Updates on the Management of Myelofibrosis: Focus on Options After First-Line Treatment Failure

Dynamic International Prognostic Scoring System (DIPSS)

Variable	0 point	1 point	2 points
Age (y)	≤65	>65	
WBC (K/mm^3)	≤25	>25	
Hemoglobin (g/dL)	≥10		<10
PB blasts (%)	<1	≥1	
Constitutional symptoms	No	Yes	

Abbreviations: PB, peripheral blood; WBC, white blood cells. DIPSS score: Low (0), INT-1 (1-2), INT-2 (3-4), High (5-6).

Overview of FDA-Approved JAK Inhibitors

	Ruxolitinib (Jakafi)	Fedratinib (Inrebic)	Pacritinib (Vonjo)
Indication	INT/High-risk MF	INT-2/High-risk MF	INT/High-risk MF with PLT <50K/mm^3
Mechanism of action	JAK 1/2 inhibitor	JAK2 inhibitor	JAK2 inhibitor
Starting dose	PLT >200K/mm^3: 20 mg PO BID PLT 100-200K/mm^3: 15 mg PO BID PLT 50-100K/mm^3: 5 mg PO BID PLT <50k/mm^3: not indicated	400 mg PO daily if PLT ≥50K/mm^3	200 mg PO BID
Administration	Without regard to meals	Without regard to meals. Taking with high-fat meal may reduce nausea/ vomiting	Without regard to meals

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Point-of-Care Reference Tool

Overview of FDA-Approved JAK Inhibitors

	Ruxolitinib (Jakafi)	Fedratinib (Inrebic)	Pacritinib (Vonjo)
Dosage forms	5, 10, 15, 20, 25 mg tablets	100 mg capsules	100 mg capsules
Key adverse events	Myelosuppression, withdrawal if abruptly discontinued, infections (TB, HSV, PML, hepatitis B), hyperlipidemia, secondary malignancies, nonmelanoma skin cancers, major adverse cardiac events, thrombosis	Myelosuppression, nausea, vomiting, diarrhea, amylase/lipase elevations, Wernicke encephalopathy, secondary malignancies, major adverse cardiac events, thrombosis	Myelosuppression, diarrhea, secondary malignancies, major adverse cardiac events, thrombosis
Drug interactions	Fluconazole and strong CYP3A4 inhibitors	Strong CYP3A4 inhibitors, dual CYP3A4 + 2C19 inhibitors. Avoid use with moderate/strong CYP3A4 inducers	Strong CYP3A4 inhibitors, inducers. Avoid concurrent use with sensitive P-gp substrates
Hold parameters	PLT <50K/mm^3 or ANC <500/mm^3	PLT 25-50K/mm^3 with active bleeding or <25K/mm^3 or ANC <500/mm^3	For clinically significant thrombocytopenia lasting ≥7 days, moderate bleeding requiring intervention. Significant diarrhea (grade 3-4) despite optimal supportive care. QTc >500 msec or >60 msec from baseline
Other major points	Avoid abrupt discontinuation, taper or consider corticosteroids to limit withdrawal symptoms/disease flare	Check thiamine level at baseline, replete if deficient. If on prior ruxolitinib, taper off before starting fedratinib. Consider antiemetic prophylaxis, therapeutic antidiarrheals	If on prior ruxolitinib, taper off before starting pacritinib. Avoid if QTc >480 msec prior to treatment, hold if QTc >500 msec on treatment. Correct preexisting hypokalemia. Consider therapeutic antidiarrheals. Hold 7 days prior to elective surgery or invasive procedures due to bleeding risk. Restart only after hemostasis assured

Abbreviations: ANC, absolute neutrophil count; HSV, herpes simplex virus; INT, intermediate; JAK, Janus kinase; MF, myelofibrosis; P-gp, P-glycoprotein; PLT, platelets; PML, progressive multifocal leukoencephalopathy; QTc, corrected QT interval; TB, tuberculosis.

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Consider JAK inhibitor Failure If:	
Pattern of Failure	**Definition**
Suboptimal spleen response	<25% ↓ in palpable spleen length after ≥3 mo optimally dosed JAK inhibitors
Loss of spleen response	≥50% ↑ in spleen length from best response
Transfusion-dependent anemia	≥4 units of RBC in 8 wk occurring ≥6 mo from RUX initiation
Severe thrombocytopenia	Unable to maintain unsupported PLT >25K/mm^3 (>35-50K/mm^3 if on anticoagulation)
Suboptimal symptom response	<50% ↓ in MF-SAF TSS after 3 mo of optimally dosed JAK inhibitor
Loss of symptom response	≥50% ↑ in MF-SAF TSS from best response
AP/BP transformation	
Secondary cancers	
Infections	

AP/BP, accelerated/blast phase; ↑/↓, increase/decrease; MF-SAF, Myelofibrosis Symptom Assessment Form Total Symptom Score; RBC, red blood cells; RUX, ruxolitinib.

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