PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

FEDRATINIB MYELOFIBROSIS

PROTOCOL REF: MPHAFMYEL
(Version No. 1.0)

Approved for use in:

- For the treatment of patients with intermediate-2 or high risk myelofibrosis previously treated with ruxolitinib
- Blueteq application is required – please see Blueteq website for full criteria

Dosage:

Drug	Dose	Route	Frequency
Fedratinib	**400mg**	Oral	Once daily (continuously)

Fedratinib should continue until progression or unacceptable toxicity

Administration:

- Baseline testing of thiamine (vitamin B1) levels should be obtained prior to starting treatment with fedratinib, periodically during treatment and as clinically indicated. Fedratinib treatment should not be started in patients with thiamine deficiency, until thiamine levels have been corrected (see non-haematological impairment below for details).
- If there is a delay in thiamine results then thiamine 100mg OD should be prescribed until the levels are available and within normal range.
- The capsules should not be opened, broken or chewed. They should be swallowed whole and preferably with water.
- Administration of fedratinib with a high fat meal may reduce the incidence of nausea and vomiting. Therefore, it is recommended to be taken with food.

- If a dose is missed, the next scheduled dose should be taken the following day. Extra capsules should not be taken to make up for the missed dose.
- Grapefruit or grapefruit juice should be avoided in patients receiving fedratinib
- Oral steroids may be required for ruxolitinib withdrawal syndrome prior to starting fedratinib

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

- Allopurinol PO 300mg OD or 100mg OD if CrCl < 20ml/min (for first cycle only).
- Thiamine PO 100mg OD if clinically necessary
- Ondansetron PO 8mg BD PRN
- Loperamide PO 4mg stat and then 2mg PRN after each episode of loose stools.

Interactions:

Fedratinib is metabolised by multiple CYPs *in vitro* with the predominant contribution from CYP3A4 and with a lesser contribution from CYP2C19, and flavin-containing monooxygenases (FMOs)

Concomitant administration of fedratinib with strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) increases fedratinib exposure. Increased exposure of fedratinib may increase the risk of adverse reactions. In place of strong CYP3A4 inhibitors, consider alternative therapies that do not strongly inhibit CYP3A4 activity. If strong CYP3A4 inhibitors cannot be replaced, the dose of fedratinib should be reduced to 200mg OD. Patients should be carefully monitored (e.g. at least weekly) for safety. In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, the fedratinib dose should be increased to 300 mg once daily during the first two weeks after discontinuation of the CYP3A4 inhibitor and then 400 mg once daily thereafter as tolerated.

Prolonged co-administration of a moderate CYP3A4 inhibitor (e.g aprepitant, ciprofloxacin, cyclosporine, diltiazem, erythromycin, fluconazole, verapamil) may require close safety monitoring and if necessary, dose modifications based on adverse reactions. Grapefruit or grapefruit juice can inhibit CYP3A4 activity and should be avoided in patients receiving fedratinib.

Agents that simultaneously inhibit CYP3A4 and CYP2C19 (e.g. fluconazole, fluvoxamine) or the combination of inhibitors of CYP3A4 and CYP2C19 may increase Inrebic exposure and should be avoided in patients receiving fedratinib.

Agents that strongly or moderately induce CYP3A4 (e.g. phenytoin, rifampicin, efavirenz) can decrease fedratinib exposure and should be avoided in patients receiving Inrebic.

If fedratinib is to be co-administered with substrate of CYP3A4 (e.g. midazolam, simvastatin), CYP2C19 (e.g. omeprazole, S-mephenytoin) or CYP2D6 (e.g. metoprolol, dextromethorphan), dose modifications of co-administered medicines should be made as needed with close monitoring of safety and efficacy.

If fedratinib is to be co-administered with agents that are renally excreted via organic cation transporter (OCT)2 and multidrug and toxin extrusion (MATE)1/2 K (e.g. metformin), caution should be exercised and dose modifications should be made as needed.

For more detailed interactions please refer to the SPC

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, encephalopathy, including Wernicke's encephalopathy, hepatic toxicity, elevated amylase, lipase and creatinine levels.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X			X	As clinically indicated
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
FBC	X	X	X	X	Can be reduced to every three months in stable patients
U&E & LFTs & Magnesium	X	X	X	X	Can be reduced to every three months in stable patients
Amylase and lipase	X	X	X	X	Can be reduced to every three months in stable patients
CrCl (Cockcroft and Gault)	X	X	X	X	Can be reduced to every three months in stable patients
Thiamine (vitamin B1)	X	X	X	X	Can be reduced to every three months in stable patients
Clinical exam of spleen size or ultrasound of spleen if not palpable	X				Repeat if clinically indicated
Weight recorded	X	X	X	X	Every cycle
Blood glucose	X				Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle 1:

Proceed with cycle 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 50 x 10^9/L

Subsequent cycles:

Haematologic toxicity	Dose reduction
Grade 3 thrombocytopenia with active bleeding (platelet count < 50 x 10^9/L) or Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)	Interrupt fedratinib dose until resolved to grade 2 (platelet count ≥ 50 x 10^9/L) or baseline. Restart dose at 100 mg daily below the last given dose.
Grade 4 neutropenia (absolute neutrophil count < 0.5 x 10^9/L)	Interrupt fedratinib dose until resolved to grade 2 (ANC ≥ 1.0 x 10^9/L) or baseline. Restart dose at 100 mg daily below the last given dose. Granulocyte growth factors may be used at the physician's discretion.
Grade 3 and higher anaemia, transfusion indicated (haemoglobin level < 80 g/L)	Interrupt fedratinib dose until resolved to grade 2 (haemoglobin level ≥80 g/L) or baseline. Restart dose at 100 mg daily below the last given dose.
Recurrence of a Grade 4 haematologic toxicity	Discontinuation as per physician's discretion.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Dosing in renal and hepatic impairment:

Renal	If CrCl (by Cockroft and Gault) is between 15 and 30ml/min the dose should be reduced to 200mg OD. Due to potential increase of exposure, patients with pre-existing moderate renal impairment may require at least weekly safety monitoring and if necessary, dose modifications based on adverse reactions

Hepatic	Cycle 1	Fedratinib has not been evaluated in patients with severe hepatic impairment (i.e. Child-Pugh class C or total bilirubin >3 times ULN and any AST increase) and so should be avoided in these patients. No modification of the starting dose is required for patients with mild to moderate hepatic impairment.	
	Subsequent cycles	ALT > 5.0 x ULN (> 165 units/L in women and > 205 units/L in men) or bilirubin > 3.0 ULN (>62 micromols/L)	Interrupt fedratinib dose until resolved to ≤ Grade 1 (ALT (> ULN - 3.0 x ULN) or bilirubin (> ULN - 1.5 x ULN)) or baseline. Restart dose at 100 mg daily below the last given dose. Monitor ALT, AST and bilirubin (total and direct) every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment with fedratinib.

Other non-haematological impairment

Non-haematological toxicity	Dose reduction
≥ Grade 3 nausea, vomiting or diarrhoea not responding to supportive measures within 48 hours	Interrupt fedratinib dose until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose.
≥ Grade 3 amylase / lipase (> 2.0 to 5.0 x ULN)	Interrupt fedratinib dose until resolved to Grade 1 (> ULN - 1.5 x ULN) or baseline. Restart dose at 100 mg daily below the last given dose. Monitor amylase / lipase every 2 weeks for at least 3 months following the dose reduction. If re-occurrence of a Grade 3 or higher elevation, discontinue treatment with fedratinib.
≥ Grade 3 other non-haematologic toxicities	Interrupt fedratinib dose until resolved to ≤ Grade 1 or baseline. Restart dose at 100 mg daily below the last given dose.
Management of thiamine levels and Wernicke's encephalopathy (WE)	**Dose reduction**
For thiamine levels < normal range (66 to 200 nmol/L*) but ≥ 30 nmol/L without signs or symptoms of WE	Interrupt fedratinib treatment. Dose with daily 100 mg oral thiamine until thiamine levels are restored to normal range. Consider re-starting fedratinib treatment when thiamine levels are within normal range.
For thiamine levels < 30 nmol/L without signs or symptoms of WE	Interrupt fedratinib treatment. Initiate treatment with parenteral thiamine at therapeutic dosages (NB this will require an inpatient stay) until thiamine levels are restored to normal range. Consider re-starting fedratinib treatment when thiamine levels are within normal range.
For signs or symptoms of WE regardless of thiamine levels	Discontinue fedratinib treatment and immediately administer parenteral thiamine at therapeutic dosages (NB this will require an inpatient stay).

*NB these values are different to the SPC but match the RLUH's lab handbook

References:

1. https://www.medicines.org.uk/emc fedratinib (Revised 08/11/2021; accessed 23/12/21)
2. RLUH's Lab Handbook (http://rlbuhtnet/jps/) (accessed 23/12/2021)

Circulation/Dissemination

Date added into Q-Pulse	22nd June 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
		Aileen McCaughey	V1.0