

LENALIDOMIDE, CYCLOPHOSPHAMIDE AND WEEKLY DEXAMETHASONE

INDICATIONS

Relapsed or refractory multiple myeloma in patients who have received two or more prior lines of therapy (NICE TA171), i.e. for 3rd line or beyond

This combination is not funded by NHS England. Individual funding must be agreed prior to initiation.

Note: Lenalidomide, cyclophosphamide and dexamethasone is the preferred option for younger and fit patients. If stem cells required after this regimen consider no more than 4 cycles prior to harvest. Lenalidomide, dexamethasone (low dose) is the preferred protocol for patients with poor performance status and generally frail (please see separate protocol).

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
 - FBC & film
 - Clotting screen
 - U&Es, LFTs
 - Calcium
 - Albumin
 - Uric acid
 - CRP
 - Thyroid Function.
 - Baseline random blood glucose level
 - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
 - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
 - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio, Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
 - Serum free light chain assay (Freelite)
 - β_2 microglobulin
 - LDH
 - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
 - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
 - Group and save
 - Imaging as per NICE/network guidance and clinical presentation

**Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ**

Additional Investigations

- o Plasma viscosity if hyper viscosity suspected
 - o If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology
2. Fertility - all patients should be offered fertility advice, as appropriate.
 3. Hydration - fluid intake of at least 3 litres /day should be attempted
 4. Document patient’s height and weight, dose on actual body weight.
 5. Treatment must be agreed at the relevant MDT.
 6. Document patient’s performance status.
 7. Counselling - all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA (National Patient Safety Agency) recommendation and chemotherapy measures.
 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. Obtain written consent for the treatment including signing Celgene risk Pregnancy Prevention Programme forms.

REGIMEN SPECIFIC PRE ASSESMENT

1. The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the Celgene Pregnancy Prevention Programme.
2. Clinical assessment of thrombo-embolic risk.

DRUG REGIMEN

Lenalidomide	The starting dose of lenalidomide is 25 mg orally once daily on days 1 to 21. See dose reductions below.
Cyclophosphamide	Orally either 500 mg on days 1 and 8 or 50 mg continuously on days 1 to 21.
Dexamethasone	40 mg PO daily on days 1, 8, 15 and 22 of each cycle. The dose may need to be reduced (prior to cycle 1 or at later cycles) in the elderly or if steroid-related side effects develop

CYCLE FREQUENCY

Cycle length: 28 days - i.e. 3 weeks on lenalidomide then 1 week off.

Response should be assessed every cycle.

DOSE MODIFICATIONS

Myelosuppression:

If the low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered.

If low counts are felt to be related to treatment, It is preferable to reduce cyclophosphamide prior to dose-reducing Lenalidomide.

If the neutrophil count falls below $1.0 \times 10^9/L$ or platelets below $50 \times 10^9/L$, cyclophosphamide should be temporarily delayed until neutrophils $>1.0 \times 10^9/L$ and platelets $>50 \times 10^9/L$, restart at same dose.

If recurrent cytopenias occur (neutrophils $<1.0 \times 10^9/L$ or platelets $<50 \times 10^9/L$ on day 1 of subsequent cycles), consider dose reduction of cyclophosphamide.

Lenalidomide treatment should not normally be given if the Absolute Neutrophil Counts (ANC) $< 0.5 \times 10^9/L$, and/or platelet count $< 30 \times 10^9/L$.

Recommended dose adjustments during treatment and restart of treatment:

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.

Note: Consider re-escalating lenalidomide dose, provided that toxicities have completely resolved. Starting dose = 25 mg/day.

Dose reduction steps

Starting dose	25 mg
Dose level -1	15 mg
Dose level -2	10 mg
Dose level -3	5 mg

Thrombocytopenia:

When platelets	Recommended Course
First fall to $< 30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at 15 mg/day
For each subsequent drop below $30 \times 10^9/L$	Interrupt lenalidomide treatment
Return to $\geq 30 \times 10^9/L$	Resume lenalidomide at next lower dose level (i.e. if on 15 mg, reduce to 10 mg - or if on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

Neutropenia:

When neutrophils	Recommended Course
First fall to $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to $\geq 0.5 \times 10^9/L$ when neutropenia is the only observed toxicity	Resume lenalidomide at 25 mg once daily.
Return to $\geq 0.5 \times 10^9/L$ when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at 15 mg once daily.
For each subsequent drop below $< 0.5 \times 10^9/L$	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to $\geq 0.5 \times 10^9/L$	Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10mg - or if was on 10 mg, reduce to 5 mg) once daily. Do not dose below 5 mg once daily.

Renal/Hepatic Impairment:

Lenalidomide:

Renal		Hepatic
CrCl 30- 50 ml/min	10mg once daily*	No formal studies. No specific dose recommendations
CrCl < 30 ml/min, no dialysis	15 mg every other day**	
CrCl < 30 ml/min, requiring dialysis	5 mg once daily***	
*Can increase to 15mg OD if no response and patient tolerating ** Can increase to 10mg OD if no response and patient tolerating *** On dialysis day, administer dose after dialysis/		

Cyclophosphamide:

Renal		Hepatic
Clinical decision		Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision.
GFR > 20 ml/min	100% dose	
GFR 10 - 20 ml/min	75% dose	
GFR < 10 ml/min	50% dose	

Neuropathy: Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon.

INVESTIGATIONS - Pre-treatment and during treatment:

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC & U&E's – consider fortnightly for first cycle, then monthly.
- Ca⁺⁺, LFTs – monthly.
- Ig's, paraprotein, urinary BJP and serum free light chain levels in patients with light chain disease - monthly.

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- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300mg daily for 7 days only for cycle 1 only. Aim to start day before chemotherapy
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min)
- Consider prophylactic fluconazole 50mg OD if appropriate
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Thromboprophylaxis/anticoagulation, see VTE section below.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Prescribe loperamide if needed for diarrhoea.
- Consider cholestyramine if suspicion of bile salt malabsorption with lenalidomide

EMETIC RISK

Moderate emetic risk on weekly cyclophosphamide days

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic:** The Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.
- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with lenalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

1. Prophylactic low-molecular weight heparin OR
2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

If VTE occurs, lenalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **Myelosuppression:** including neutropenia and thrombocytopenia which may require dose interruptions and reductions. 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.

- **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
- **Diarrhea:** was reported in 42% of patients requiring use of 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 (cholestyramine).
- **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.
- **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.
- **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.
- **There is an MHRA alert on the increased risk of secondary malignancies** in three large trials of lenalidomide treatment. The MHRA recommend vigilance in reporting such events promptly. The quoted incidence is 3 to 4% per annum.
- Cases of hypothyroidism have been reported in patients on lenalidomide. Baseline assessment of thyroid function and ongoing monitoring are recommended.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

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5. Revlimid® (lenalidomide) 25mg capules. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, 23 May 2019
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REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Pre assessment, dose modification, special warnings reviewed	May 2016	3.3	May 2018
Dr Jaimal Kothari Consultant	Regimen specific pre assessment included	May 2016	3.3	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated drug regimen, concurrent medications and references	July 2017	3.4	June 2018
Nadjoua Maouche (Haematology Pharmacist)	Standardise VTE information, assessment, investigation, concurrent medication, adverse effects sections.	June 2018	3.5	June 2019
Myeloma Protocol Review 2019	Update of indications, and references	July 2019	3.6	June 2020
Faouzi Djebbari (Advanced Haematology Pharmacist)	Update of indication, dosing schedule	Nov 2019	3.7	June 2020