Lenalidomide and dexamethasone (Rd) – first line

Indication

First line treatment of transplant ineligible patients with multiple myeloma in whom thalidomide is contraindicated (including for pre-existing conditions that it may aggravate) or who cannot tolerate thalidomide having commenced thalidomide-containing treatment and toxicity has forced its discontinuation at a time when the patient had neither demonstrated refractory disease nor relapsed after responding to thalidomide-containing systemic therapy.

(NICE TA587)

ICD-10 codes

Codes with a pre-fix C90

Regimen details

Day	Drug	Dose	Route
1-21	Lenalidomide	25mg OD	PO
1, 8, 15 and 22	Dexamethasone	40mg OM	PO

Continue lenalidomide and dexamethasone therapy until disease progression or intolerance.

Cycle frequency

28 days

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

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.

Dexamethasone is available as 500microgram, 2mg, 4mg and 40mg tablets. The dose should be taken in the morning, with or after food.

Pre-medication

Nil

Emetogenicity

This regimen has low emetogenic potential. Routine antiemetic is not required.

Additional supportive medication

Thromboprophylaxis is required unless contraindicated. Address modifiable risk factors. Assess an individual patient's underlying risk factors for VTE (e.g. Myeloma Academy risk scoring system). For patients with additional thromboembolic risk factors (such as immobility, dexamethasone >20mg/day) prophylactic LMWH (or equivalent) is recommended for at least the first 4 cycles. It may then be appropriate to switch to aspirin.
H_2 antagonist or proton pump inhibitor.
Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for the first cycle only.
Bisphosphonates as per local policy.
Antifungal, antiviral and antibiotic/PCP prophylaxis as per local policy.

Extravasation

N/A

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
Hepatitis B virus status (HBsAg & HBc antibody)	Pre treatment

Hepatitis B virus status should be established before initiating treatment with lenalidomide.

Other recommended investigations :
Serum glucose and calcium
Serum protein electrophoresis (or alternative measure of response if M protein not measurable). Consider coagulation screen
Baseline thyroid function.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	Weekly for first 8 weeks, then within 72 hours of subsequent cycles
U+Es (including creatinine)	72 hours
LFTs	72 hours
Pregnancy test, in women of childbearing age	Within 3 days of next cycle

Other recommended investigations:
Glucose as clinically indicated whilst taking dexamethasone,
Blood pressure as clinically indicated whilst taking dexamethasone,
Serum calcium,
Ongoing monitoring of thyroid function,
Serum electrophoresis (or alternative biological measure of response if M protein not measurable).

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	≥ 50mL/min
ALT	≥ ULN

Dose modifications

Dose adjustments for lenalidomide and dexamethasone are made as per the table below:

	Lenalidomide*	Dexamethasone*
Starting dose	25mg	40mg
Dose level - 1	20mg	20mg
Dose level - 2	15mg	12mg
Dose level - 3	10mg	8mg
Dose level - 4	5mg	4mg
Dose level - 5	2.5mg	-

*Dose reduction for each agent can be managed independently

Alternative dose adjustments may include keeping at the same dose and reducing to an alternate day regimen. Evaluate dexamethasone dose, taking into account the condition and disease status of the patient.

- **Haematological toxicity**

Treatment should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L (if bone marrow infiltration may initiate treatment if platelets ≥ 30 x 10^9/L)).

Thrombocytopenia

Platelets (x 10^9/L)	**Action**
< 25	Stop lenalidomide dosing for remainder of cycle
On recovery ≥ 50	Continue with next cycle with one dose level reduction

Neutropenia

Neutrophils (x 10^9/L)	**Action**
< 0.5 (first occurrence)	Interrupt lenalidomide treatment
On recovery > 1.0 (if neutropenia is the only observed toxicity)	Resume lenalidomide at same dose
On recovery ≥ 0.5 or when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at with one dose level reduction
For each subsequent drop below < 0.5	Interrupt lenalidomide treatment On recovery to ≥ 0.5 resume lenalidomide with one dose level reduction

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.

For haematological toxicity the dose of lenalidomide may be re-introduced to the next higher dose level (up to the starting dose) upon improvement in bone marrow function (no haematological toxicity for at least 2 consecutive cycles: neutrophils ≥1.5 x 10^9/L with a platelet count ≥ 100 x 10^9/L at the beginning of a new cycle).

- **Renal impairment**

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

CrCl (mL/min)	**Lenalidomide dose**
≥ 50	Full dose
30-49	10mg OD (may escalate to 15mg OD after 2 cycles if patient not responding but is tolerating treatment)
< 30 (not requiring dialysis)	7.5mg daily or 15mg alternate days.
< 30 (requiring dialysis)	5mg OD (taken after dialysis on dialysis days)

- **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 (except alopecia), clinical judgement should determine whether to discontinue treatment or to continue treatment at a reduced dose (following recovery to ≤ grade 2 toxicity). Refer to 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.

Steroid side effects:
For any severe steroid-related side effect, consider alternative steroid dosing (as per modifications above).

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

- **Serious side effects**

Pneumonia/lung infection
Myelosuppression
Teratogenicity (contraindicated unless all of the conditions of the Pregnancy Prevention Programme are met)
Venous thromboembolism
Psychosis
Viral reactivation in patients previously infected with the varicella zoster or hepatitis B viruses (HBV).
Myocardial infarction/arterial thromboembolism
Thyroid disorders
Second primary malignancies

Frequently occurring side effects
Myelosuppression
Constipation, diarrhoea
Nausea and vomiting
Fatigue
Sleep disturbance
Insomnia
Hyperglycaemia
Fluid retention
Dyspepsia

- **Other side effects**

Reduced appetite
Blurred vision
Altered LFTs

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

Erythropoietic agents: increased risk of thrombosis – use with caution

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

Digoxin: may increase plasma digoxin levels – monitor levels

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

Additional comments

References

- Summary of Product Characteristics: Lenalidomide (Celgene) accessed 04 July 2019 via www.medicines.org.uk
- National Institute for Clinical Excellence. Technology Appraisal Guidance 587. Accessed 04 July 2019 via www.nice.org.uk
- Lotfi Benboubker, M.D. et al the FIRST Trial Team. Lenalidomide and Dexamethasone in Transplant-Ineligible Patients with Myeloma. N Engl J Med 2014; 371:906-917
- https://assets.publishing.service.gov.uk/media/584e872440f0b60e4a00007d/Revlimid_DHPC_UK_FINAL.pdf
- https://academy.myeloma.org.uk/wp-content/uploads/sites/2/2018/01/Myeloma-Academy-Best-Practice-VTEs-2017.pdf

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Date: July 2019