Thames Valley
Strategic Clinical Network

LENALIDOMIDE for MDS

INDICATION

Licensed / Funded (NICE TA 322 – BLUETEQ required)

Treatment of patients with transfusion-dependent anaemia (< 8 consecutive weeks without RBC transfusions within 16 weeks prior to commencing treatment) due to IPSS-R very low/low/intermediate risk myelodysplastic syndromes (MDS) associated with an isolated deletion 5q cytogenetic abnormality (or in the presence of 1 additional abnormality) when other therapeutic options are insufficient or inadequate.

TREATMENT INTENT

To improve symptoms by increasing the haemoglobin

PRE-ASSESSMENT

1. Blood tests - FBC, U&Es, LDH, urate, creatinine, LFTs, TFTs, Hepatitis B core antibody and Hepatitis B sAg, Hepatitis C antibody, group and save
2. Ensure histology is confirmed prior to administration of chemotherapy and document in notes
3. Record stage of disease
4. Myeloid gene panel including p53 status. If p53 mutation is detected, discuss risk/benefit of treatment at MDT.
5. ECG +/- Echo – *if clinically indicated*
6. Record performance status (WHO/ECOG)
7. Record height and weight (also needed to calculate CrCl)
8. 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 and obtain written consent
9. Ensure fertility advice given (see fertility guidelines). **For women of childbearing potential:** Urine pregnancy test is required every 4 weeks in women aged 12 – 55 years of age unless they have been sterilised or undergone a hysterectomy. Women of childbearing potential should be advised to use effective contraception during and up to 4 weeks after end of treatment. **For men:** Advise to use effective contraception during and up to 7 days after end of treatment.
10. Ensure pre-treatment counselling in line with national recommendations for oral systemic anti-cancer therapy (SACT).
11. Treatment should be agreed in the relevant MDT.
12. Complete **Treatment Initiation Form** as per Pregnancy Prevention Programme before **Cycle 1** and **Prescription Authorisation Form** for each cycle.

DRUG REGIMEN / CYCLE FREQUENCY

LENALIDOMIDE 10mg PO once daily on days 1-21 of 28 day cycle

Only start if ANC ≥ 0.5 x 10^9/L and Plt ≥ 25 x 10^9/L

RESTAGING

Responses can be monitored by improvement in haemoglobin. Most patients will have started to respond within 3 months. A repeat bone marrow to confirm response is not necessary but is advisable where a responder is losing their response.

Discontinue Lenalidomide in patients without at least a minor erythroid response within 4 months of therapy initiation, demonstrated by at least a 50% reduction in transfusion requirements or, if not transfused, a 10g/L rise in Hb.

DOSE MODIFICATIONS

Dose Levels (when GFR ≥ 50mL/min)

Starting dose	10mg PO once daily on days **1-21** of 28 day cycle
Please note that for dose level -1 and below, lenalidomide duration is 28 days each cycle.	
Dose level -1	5mg PO once daily on days **1-28 of** 28 day cycle (if starting dose is 10mg)
Dose level -2	2.5mg daily on day **1-28** of 28 day cycle
Dose level -3	2.5mg PO once daily on alt days **1-28** of 28 day cycle

Thrombocytopenia

Platelet count	**Modification**
< 25 x 10^9/L	Interrupt Lenalidomide treatment
Return to ≥ 25 x 10^9/L to < 50 x 10^9/L on at least 2 occasions for ≥ 7 days or recover to ≥ 50 x 10^9/L at any time	Resume Lenalidomide at next lower dose level (Dose level -1, -2 or -3)

Neutropenia

ANC	**Modification**
< 0.5 x 10^9/L	Interrupt Lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume Lenalidomide at next lower dose level (Dose level -1, -2 or -3)

Other Non-Haematologic Toxicities

Toxicity	Modification
Grade 2 / 3 skin rash	Interrupt or discontinue Lenalidomide
Angioedema, Grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is suspected	Discontinue Lenalidomide Do NOT resume
Any other Grade 3 / 4 toxicity	Stop Lenalidomide. Restart at next lower dose level when toxicity has resolved to ≤ Grade 2 depending on clinician's discretion.

Renal Impairment

GFR	Dose adjustment	
30 to 50mL/min	Starting dose	5mg PO once daily on days 1-21 of 28 day cycle
	Dose level -1*	2.5mg PO once daily1-28 of 28 day cycle
	Dose level -2*	2.5mg PO once daily on alt days 1-28 of 28 day cycle
< 30mL/min not requiring dialysis	Starting dose	2.5mg PO once daily 1-21 of 28 day cycle
	Dose level -1*	2.5mg PO once daily on alt days 1-28 of 28 day cycle
	Dose level -2*	2.5mg PO twice a week days 1-28 of 28 day cycle
End Stage Renal Disease < 30mL/min requiring dialysis On dialysis days, administer dose following dialysis.	Starting dose	2.5mg PO once daily 1-21 of 28 day cycle
	Dose level -1*	2.5mg PO once daily on alt days 1-28 of 28 day cycle
	Dose level -2*	2.5mg PO twice a week days 1-28 of 28 day cycle

* Recommended dose reduction steps during treatment and restart of treatment to manage Grade 3 / 4 neutropenia or thrombocytopenia, or other Grade 3 / 4 toxicity related to Lenalidomide

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INVESTIGATIONS

- FBC (including haematocrit)at baseline, every week for the first 8 weeks of lenalidomide, then monthly thereafter
- U&E, LFT & TFTs at baseline and as clinically indicated.
- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle
- Annual myeloid panel assessment for TP53 mutations (in PB or BM)

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Pregnant women.

Women of childbearing potential unless all of the conditions of the Pregnancy Prevention Programme are met.

SPECIAL WARNINGS / PRECAUTIONS / MONITORING

Pregnancy Warning - Teratogenicity

The Pregnancy Prevention Programme (PPP) conditions must be fulfilled for all patients unless there is reliable evidence the patient does not have childbearing potential.

Healthcare Professional's Information Pack (HCPIP) must be accessed. The pack contains the information and materials needed for prescribing and dispensing Lenalidomide, including information about the Pregnancy Prevention Programme (PPP).

- It is a requirement of the PPP that all healthcare professionals ensure that they have read and understood this pack before prescribing or dispensing Lenalidomide for ANY patient.
- Pharmacies must register with using the Pharmacy Registration Form, to be able to order and dispense Lenalidomide.
- Every prescription for Lenalidomide must be accompanied by a Prescription Authorisation Form (PAF). This form must be signed by prescriber and pharmacist

Myocardial infarction

Patients with known risk factors – including prior thrombosis – should be closely monitored, and all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia) minimised.

Venous and arterial thromboembolic events

MDS patients on Lenalidomide monotherapy are at risk of venous thromboembolism (predominantly deep vein thrombosis and pulmonary embolism), but to a lesser extent than in patients with MM.

Monitor patients with known risk factors for thromboembolism (including prior thrombosis) and minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia). Concomitant erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk - use erythropoietic agents or other agents that may increase risk of thrombosis eg. hormone replacement therapy (HRT), with caution. **If Hb > 120g/L, discontinue erythropoietic agents.**

Neutropenia and thrombocytopenia

Perform FBC (incl. haematocrit) at baseline, every week for the first 8 weeks of Lenalidomide treatment, then monthly thereafter. Monitor patients with neutropenia for signs of infection. Patients should be advised to monitor themselves for bleeding or bruising, especially if prophylactic VTE treatments are concomitantly administered. Follow dose modifications for haematological toxicity as per section above.

Thyroid disorders

Hypo- and hyperthyroidism reported. Baseline and ongoing monitoring of thyroid function recommended.

Peripheral neuropathy

Patients should be advised to report prickling, numbness and paraesthesia. Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant neurotoxicity is uncommon.

Allergic reactions

Allergic reaction/hypersensitivity reactions reported. Monitor patients with previous allergy to Thalidomide, as possible cross-reaction between Lenalidomide and Thalidomide was reported.

Severe skin reactions

Discontinue Lenalidomide for exfoliative or bullous rash, or if SJS or TEN is suspected, and do not resume. Interrupt or discontinue Lenalidomide for other forms of skin reaction depending on severity. Patients with a history of severe rash associated with Thalidomide should not receive Lenalidomide.

Rash

Antihistamines and topical corticosteroids can often be used to treat limited, localized, treatment-related rash, but lenalidomide interruption or discontinuation should be considered for grade 2/3 rash. Re-challenge with lenalidomide is reasonable in patients who do not have a severe rash and will often allow continued treatment. Lenalidomide must be discontinued for angioedema, grade 4 rash, and exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected, and should not be resumed after discontinuation for these reactions

Diarrhoea

This can be managed with antidiarrheal medication (loperamide), supportive care and adequate hydration. Bile salt malabsorption occurs in a small proportion of patients on lenalidomide, consider dietary adjustments with low fat meal intake and prescribing bile acid sequestrants (colestyramine).

Drowsiness, somnolence and sedation

Take the dose at night time. Lenalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking lenalidomide.

Dizziness and orthostatic hypotension

Patients should be advised that lenalidomide may cause orthostatic hypotension and that, if affected, they should sit upright for a few minutes prior to standing up from a recumbent position.

Secondary malignancies

There is an MHRA alert on an increased risk of secondary malignancies in three large trials of lenalidomide treatment. The MHRA recommend vigilance in reporting such events promptly. Quoted incidence is 3 to 4% per annum.

Lactose intolerance

Avoid Lenalidomide in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

Progression to acute myeloid leukaemia in low- and intermediate-1-risk MDS

Karyotype

The benefit/risk ratio of Lenalidomide when MDS is associated with del (5q) and complex cytogenetics is unknown. Lenalidomide treatment may be associated with risk of acquisition of TP53 mutations.

TP53 status

A TP53 mutation is present in 20 to 25% of lower-risk MDS del 5q patients and is associated with a higher risk of progression to AML. Selected patients should be monitored for emergence or expansion of TP53 mutant clones (e.g. via PB sampling) every 12 months. Those with TP53 mutations but are still responsive to Lenalidomide should be considered for allo-SCT if appropriate, and/ or be closely monitored for evolving disease progression to high risk MDS/ AML.

Hepatic disorders

The mechanisms of severe drug-induced hepatotoxicity remain unknown although pre-existing viral liver disease, elevated baseline liver enzymes, and antibiotic treatment may be risk factors. Monitor liver function, particularly with a history of or concurrent viral liver infection or when Lenalidomide is combined with medicinal products known to cause liver dysfunction.

CONCURRENT MEDICATION

Consider prophylactic antithrombotic medicines for patient with risk factor(s) – See VTE section above.
Prescribe loperamide if needed for diarrhoea.
Consider colestyramine if suspicion of bile salt malabsorption with lenalidomide

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EMETIC RISK

Minimal

INTERACTIONS

Erythropoietic agents

Or other agents that may increase the risk of thrombosis e.g. HRT – use with caution

Digoxin

Monitor Digoxin concentration during Lenalidomide treatment.

Statins

Increased risk of rhabdomyolysis when statins are administered with Lenalidomide, which may be simply additive. Close clinical and laboratory monitoring is needed especially during the first weeks of treatment.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Very commonly reported:
Bacterial, viral and fungal infections (including opportunistic infections), pneumonia, myelosuppression, hypothyroidism, decreased appetite, dizziness, headache, epistaxis, diarrhoea, abdominal pain (including upper), nausea, vomiting, constipation, rashes, dry skin, pruritus, muscle spasms, musculoskeletal pain (including back pain and pain in extremity), arthralgia, myalgia, fatigue, peripheral oedema, Influenza like illness syndrome (including pyrexia, cough, pharyngitis, myalgia, musculoskeletal pain, headache)

For all other adverse effects, refer to SPC.

TREATMENT RELATED MORTALITY

Risk of death is <1%

REFERENCES

1. NICE TA322. Lenalidomide for treating myelodysplastic syndromes associated with an isolated deletion 5q cytogenetic abnormality. Last updated: 26/6/2019. Accessed 5/11/2021 via https://www.nice.org.uk/guidance/ta322.
2. Bristol-Myers Squibb. Lenalidomide Summary of Product Characteristics. Updated 26/9/2022. Accessed on 5/10/2022 via http://www.medicines.org.uk/emc

REVIEW

Name	Revision	Date	Version	Review date
Julia Wong	New protocol	March 2017	1.0	March 2019
Dr Lynn Quek	Annual Protocol meeting	October 2019	1.1	October 2021
Yen Lim, Haematology Pharmacist Dr Alex Sternberg & Dr Oni Chowdhury, Consultant Haematologists NSSG Myeloid Group	Updated dosing, special precautions and investigations. Annual protocol meeting.	November 2022	2.0	November 2024