Thames Valley
Strategic Clinical Network

RUXOLITINIB

INDICATION

Licensed & Funded Indication / NICE TA 386 (BLUETEQ required)

Ruxolitinib is recommended as an option for treating disease-related splenomegaly or symptoms in adults with Primary Myelofibrosis, Post Polycythaemia Vera Myelofibrosis or Post Essential Thrombocythaemia Myelofibrosis in people with intermediate-2 or high-risk disease.

Licensed / Unfunded Indication (Individual funding must be agreed prior to initiation)

Treatment of adult patients with polycythaemia vera (PV) who are resistant to or intolerant of hydroxycarbamide.

Available as 5mg, 10mg, 15mg and 20mg tablets

TREATMENT INTENT

Disease modification

Spleen and/or symptom response- the latter should be monitored using the MPN-Symptom Assessment Form (MPN-SAF) LINK

PRE-ASSESSMENT

1. Investigations to include FBC, blood film and manual differential, coagulation screen, urea, creatinine, electrolytes, liver function tests, calcium, lipid profile, glucose, amylase, iron studies, urate, serum erythropoietin level
2. HIV, Hepatitis B (including HB surface Ag and HB core antibodies) and C testing
3. Ensure diagnosis is confirmed prior to commencing treatment by WHO or BSH criteria
4. Risk stratification by IPSS, DIPSS or similar scoring system to confirm INT-2 or high risk
5. Pregnancy Test - for all women of childbearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. ECG (most TKIs can affect the QT interval)
9. Consider echocardiogram in selected patients at risk of cardiac disease
10. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
11. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice (see fertility guidelines). Consider sperm storage/ cryopreservation in appropriate patients.
12. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.

13. Consider skin surveillance for patient with high risk of skin tumour.
14. Counsel patient regarding potential increase in infections including shingles, and consider prophylactic aciclovir, especially in those patients with a prior history of shingles. Live shingle vaccine is not recommended but patients should have the inactivated vaccine if eligible.
15. Treatment should be agreed in the relevant MDT.
16. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT)

DRUG REGIMEN / CYCLE FREQUENCY

Diagnosis	Platelet count x 10^9/L	Starting dose
MF	> 200	**RUXOLITINIB** 20mg PO twice a day continuous
	100 - 200	**RUXOLITINIB** 15mg PO twice a day continuous
	50 - 100	**RUXOLITINIB** max 5mg PO twice a day continuous, titrated cautiously
PV	**RUXOLITINIB** Starting dose: 10mg twice a day continuous (5mg if platelets between 100-200), titrated cautiously up to a maximum of 25mg twice a day	

The starting dose should not be increased within the first 4 weeks of treatment and thereafter no more frequently than at 2 week intervals. A lower starting dose can be considered in patients with borderline anaemia (Hb <110g/L) at baseline.

DOSE MODIFICATIONS

Avoid abrupt discontinuation as this can cause cytokine storm. If urgent treatment interruption required, consider concurrent corticosteroids (e.g. 0.5mg/kg prednisolone), and if possible, taper dose over 2 weeks.
Ensure patient has a supply of ruxolitinib 5mg tablets to allow for dose titration and is counselled on the reduction plan.

Dose Reduction - Haematological

Count	Modification
Plt < 50 x 10^9/L or ANC < 0.5 x 10^9/L or Hb < 80g/L in PV	Stop ruxolitinib. Once recovered above these levels, resume ruxolitinib 5mg PO twice a day and gradually increase based on careful monitoring of FBC. Neutropenia is rare with ruxolitinib and other causes such as disease progression should be considered.
Plt < 100 x 10^9/L or Hb < 100g/L in PV	Consider dose reduction to avoid dose interruptions for thrombocytopenia

Dose Escalation

If efficacy is considered insufficient and blood counts are adequate, ruxolitinib doses may be increased by a maximum of 5mg PO twice a day, up to the maximum dose of 25mg PO twice a day.

Concomitant strong CYP3A4 inhibitors or Fluconazole up to 200mg daily
When ruxolitinib is administered with strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole) the unit dose of ruxolitinib should be reduced by approximately 50%, administered twice a day.

Renal impairment

<table>
<tr><th>GFR</th><th>Modification</th></tr>
<tr><td>< 30 mL/min</td><td>Starting dose should be reduced by 50% administered twice a day.</td></tr>
<tr><td>End-stage renal disease on haemodialysis</td><td>
<table>
<tr><th>Platelet count x 10^9/L</th><th>Starting dose</th></tr>
<tr><td>> 200</td><td>RUXOLITINIB 20mg PO single dose, or
RUXOLITINIB 10mg PO 12 hours apart</td></tr>
<tr><td>100 - 200</td><td>RUXOLITINIB 15mg PO single dose</td></tr>
<tr><td colspan="2">Administer only on haemodialysis days following dialysis.</td></tr>
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Hepatic impairment

Impairment	Modification
Any	Starting dose should be reduced by 50% to be administered twice a day. Subsequent doses should be adjusted based on monitoring of safety and efficacy. Monitor FBC at least every 1 - 2 weeks for 6 weeks then as clinically indicated thereafter once liver function and blood counts have stabilised. Titrate dose to reduce the risk of cytopenia.

MONITORING OF DISEASE RESPONSE

Treatment may be continued as long as the benefit-risk remains positive.

Symptoms should be monitored using the MPN-SAF. Spleen size can be monitored by physical examination with measurement of the spleen (no need for regular imaging). For patients who have demonstrated some degree of clinical improvement, it is recommended that ruxolitinib be discontinued if they sustain an increase in their spleen length of 40% compared with baseline size (roughly equivalent to a 25% increase in spleen volume) and no longer have tangible improvement in disease-related symptoms.

Treatment should be discontinued after 24 weeks if there has been no reduction in spleen size or improvement in symptoms since starting therapy. See BSH guidelines for more information.

INVESTIGATIONS

- See pre-assessment above
- Disease monitoring, per BSH guidelines.
- Monitoring for toxicity
- Baseline ECG + at least one ECG following ruxolitinib initiation, if new symptoms or abnormal at baseline
- 1-2 weeks in first month on treatment: FBC, U&E, LFT, Bone profile
- Monthly for next 2 months: FBC, U&E, LFT and Bone profile, glucose, amylase
- 3-4 monthly: FBC, U&E, LFT, Bone profile
- Consideration should also be given to Echo in selected patients – for exclusion of pericardial effusion and assessment of left ventricular function.

CONCURRENT MEDICATION

Allopurinol 300mg PO once daily for 7 days if required
Consider aspirin 75mg PO once daily in PV or MF patients with significant thrombocytosis or risk of thrombosis.
Recommend aciclovir 200mg PO three times a day if patient had previous episode of VZV reactivation.
Consider concomitant erythropoietin if pre-treatment Hb is < 100g/L and serum erythropoietin level <500.

EMETIC RISK

Low

DRUG INTERACTIONS

(Consult with pharmacist and refer to SPC for full details)

- Concomitant use of CYP3A4 inducers should be avoided (e.g. dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St John's Wort) as they may significantly reduce exposure to ruxolitinib, potentially increasing the risk of therapeutic failure.
- Caution should be taken when co-administering ruxolitinib with CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole, erythromycin, clarithromycin), as they could increase ruxolitinib exposure. Avoid the concomitant use of ruxolitinib with fluconazole doses greater than 200 mg daily.
- More frequent monitoring (e.g. twice a week) of haematology parameters and of clinical signs and symptoms of Ruxolitinib related adverse drug reactions is recommended while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes.
- Ruxolitinib may inhibit P-glycoprotein and breast cancer resistance protein (BCRP) in the intestine. This may result in increased systemic exposure of substrates of these transporters, such as dabigatran etexilate, ciclosporin, rosuvastatin and potentially digoxin. Therapeutic drug monitoring (TDM) or clinical monitoring of the affected substance is advised. It is possible that the potential inhibition of P-gp and BCRP in the intestine can be minimised if the time between administrations is kept apart as long as possible.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

(Consult with pharmacist and refer to SPC for full details)

Very commonly reported:
Ruxolitinib is immunosuppressive and patients are at risk of opportunistic infections.
Urinary tract infections, HZV reactivation, anaemia, thrombocytopenia, neutropenia, bleeding, bruising, weight gain, hypercholesterolaemia, dizziness, headache, raised transaminases, hypertriglyceridaemia

Risk of skin tumours, typically non-melanoma, with squamous cell carcinomas often presenting with an aggressive phenotype. New skin lesions occurring in patients on ruxolitinib should warrant prompt dermatology referral. Patients should be appropriately counselled and referral to dermatologist made for skin surveillance in high-risk cases (history of skin cancer). In patients with aggressive SCC with myelofibrosis receiving ruxolitinib treatment, consider fedratinib as an alternative JAK inhibitor.

Surgery: discuss with haematology in advance for perioperative management of ruxolitinib. Usual advice would be to continue with ruxolitinib treatment in order to avoid withdrawal reactions perioperatively.

TREATMENT RELATED MORTALITY

Extremely rare (<1%).

REFERENCES

1. NICE TA386. Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis. Published 23/3/2016. Accessed from https://www.nice.org.uk/guidance/ta386
2. Novartis. Ruxolitinib Summary of Product Characteristics. Updated 5/4/2022. Accessed on 9/11/2022 via https://www.medicines.org.uk/emc
3. Reilly et al (2014) Use of JAK inhibitors in the management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and Management of Myelofibrosis. BJH 167(3):418-420
4. Tefferi et al (2013) Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood 122(8):1395-1398
5. Barosi et al (2013) Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 121(23):4778-4781
6. Reilly et al (2012) Guideline for the diagnosis and management of myelofibrosis. BJH 158(4):453-471.
7. Scherber et al (2011) The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. Blood 118(2):401-408.
8. Mesa et al (2011) Evaluating the serial use of the myelofibrosis symptom assessment form for measuring symptomatic improvement. Cancer 117(21) 4869-4877

REVIEW

Name	Revision	Date	Version	Review date
Julia Wong Cheuk-kie Cheung	New protocol	Aug 2016	1.0	
Cheuk-kie Cheung, Haematology Pharmacist.	General formatting	May 2017	1.1	
Cheuk-kie Jackie Cheung, Haematology Pharmacist. Dr Bethan Psaila, Consultant Haematologist NSSG Myeloid Group	Annual protocol meeting	Oct 2019	1.2	Oct 2021
Yen Lim, Haematology Pharmacist, Prof Adam Mead & Prof Bethan Psaila, Consultant Haematologists NSSG Myeloid Group	Annual protocol meeting. Additional information added to adverse effects section.	Nov 2022	2.0	Nov 2024