

Chemotherapy Protocol

Myelofibrosis

Ruxolitinib

Regimen

- Myelofibrosis – Ruxolitinib

Indication

- 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.

Toxicity

Drug	Adverse Effect
Ruxolitinib	Myelosuppression, infection, bruising, dizziness, headache, constipation, diarrhoea, hypertension, weight gain, hypercholesterolaemia, progressive multifocal leukoencephalopathy

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, LFTs and U&Es prior to starting treatment and then every two to four weeks until the dose is stabilised. Once stabilised consider conducting these investigations every two to three months.
- Check for active infections prior to starting treatment. Consider screening for latent tuberculosis or herpes zoster. Patients must be screened for HIV and HepB infection including HepBsAg and HepBcAb to detect latent infection at risk of reactivation with ruxolitinib.
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Dose Modifications

Management of adverse events may require dose reduction, temporary interruption, or discontinuation of treatment. Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on

the clinical circumstances. Many patients are unsuitable for the recommended starting doses due to anaemia and other co-morbidities. Always discuss the starting dose with the relevant consultant.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependant on clinical circumstances and treatment intent.

Note that the haemoglobin nearly always falls on initial therapy with ruxolitinib before plateau at around 6 weeks. Consider starting erythropoietin stimulation if the patient is symptomatic of anaemia or where the haemoglobin is less than 8g/dL (80g/L). This may partially or wholly offset the need for transfusion. If patient becomes transfusion dependent on treatment, review of suitability of ruxolitinib continuation is needed. If unavoidable, consider iron chelation therapy according to guidelines.

Neutrophils ($\times 10^9/L$)	Ruxolitinib dose
Less than 0.5	Discontinue

Platelets ($\times 10^9/L$)	Ruxolitinib dose
Less than 50	Discontinue
50 - 100	Consider dose reduction, ideally avoid treatment interruptions for thrombocytopenia

Hepatic impairment

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50%, to be administered twice a day. Subsequent doses should be adjusted based on careful monitoring of safety and efficacy.

Patients diagnosed with hepatic impairment while receiving ruxolitinib should have complete blood counts, including a white blood cell count differential, monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with ruxolitinib and as clinically indicated thereafter once their liver function and blood counts have been stabilised.

Renal Impairment

Drug	Renal impairment	Guidance
Ruxolitinib	Mild / moderate	No dose adjustment required
	Severe (CrCl less than 30ml/min)	Recommended starting dose (based on platelet count) should be reduced by 50%.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC toxicities refer to manufacturer information.

Infections

Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal and viral infections. Ruxolitinib therapy should not be started until active serious infections have resolved. Physicians should carefully observe patients receiving ruxolitinib for signs and symptoms of infections and initiate appropriate treatment promptly. There is a substantially increased risk of reactivation of Herpes Zoster (HZV). All patients should have HZV status checked before starting including HZV titres. All patients with history of shingles or seropositive should be commenced on aciclovir, the minimum dose is 400mg twice a day. Educate patients about early signs and symptoms of herpes zoster, advising that the dose of acyclovir should be increased to 800mg three times a day and consultant notified in the event of reactivation. There is also need for vigilance for tuberculosis reactivation in view of case reports.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered. If PML is suspected, further dosing must be suspended until PML has been excluded.

Skin

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma, have been reported in patients treated with ruxolitinib. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Lipid Abnormalities

Treatment with ruxolitinib has been associated with increases in lipid parameters including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Lipid monitoring and treatment of dyslipidaemia according to clinical guidelines is recommended.

[Regimen](#)

Idiopathic Myelofibrosis,

28 day cycle until disease progression, intolerance or patient chooses to stop treatment (12 cycles will be set in ARIA).

Drug	Platelets (x10 ⁹ /L)	Starting Dose	Maximum Dose	Days	Administration
Ruxolitinib	50 – 99	5mg twice a day	25mg twice a day	1-28 inclusive	Oral
	100 - 200	15mg twice a day			
	more than 200	20mg twice a day			

Post Polycythaemia Vera Myelofibrosis

28 day cycle until disease progression, intolerance or patient chooses to stop treatment (12 cycles will be set in ARIA).

Drug	Dose	Days	Administration
Ruxolitinib	10mg twice a day	1-28 inclusive	Oral

[Dose Information](#)

- If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5mg twice a day, up to the maximum dose of 25 mg twice a day.
- The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at two week intervals.
- The maximum dose of ruxolitinib is 25 mg twice daily.
- Ruxolitinib should be taken every day at the same time, either with or without food.
- Following interruption or discontinuation of ruxolitinib, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of ruxolitinib contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of ruxolitinib may be considered, although the utility of the tapering is unproven. Prednisolone given in modest dosage may help withdrawal symptoms during and after cessation of drug. Always discuss with patient's consultant.
- If a dose is missed the patient should not take an additional dose but rather the next dose that is due.

[Additional Information](#)

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to ruxolitinib.
- Ruxolitinib is associated with drug interactions. 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%, to be administered twice a day. More frequent monitoring (eg twice a week) of haematological parameters and of clinic signs and symptoms of ruxolitinib related adverse drug reactions is recommended. It is inadvisable to prescribe ruxolitinib while on strong CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes and alternatives to the interacting drugs should be considered

[Coding](#)

- Procurement – X71.3
- Delivery – X72.2

References

1. The National Institute for Health and Clinical Excellence (2016) Technology Appraisal 386. Ruxolitinib for treating disease related splenomegaly or symptoms in adults with myelofibrosis. London:DOH.
2. Reilly et al. 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. Br J Haem 2014; 167(3): 418-420.
3. Harrison C et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med (2012); 366 (9): 787-98.
4. Verstovsek S et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med (2012); 366 (9): 799-807.

REGIMEN SUMMARY

Ruxolitinib

Day One

1. Warning – Check Dose

Administration Instructions

The dose of ruxolitinib varies depending on the indication and the neutrophil and platelet count. The dose is set at the lowest possible starting dose of 5mg twice a day. This may need to be altered on cycle one and in subsequent cycles depending on the severity of the condition, co-morbidities and tolerance. Please refer to the protocol for further information

Oral chemotherapy

2. Ruxolitinib 5mg twice a day continuous oral

Administration Instructions

The dose of ruxolitinib varies depending on the indication and the neutrophil and platelet count. The dose is set at the lowest possible starting dose of 5mg twice a day. This may need to be altered on cycle one and in subsequent cycles depending on the severity of the condition, co-morbidities and tolerance. Please refer to the protocol for further information.

Oral chemotherapy.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	January 2019	None	Stuart Martin Pharmacist	Dr Andrew Duncombe Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
 NHS Isle of Wight
 Portsmouth Hospitals NHS Trust
 Salisbury NHS Foundation Trust
 University Hospital Southampton NHS Foundation Trust
 Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.