; **Published:** April 28, 2023

***Corresponding author:** Nahla A M Hamed, Professor of Hematology, Faculty of Medicine, Alexandria University, Egypt

Abstract

Ruxolitinib is often chosen as the first-line treatment of myelofibrosis because it can reduce the size of the spleen and improves the constitutional symptoms rapidly. However, these responses could frequently be accompanied by anemia and thrombocytopenia, especially in the early period of the treatment. Moreover, some patients may become ruxolitinib refractory or intolerant during the course of the disease. Ruxolitinib-intolerant patients, as opposed to ruxolitinib-resistant patients, are more likely to respond to an alternative JAK inhibitor.

Abbreviations: MF: Myelofibrosis; RR6: Response to Ruxolitinib after six months; ACVR1: Activin A Receptor Type 1; IRAK1: Interleukin-1 receptor-associated kinase 1; FLT3: Fms-like tyrosine kinase 3; WE: Wernicke Encephalopathies

Introduction

The approved first- and second line therapy of myelofibrosis (MF) are the JAK inhibitors ruxolitinib, fedratinib and pacritinib. Momelotinib is a new JAK1/2 Inhibitor, like ruxolitinib which is currently in late stage for clinical development in MF [1].

Ruxolitinib

It is often chosen as the first-line treatment of MF because it can reduce the size of the spleen, and improves the constitutional symptoms rapidly, eventually leading to improvement of the overall survival. These responses could frequently be accompanied by anemia and thrombocytopenia, especially in the early period of the treatment. Moreover, some patients may become ruxolitinib refractory or intolerant during the course of the disease. Recently, a prognostic model named Response to Ruxolitinib after six months (RR6), allows early identification of MF patients (in terms of risk of progression and overall survival) who might benefit from an earlier treatment shift. RR6 divided the patients into three risks categories according to the administered dose of ruxolitinib, the reduction in palpable splenic length, and the red blood cell transfusion requirement (any quantity). One point is assigned to the presence of a single of the described variables. These parameters are evaluated at the baseline and after 3 and 6 months of treatment [1].

Pacritinib

It is a potent kinase inhibitor that selectively inhibits JAK2 and avoids JAK1. It also inhibits fms-like tyrosine kinase 3 (FLT3), activin A receptor type 1 (ACVR1) and interleukin-1 receptor-associated kinase 1 (IRAK1). It exerts its clinical activity in MF via inhibiting two distinctive pathways: JAK/signal transducer and activator of transcription and toll-like receptor/ Myddosome/ IRAK1. Selective IRAK1 inhibition likely provides two benefits: 1) decrease of NFκB signaling through upstream targets such as IL-1 and alarmins, and 2) less dependence on inhibition of JAK2 since the IRAK1 pathway is an independent driver of MF disease course. Pacritinib ameliorates the disease severity through its high specificity to these two distinct pathways JAK2 and IRAK1 combined with its negligible inhibition of JAK1. This will result ultimately in potent anti-inflammatory and clinical activity with lower levels of myelosuppression [2].

Fedratinib

A potent JAK2 inhibitor that is active against wild-type and mutationally activated JAK2 [2]. It also exhibits off target inhibitory activity against FLT3. However, it has low inhibitory activity against JAK1 [3].

Momelotinib

It is an inhibitor of JAK1/2, ACVR1, and FLT3. It is currently in late-stage of clinical development for MF. ACVR1 is thought to modulate hepcidin expression and iron availability for erythropoiesis [3].

Choice of an alternative JAK inhibitor

Ruxolitinib-intolerant patients, as opposed to ruxolitinib-resistant patients, are more likely to respond to an alternative JAK inhibitor [4]. The choice of a JAK inhibitor could depend on the line of treatment and on the risk of onset of severe anemia and/or thrombocytopenia [5].

Fedratinib

Fedratinib was approved in 2019 for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (PPV or PET) MF with platelet counts ≥ 50 × 10^9 /L. Fedratinib may be used in the frontline setting or following previous ruxolitinib treatment. It is currently approved for use in patients intolerant or resistant to treatment with ruxolitinib. The reported response rates of the splenic size to fedratinib 400 mg/day were 36% compared to placebo (1%). This response rate was similar to that seen with ruxolitinib (JAKARTA-1). By contrast, in JAK inhibitor-naïve cases, the splenic size response rate was 0% in patients shifted to fedratinib after prior treatment with ruxolitinib ≥ 20 mg BID dosing. Accordingly, fedratinib might be considered in patients who are ruxolitinib intolerant while increasing the dose of ruxolitinib is initially preferred for ruxolitinib resistant patients. The recommended starting dose is 400 mg/day oral [3].

Pacritinib

It was approved by the US Food and Drug Administration (FDA) on 28 February 2022 for the treatment of adult patients with intermediate or high-risk primary MF, PPV-MF or PET-MF and severe thrombocytopenia (platelets <50 × 10^9 /L). The recommended dose is 200 mg BID [3,4]. Pacritinib should be confirmed as a valuable second-line option after prior JAK inhibitor exposure [5].

Momelotinib

It could be confirmed as a valuable option in patients with myelofibrosis associated with anemia. The effect of momelotinib on anemia could be explained by its capacity to decrease hepcidin production [5].

Toxicities of individual JAK inhibitors therapies

The non-hematological toxicity profile seems to be different between the four JAK inhibitors. Some adverse events are more specific to some drugs for example more gastro-intestinal effects are seen with fedratinib and pacritinib treatment [5].

Side effects of ruxolitinib [4]

i. Anemia

ii. Thrombocytopenia

iii. Opportunistic infections

iv. Poor immune response to vaccines

v. Withdrawal syndrome resembles systemic inflammatory response syndrome. It is seen with abrupt drug discontinuation and is characterized by acute relapse of disease symptoms, accelerated splenomegaly, worsening of cytopenias and occasional hemodynamic decompensation, including a septic shock-like syndrome.

Side effects of fedratinib [4]

i. Anemia

ii. Thrombocytopenia

iii. Gastrointestinal disturbance

iv. Elevations of serum liver function tests and pancreatic enzymes

v. Wernicke's encephalopathy (WE): few cases of WE occurred during fedratinib clinical trials. This is rarely of concern and is easy to manage. Vitamin B1 or thiamine deficiency is rare in MPN patients regardless of the therapy received. It has been proved that an appropriate thiamine level could prevent WE. Thiamine level should be carefully checked prior to prescribing fedratinib and every three months. Thiamine should be repleted when needed and supplemented before starting fedratinib therapy [5].

Side effects of pacritinib [4]

i. Rare cardiac events

ii. Severe diarrhea

iii. Nausea

iv. Edema

Side effects of momelotinib [4]

i. Low grade peripheral neuropathy

ii. Abnormalities of liver function and pancreatic enzyme

iii. Thrombocytopenia

iv. First-dose effect including dizziness, nausea, hypotension, headache and flushing.

Conclusion

Ruxolitinib-intolerant patients are more likely to respond to an alternative JAK inhibitor. The choice of a JAK inhibitor in these

How to cite this article: Nahla A M Hamed. Overview of the Therapeutic Landscape of JAK Inhibitors in Myelofibrosis. Canc Therapy & Oncol Int J. 2023; 23(5): 556121. DOI: 10.19080/CTOIJ.2023.23.556121

patients could depend on the line of treatment and the risk of onset of severe anemia and/or thrombocytopenia.

References

1. Duminuco A, Nardo A, Garibaldi B, Vetro C, Longo A, et al. (2022) Prediction of survival and prognosis migration from gold-standard scores in myelofibrosis patients treated with ruxolitinib applying the RR6 prognostic model in a monocentric real-life setting. J Clin Med 11(24): 7418.
2. Talpaz M, Kiladjian JJ (2021) Fedratinib, a newly approved treatment for patients with myeloproliferative neoplasm-associated myelofibrosis. Leukemia 35(1): 1–17.
3. Mascarenhas J (2022) Pacritinib for the treatment of patients with myelofibrosis and thrombocytopenia. Expert Review of Hematology 15(8): 671–684.
4. Tefferi A (2023) Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol 98(5): 801-821.
5. Sureau L, Orvain C, Ianotto J-C, Ugo V, Kiladjian J-J, et al. (2021) Efficacy and tolerability of Janus kinase inhibitors in myelofibrosis: a systematic review and network meta-analysis. Blood Cancer Journal 11(7): 135.

DOI: 10.19080/CTOIJ.2023.23.556121

How to cite this article: Nahla A M Hamed. Overview of the Therapeutic Landscape of JAK Inhibitors in Myelofibrosis. Canc Therapy & Oncol Int J. 2023; 23(5): 556121. DOI: 10.19080/CTOIJ.2023.23.556121