RUXOLITINIB

INDICATION

Licensed / NICE TA386

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

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

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, urate, serum erythropoietin level
2. Ensure diagnosis is confirmed prior to commencing treatment by WHO or BSH criteria
3. Pregnancy Test - for all women of childbearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
4. Record performance status (WHO/ECOG).
5. Record height and weight.
6. ECG (most TKIs can affect the QT interval)
7. Consider echo in selected patients at risk of cardiac disease
8. Hepatitis B (including HB surface Ag and HB core antibodies) and C testing (reactivation of HBV has been reported with ruxolitinib)
9. 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.
10. 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.
11. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
12. Consider skin surveillance for patient with high risk of skin tumour.
13. Counsel patient regarding potential increase in infections including shingles, and consider prophylactic acyclovir, especially in those patients with a prior history of shingles. Live shingle vaccine is not recommended.

14. Treatment should be agreed in the relevant MDT.

15. Ensure pre-treatment counselling in line with NPSA recommendation and chemotherapy measures.

### DRUG REGIMEN / CYCLE FREQUENCY

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Platelet count $\times 10^9$/L</th>
<th>Starting dose</th>
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</thead>
<tbody>
<tr>
<td>MF</td>
<td>&gt; 200</td>
<td>RUXOLITINIB 20mg PO twice a day continuous</td>
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<tr>
<td></td>
<td>100 - 200</td>
<td>RUXOLITINIB 15mg PO twice a day continuous</td>
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<tr>
<td></td>
<td>50 - &lt;100</td>
<td>RUXOLITINIB max 5mg PO twice a day continuous, titrated cautiously</td>
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<tr>
<td>PV</td>
<td></td>
<td>RUXOLITINIB max 5mg PO twice a day continuous, titrated cautiously</td>
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</table>

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. Consider concurrent EPO treatment in patients with level < 500.

### DOSE MODIFICATIONS

Avoid abrupt discontinuation as this can cause cytokine storm. If urgent treatment interruption required, consider concurrent corticosteroids, and if possible, taper dose.

#### Dose Reduction - Haematological

<table>
<thead>
<tr>
<th>Count</th>
<th>Modification</th>
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</thead>
<tbody>
<tr>
<td>Plt &lt; 50 $\times 10^9$/L or</td>
<td>Stop ruxolitinib. Once recovered above these levels, resume ruxolitinib 5mg PO twice a day and gradually increased based on careful monitoring of FBC including white blood cell count differential.</td>
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<tr>
<td>ANC &lt; 0.5 $\times 10^9$/L or</td>
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<tr>
<td>Hb &lt; 80g/L in PV</td>
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<tr>
<td>Plt &lt; 100 $\times 10^9$/L or</td>
<td>Consider dose reduction to avoid dose interruptions for thrombocytopenia</td>
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<tr>
<td>Hb &lt; 100g/L in PV</td>
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#### 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

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.

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.

Renal impairment

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

<table>
<thead>
<tr>
<th>Impairment</th>
<th>Modification</th>
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<tbody>
<tr>
<td>Any</td>
<td>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. Monitored 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.</td>
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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
- Weekly in first month on treatment: ECG (at least one ECG following ruxolitinib initiation, if new symptoms or abnormal at baseline), FBC, U&E, LFT, Bone
- Monthly for next 2 months: ECG as clinically indicated, FBC, U&E, LFT and Bone, glucose, amylase.
- 3-4 monthly: Lipids, glucose, amylase, FBC, U&E, LFT, Bone
- 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.

Consider aciclovir 200mg PO three times a day if patient had previous episode of VZV reactivation.

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.

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 infection.
Urinary tract infections, HZV reactivation, anaemia, thrombocytopenia, neutropenia, bleeding, bruising, weight gain, hypercholesterolaemia, dizziness, headache, raised ALT, raised AST

Surgery: discuss with haematology in advance for perioperative management of ruxolitinib.
TREATMENT RELATED MORTALITY

Extremely rare (<1%).

REFERENCES


Review

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Julia Wong Cheuk-kie Cheung</td>
<td>New protocol</td>
<td>Aug 2016</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Cheuk-kie Cheung, Haematology Pharmacist.</td>
<td>General formatting</td>
<td>May 2017</td>
<td>1.1</td>
<td></td>
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<tr>
<td>Cheuk-kie Jackie Cheung, Haematology Pharmacist, Dr Bethan Psaila, Consultant Haematologist NSSG Myeloid Group</td>
<td>Annual protocol meeting</td>
<td>Oct 2019</td>
<td>1.2</td>
<td>Oct 2021</td>
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