

Chemotherapy Protocol

MULTIPLE MYELOMA

RCD-CYCLOPHOSPHAMIDE-DEXAMETHASONE-LENALIDOMIDE

There are multiple versions of this protocol in use. Please ensure you have the correct protocol for the relevant diagnosis.

Regimen

- Multiple Myeloma – RCD-Cyclophosphamide-Dexamethasone-Lenalidomide

Indication

- Relapsed or refractory myeloma in patients having received at least one prior therapy

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Dexamethasone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Lenalidomide	Peripheral neuropathy, pneumonia, infections, venous thrombotic events, respiratory dysfunction, rashes, hypokalaemia, hypomagnesaemia, hypocalcaemia, teratogenic risk, GI disturbances, flu-like symptoms.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC, LFTs and U&Es prior to each cycle
- Paraprotein and or light chains prior to each cycle
- Calcium and magnesium levels at regular intervals throughout treatment
- Perform a venous thromboembolism (VTE) risk assessment prior to starting treatment. Prescribe thromboprophylaxis for patients with additional risk factors
- Monitor thyroid function at the start of treatment and every six months thereafter.
- Regular monitoring of blood glucose is considered good practice

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion or erythropoietin if the patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Dose modifications based on haematological parameters apply to cyclophosphamide only.

Please note it is likely that myelosuppression prior to initial treatment in previously untreated patients will be a reflection of bone marrow infiltration. Unless there is evidence suggesting another cause, patients should be given at least the first cycle of treatment with unmodified doses.

Dose modifications for haematological toxicity apply to lenalidomide only.

Consider growth factor support as an alternative to the options below, particularly where there is evidence of bone marrow suppression.

Neutrophils ($\times 10^9/L$)	Dose Modifications (lenalidomide)
1 or more	100%
Less than 1	1 st Occurrence Delay until recovery has occurred. Restart at full dose. 2 nd Occurrence Delay until recovery has occurred. Restart at a dose of 15mg. 3 rd Occurrence Delay until recovery has occurred. Restart at a dose of 10mg. 3 rd Occurrence Delay until recovery has occurred. Restart at a dose of 5mg.
Platelets ($\times 10^9/L$)	Dose Modifications (lenalidomide)
50 or more	100%
Less than 50	1 st Occurrence Delay until recovery has occurred. Restart at a dose of 15mg. 2 nd Occurrence Delay until recovery has occurred. Restart at a dose of 10mg. 3 rd Occurrence Delay until recovery has occurred. Restart at a dose of 5mg.

Hepatic Impairment

Drug	Bilirubin $\mu\text{mol/L}$		AST/ALT units/L	Dose (% of original dose)
Cyclophosphamide	more than 30	or	2-3xULN	Clinical decision. Evidence that exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary.
Lenalidomide				No dose adjustments needed

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide	more than 20	100%
	10-20	75%
	less than 10 or serum creatinine greater than 300micromol/L	omit
Lenalidomide	Greater than 50	100%
	30-50	Start treatment with 10mg once a day. The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to treatment and is tolerating the treatment
	Less than 30	Start treatment with 15mg on alternate days
	Less than 30 and requiring dialysis	5 mg once a day On dialysis days, the dose should be administered following dialysis.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Lenalidomide

Allergic reaction or hypersensitivity NCI-CTC grade 2 then withhold treatment until symptoms have resolved to grade 1 or below, restart treatment at a daily dose of 15mg once a day. For NCI-CTC grade 3 or above then discontinue lenalidomide.

Desquamating rash of NCI-CTC grade 3 and above or grade 4 non-desquamating rash, discontinue lenalidomide.

There is an increased risk of thrombosis and some form of prophylaxis is recommended. A low molecular weight heparin or warfarin should be prescribed initially. If patients are treated with either a low molecular weight heparin or warfarin consider switching patients to aspirin after six cycles of therapy or after maximum response is achieved. A high index of suspicion for venous thrombo-embolism should be maintained. If a venous thrombosis or embolism NCI-CTC grade 3 or above then stop treatment and start anticoagulation. Lenalidomide may be reinstated at the clinician's discretion, if the patient is fully anti-coagulated.

Due to the potential for teratogenicity all women of child bearing potential are required to ensure adequate contraception, including a barrier method, is used. Additionally a negative

pregnancy test is required prior to commencing each cycle of therapy. Men are required to undertake to use a barrier method of contraception.

In general for all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. Reduce the daily dose to 15mg. On subsequent occurrences delay until recovery the dose may then be reduced to 10mg and 5mg consecutively. If a dose of 5mg is not tolerated treatment should be stopped.

Dexamethasone

For patients who are elderly or unable to tolerate the standard dose of dexamethasone the dose may be reduced to 20mg once a day in the morning.

Regimen

28 day cycle until disease progression (26 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Cyclophosphamide*	500mg	1, 8	Oral
Dexamethasone**	40mg once a day in the morning	1, 8, 15, 22	Oral
Lenalidomide	25mg once a day in the morning	1-21 incl.	Oral

*Cyclophosphamide should generally be stopped after 12 months of treatment or earlier if a maximum response is achieved.

**20mg dose is recommended in those with frailty and co-morbidities.
Dexamethasone may be stopped when the maximal response is reached.

Dose Information

- Cyclophosphamide is available as 50mg tablets
- Dexamethasone is available as 500microgram and 2mg tablets
- Lenalidomide is available as 25mg, 15mg, 10mg and 5mg tablets

Administration Information

- Dexamethasone should be taken in the mornings, with or after food.
- Cyclophosphamide tablets should be swallowed whole with a full glass of water
- Lenalidomide capsules should be swallowed whole, not chewed

Additional Therapy

- Antiemetics
 - metoclopramide 10mg three times a day when required oral
 - ondansetron 8mg once a day on days 1, 8 oral
- Consider allopurinol 300mg once a day for 7 days in cycle 1 only
- Thromboprophylaxis a low molecular weight heparin according to local formulary choice. Aspirin may be considered after six cycles or when maximal response is achieved.
- Consider anti-infective prophylaxis in high risk patients, including:
 - aciclovir 400mg twice a day oral
 - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only oral
- Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- Patient, prescriber and supplying pharmacy must comply with a pregnancy prevention programme. Every prescription must be accompanied with a completed Prescription Authorisation Form, which must be sent back to Celgene.
- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.

Coding

- Procurement – X71.5
- Delivery – X73.1

References

- 1.Kumar S, Lacy M, Hayman S et al. Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial. Am J Haematol 2011; 86(8): 640-5
- 2.Schey S, Morgan G, Ramasamy K et al. The addition of cyclophosphamide to lenalidomide and dexamethasone in multiply relapsed/refractory myeloma patients; a phase I/II study. Br J Haem 2010; 150 ;3 ;326-333

REGIMEN SUMMARY

RCD-Cyclophosphamide-Dexamethasone-Lenalidomide

Cycle 1

Take Home Medicines

1. Warning – Pregnancy Prevention Programme

Administration Instructions

Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

2. Cyclophosphamide 500mg once a day on days 1 and 8 oral

Administration Instructions

Please supply two doses of cyclophosphamide; ONE dose to be taken on day 1 and ONE dose to be taken on day 8 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

Oral chemotherapy. Only available as 50mg tablets, please ensure dose modifications occur in multiples of 50mg.

Swallow whole, not chewed with plenty of water.

3. Dexamethasone 40mg once a day on days 1, 8, 15 and 22 oral

Administration Instructions

Please supply four doses of dexamethasone; ONE dose to be taken on days 1, 8, 15 and 22 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

Take in the morning with or after food.

4. Lenalidomide 25mg once a day for 21 days oral

Administration Instructions

Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

Oral chemotherapy. Available as 25mg, 15mg, 10mg, 5mg and 2.5mg capsules, please ensure dose modifications occur in multiples of these strengths.

Swallow whole, not chewed with plenty of water.

5. Metoclopramide 10mg three times a day when required oral

Administration Instructions

When required for the relief of nausea. Please supply 28 tablets or nearest original pack size

6. Ondansetron 8mg once a day on day 1 and 8 oral

Administration Instructions

Please supply two doses of ondansetron; ONE dose to be taken on day 1 and ONE dose to be taken on day 8 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

Take 15-30 minutes prior to cyclophosphamide therapy

7. Allopurinol 300mg once a day for 7 days only oral

Administration Instructions

Take with or after food with plenty of water. Please supply 7 days.

8. Aciclovir 400mg twice a day for 28 days oral

Administration Instructions

Please supply 28 days or an original pack if appropriate

9. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral

Administration Instructions

Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.

This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

10. Gastric Protection

Administration Instructions

The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral

- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral
- ranitidine 150mg twice a day oral

Please dispense 28 days or nearest original pack size.

11. Thromboprophylaxis according to local formulary choice;

Administration Instructions

The choice of thromboprophylaxis is dependent on local formulary choice and may include;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 28 days or nearest original pack size.

Cycle 2-12 inclusive

Take Home Medicines

12. Warning – Pregnancy Prevention Programme

Administration Instructions

Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy.

13. Cyclophosphamide 500mg once a day on days 1 and 8 oral

Administration Instructions

Please supply two doses of cyclophosphamide; ONE dose to be taken on day 1 and ONE dose to be taken on day 8 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

Oral chemotherapy. Only available as 50mg tablets, please ensure dose modifications occur in multiples of 50mg.

Swallow whole, not chewed with plenty of water.

14. Dexamethasone 40mg once a day on days 1, 8, 15, 22 oral

Administration Instructions

Please supply four doses of dexamethasone; ONE dose to be taken on days 1, 8, 15 and 22 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

Take in the morning with or after food.

15. Lenalidomide 25mg once a day for 21 days oral

Administration Instructions

Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

Oral chemotherapy. Available as 25mg, 15mg, 10mg, 5mg and 2.5mg capsules, please ensure dose modifications occur in multiples of these strengths.

Swallow whole, not chewed with plenty of water.

16. Metoclopramide 10mg three times a day when required for nausea oral

Administration Instructions

When required for the relief of nausea. Please supply 28 tablets or nearest original pack size

17. Ondansetron 8mg once a day on day 1 and 8 oral

Administration Instructions

Please supply two doses of ondansetron; ONE dose to be taken on day 1 and ONE dose to be taken on day 8 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

18. Aciclovir 400mg twice a day for 28 days oral

Administration Instructions

Please supply 28 days or an original pack if appropriate

19. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral

Administration Instructions

Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.

This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

20. Gastric Protection

Administration Instructions

The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral
- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral
- ranitidine 150mg twice a day oral

Please dispense 28 days or nearest original pack size.

21. Thromboprophylaxis according to local formulary choice;

Administration Instructions

The choice of thromboprophylaxis is dependent on local formulary choice and may include;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 28 days or nearest original pack size.

Cycle 13 onwards

Take Home Medicines

22. Warning – Pregnancy Prevention Programme

Administration Instructions

Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

Dexamethasone 40mg once a day on days 1, 8, 15, 22 oral

Administration Instructions

Please supply four doses of dexamethasone; ONE dose to be taken on days 1, 8, 15 and 22 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

Take in the morning with or after food.

23. Lenalidomide 25mg once a day for 21 days oral

Administration Instructions

Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

Oral chemotherapy. Available as 25mg, 15mg, 10mg, 5mg and 2.5mg capsules, please ensure dose modifications occur in multiples of these strengths.

Swallow whole, not chewed with plenty of water.

24. Metoclopramide 10mg three times a day when required for nausea oral

Administration Instructions

When required for the relief of nausea. Please supply 28 tablets or nearest original pack size

25. Ondansetron 8mg once a day on day 1 and 8 oral

Please supply two doses of ondansetron; ONE dose to be taken on day 1 and ONE dose to be taken on day 8 of the cycle.

This may be dispensed as a single supply in one container or as separate supplies according to local practice.

26. Aciclovir 400mg twice a day for 28 days oral

Administration Instructions

Please supply 28 days or an original pack if appropriate

27. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral

Administration Instructions

Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.

This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

28. Gastric Protection

Administration Instructions

The choice of gastric protection is dependent on local formulary choice and may include;

- esomeprazole 20mg once a day oral
- omeprazole 20mg once a day oral
- lansoprazole 15mg once a day oral
- pantoprazole 20mg once a day oral
- rabeprazole 20mg once a day oral
- cimetidine 400mg twice a day oral
- famotidine 20mg once a day oral
- nizatidine 150mg twice a day oral
- ranitidine 150mg twice a day oral

Please dispense 28 days or nearest original pack size.

29. Thromboprophylaxis according to local formulary choice;

Administration Instructions

The choice of thromboprophylaxis is dependent on local formulary choice and may include;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 28 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 2016	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Mathew Jenner Consultant Haematologist Dr Helen Dignum Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
 NHS Isle of Wight
 Portsmouth Hospitals NHS Trust
 Salisbury Hospital NHS Foundation Trust
 University Hospital Southampton NHS Foundation Trust
 Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.