Lenalidomide & Rituximab (R^2)

Indication
Previously treated follicular lymphoma (grades 1 to 3A)
(NICE TA627)

ICD-10 codes
Codes with prefix C82

Regimen details
Cycle 1

Day	Drug	Dose	Route
1, 8, 15, 22	Rituximab	375mg/m^2	IV infusion
1-21	Lenalidomide	20mg OD	PO

Cycles 2-5

Day	Drug	Dose	Route
1	Rituximab*	375mg/m^2 Or 1400mg	IV infusion SC injection*
1-21	Lenalidomide	20mg OD	PO

*Note – subcutaneous rituximab can be used for cycles 2 – 5 under COVID-19 interim commissioning criteria

Cycles 6-12

Day	Drug	Dose	Route
1-21	Lenalidomide	20mg OD	PO

Cycle frequency
Every 28 days.

Number of cycles
12 cycles in total

Administration
Intravenous Rituximab
Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased by 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Subcutaneous Rituximab
Patients must have received a full dose of intravenous rituximab during cycle 1 without hypersensitivity reactions before being switched to the subcutaneous formulation.
Rituximab subcutaneous should be injected by slow subcutaneous injection over approximately 5 minutes into the abdominal wall (never into areas where the skin is red, bruised, tender or hard, or where there are moles or scars). The needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging. If an injection is interrupted it can be resumed at the same site, or another location may be used, as appropriate. Observe for at least 15 minutes after subcutaneous injection.

Lenalidomide
Lenalidomide is available as 2.5mg, 5mg, 7.5mg, 10mg, 15mg, 20mg and 25mg capsules.

Lenalidomide should be swallowed whole with water, either with or without food, at the same time each day. The capsules should not be broken, opened or chewed. If a dose is missed it may be taken within 12 hours, however if more than 12 hours has elapsed since the dose was due, the patient should miss the dose and resume with the usual dose the next day.
Lenalidomide must be prescribed and dispensed in accordance with the pregnancy prevention programme.

Pre-medication

Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab
- Chlorphenamine 10mg IV bolus (or 4mg PO) 15 minutes prior to rituximab
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes (or Prednisolone 25mg PO) prior to rituximab

Emetogenicity

This regimen has low emetogenic potential. Routine anti-emetic is not required.

Additional supportive medication

Allopurinol 300mg OD (or 100mg OD if creatinine clearance <20ml/min) for the first cycle.
H_2 antagonist or proton-pump inhibitor as per local policy.
Antiviral and antifungal prophylaxis as per local policy.

There is an increased risk of thrombosis with lenalidomide, thromboprophylaxis is required unless contraindicated. Address modifiable risk factors. Assess an individual patient's underlying risk factors for VTE and prescribe VTE prophylaxis as per local policy.

Extravasation

Rituximab is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Pregnancy test, in women of childbearing age	3 days

Additional investigations:
Hepatitis B core antibody and surface antigen, hepatitis C antibody, HIV viral screen.
Baseline and ongoing monitoring of thyroid function

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	72 hours
U+Es (including creatinine)	72 hours
LFTs	72 hours
Pregnancy test, in women of childbearing age	3 days

Other recommended investigations:
Ongoing monitoring if thyroid function

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Creatinine clearance	≥60ml/min
ALT	≥ULN

Dose modifications

No dose modifications are required for Rituximab

- **Haematological toxicity**

Treatment should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L (unless secondary to lymphoma infiltration of the bone marrow)

Lenalidomide dose reduction steps:

Starting dose	20mg OD
Dose level -1	15mg OD
Does level -2	10mg OD
Dose level -3	5mg OD

Thrombocytopenia:

Platelets (x 10^9/L)	Action
<50 (1st occurrence)	Interrupt lenalidomide treatment and perform FBC at least every 7 days Once recovered to ≥ 50 x 10^9/L restart at dose level - 1
<50 (2nd occurrence)	Interrupt lenalidomide treatment and perform FBC at least every 7 days Once recovered to ≥ 50 x 10^9/L restart at dose level - 2
<50 (3rd occurrence)	Interrupt lenalidomide treatment and perform FBC at least every 7 days Once recovered to ≥ 50 x 10^9/L restart at dose level – 3. Dose should not be reduced below 5mg OD

Neutropenia:

Neutrophils (x 10^9/L)	Action
Falls to <1.0 for at least 7 days ***or*** Falls to <1.0 with associated fever (temp ≥38.0°C) ***or*** Falls to <0.5 (1st occurrence)	Interrupt lenalidomide treatment and perform FBC at least every 7 days Once recovered to ≥ 1 x 10^9/L restart at dose level - 1
Falls to <1.0 for at least 7 days ***or*** falls to <1.0 with associated fever (temp ≥38.0°C) ***or*** falls to <0.5 (2nd occurrence)	Interrupt lenalidomide treatment and perform FBC at least every 7 days Once recovered to ≥ 1 x 10^9/L restart at dose level - 2
Falls to <1.0 for at least 7 days ***or*** falls to <1.0 with associated fever (temp ≥38.0°C) ***or*** falls to <0.5 (3rd occurrence)	Interrupt lenalidomide treatment and perform FBC at least every 7 days Once recovered to ≥ 1 x 10^9/L restart at dose level – 3. Dose should not be reduced below 5mg OD

At the clinician's discretion, if neutropenia is the only toxicity at any dose level, consider granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

- **Renal impairment**

Lenalidomide is excreted via the kidneys. Close monitoring of renal function is essential.

Creatinine clearance (ml/min)	Lenalidomide dose
30-59	10mg OD*
< 30, no dialysis	15mg every other day**
< 30, requiring dialysis	5mg OD***

*Can increase to 15mg OD if no response and patient is tolerating
**Can increase to 10mg OD if no response and patient is tolerating
*** On dialysis day, administer dose after dialysis

- **Hepatic impairment**

Lenalidomide has not been studied in hepatic impairment. There are no dose recommendations in hepatic impairment. If patients suffer unexplained deterioration of liver function, consider lenalidomide induced liver injury. In this case liver function should improve on discontinuation of lenalidomide.

- **Other toxicities**

For any grade 3 or 4 non-haematological toxicity, clinical judgement should determine whether to discontinue treatment or to continue treatment at a reduced dose (following recovery to ≤ grade 2 toxicity).
Refer to lenalidomide dose reduction table above for dosing guidance. Consultant decision.

Thrombosis
If a patient experiences a thromboembolic event, treatment with lenalidomide must be discontinued and anticoagulation therapy commenced. Once the patient has been stabilised on anticoagulation treatment and any complications of the thromboembolic event have been managed, lenalidomide may be restarted at the original dose, after a reassessment of risks and benefits of treatment.

Adverse effects - for full details consult product literature/ reference texts

Serious side effects

Myelosuppression
Venous thromboembolism (VTE)
Hypotension and bronchospasm (infusion related and usually transient)
Tumour lysis syndrome
Teratogenicity **(lenalidomide is contraindicated unless all of the conditions of the Pregnancy Prevention Programme are met)**
Cytokine release syndrome
Tumour flare
Secondary primary malignancy
Hepatic failure
Myocardial infarction
Pulmonary hypertension
Allergic reactions including severe cutaneous reactions
Viral reactivation in patients previously infected with the varicella zoster or hepatitis B viruses (HBV).
Progressive multifocal leukoencephalopathy

Frequently occurring side effects

Infusion reactions
Myelosuppression
Diarrhoea
Flu-like symptoms
Pruritis, rash
Headache
Local site reaction (SC rituximab only)

Other side effects

Peripheral neuropathy
Drowsiness
Dizziness and orthostatic hypotension
Thyroid dysfunction

Significant drug interactions – for full details consult product literature/ reference texts

Hormone treatments (including combined contraceptive pill, HRT) : increased risk of thrombosis – use with caution

Erythropoietic agents: increased risk of thrombosis – use with caution

Statins: increased risk of rhabdomyolysis when statins are administered with lenalidomide

Digoxin: may increase plasma digoxin levels – monitor levels

Additional comments

The conditions of the Lenalidomide Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the Pregnancy Prevention Programme. All women of child-bearing potential must use one effective method of pregnancy prevention at least 4 weeks before therapy, during therapy and for at least 4 weeks after stopping therapy. Men are required to use a barrier method of contraception during treatment.

References

- John P. Leonard, MD et al. AUGMENT: A Phase III study of Lenalidomide plus Rituximab versus placebo plus Rituximab in relapsed or refractory indolent lymphoma. J Clin Oncol. 2019; 37:1188-1199.
- NICE. Lenalidomide with Rituximab for previously treated follicular lymphoma. 7 April 2020. Available at: https://www.nice.org.uk/guidance/ta627/resources/lenalidomide-with-rituximab-for-previously-treated-follicular-lymphoma-pdf-82609022295493 (last accessed 29/01/2021)
- Summary of Product Characteristics Rituximab (Roche) accessed 29/01/2021 via www.medicines.org.uk
- Summary of Product Characteristics: Lenalidomide (Celgene) accessed 29/01/2021 via www.medicines.org.uk

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