Lenalidomide-rituximab (R-squared regimen)

(as per Leonard JP et al, CALGB 5041 trial, J Clin Oncol 2015)

INDICATION: Relapsed or refractory lymphoma

This protocol must be used in conjunction with the Celgene Pregnancy Prevention Plan

Prior to a course of treatment

- Note that lenalidomide is contraindicated if there is a history of hypersensitivity or desquamating rash with thalidomide.
- Note whether lenalidomide causes infertility is unknown – offer semen cryopreservation to males.
- Assess for neuropathy – do not use lenalidomide if there is grade 3 neuropathy (sensory loss or paraesthesiae interfering with activities of daily living or causing disability) or higher
- Check FBC – cytopenias prior to treatment should be assumed to be due to marrow infiltration. Unless there is good evidence suggesting another cause at least the first cycle should be given at full doses.
- Note lenalidomide is substantially excreted renally. Check U&Es, creat, calculated GFR, LFTs, thyroid function tests, hepatitis B and C serology, immunoglobulins – *see dose modifications*
- Written consent for course
- Assess risk of venous thromboembolism (see below)

Prior to each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function.
- Review necessary measures in the lenalidomide risk management programme.
- Assess for neuropathy – *see dose modifications*
- Check FBC: neutrophils must be > 1.0, platelets > 50 unless due to disease
- Check U&Es, creat, calculated GFR, LFTs – *see dose modifications*
- Each prescription must be accompanied by a completed prescription authorisation form.

Cycle 1	
Lenalidomide *	15mg od PO for 21 days
Rituximab	375mg/m^2 on days 8, 15, 22, 29 cycle 1 only (see template for admin of rituximab)
Cycle 2	
Lenalidomide	20mg od PO for 21 days in the absence of treatment delay in cycle 1 and resolution of previous lenalidomide toxicity
Cycle 3 onwards	
Lenalidomide	25mg od PO for 21 days in the absence of treatment delay in cycle 1 and resolution of previous lenalidomide toxicity

No more than 28 days to be dispensed * tablets are 5mg, 10mg, 15mg and 25mg

Repeat cycle every 28 days

Continue treatment for up to 12 cycles

Prophylaxis for emesis	Not required
Other medications	Allopurinol according to eGFR
	DVT prophylaxis (see below)

Dose modification for neutropenia (unless due to marrow infiltration)

• Neutrophils <1.0 on day 1	Delay treatment and check FBC weekly, restart when recovered to >1.0 at dose 5mg lower than for last cycle If delayed for >4 weeks further treatment may not be appropriate – *discuss with consultant* Use of GCSF to avoid treatment delay may be appropriate

Dose modification for thrombocytopenia (unless due to marrow infiltration)

• Platelets < 50 on day 1	Delay treatment and check FBC weekly, restart when recovered to >50 at dose 5mg lower than last cycle If delayed for >4 weeks further treatment may not be appropriate – *discuss with consultant*

Dose modification for neuropathy

• Grade 2 (sensory loss or paraesthesiae interfering with function but not activities of daily living)	Stop lenalidomide and review weekly When toxicity resolves to grade 1 or less restart at next lower dose level
• Grade 3 or 4 toxicity (sensory loss or paraesthesiae interfering with activities of daily living or causing disability)	Stop lenalidomide permanently

Dose modification impaired renal function

Creatinine clearance	Lenalidomide dose
> 50ml/min	25mg daily
30 – 49ml.min	10mg daily *
<30ml/min, not requiring dialysis	15mg every other day **
<30ml/min, requiring dialysis	5mg daily. On dialysis days give after dialysis

* may be escalated to 15mg daily after 2 cycles if the patients is not responding to treatment and is tolerating treatment.

** may be escalated to 10mg daily if the patient is tolerating treatment.

Dose modification for liver dysfunction

- If ≥ grade 3 hepatotoxicity stop lenalidomide until resolves to < grade 2
- Then restart at one dose level lower

Thromboprophylaxis

All patients must receive thromboprophylaxis for at least the first 3 months. It is suggested that low risk patients receive aspirin 75mg daily and high risk patients receive prophylactic LMWH.

Patients with any of the following are defined as high risk: diabetes or other comorbidities, immobility, cardiovascular disease, previous thromboembolic events, use of erythropoietic agents or hormone replacement therapy, renal failure

Lenalidomide Toxicities (and see template for rituximab toxicities)	
Febrile neutropenia and thrombocytopenia	Nausea and vomiting
Venous and arterial thromboembolism	Fatigue
Rash – desquamating or erythema multiforme; often resolves with continued treatment	Arthralgia, myalgia, muscle weakness
Constipation	Peripheral neuropathy
Dizziness/sinus bradycardia/atrial fibrillation/cardiac arrythmias	Hypothyroidism
Teratogenicity	Somnolence
Digoxin toxicity	Abnormal liver function tests

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