Chemotherapy Protocol

MULTIPLE MYELOMA

CTDa (28)-CYCLOPHOSPHAMIDE-DEXAMETHASONE-THALIDOMIDE (ATTENUATED)

(CTDa-28)

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

Regimen

- Multiple Myeloma – CTDa (28)-Cyclophosphamide-Dexamethasone-Thalidomide (attenuated)

Indication

- First or subsequent line treatment of multiple myeloma where high-dose therapy with autologous stem cell transplant is considered appropriate
- First line or subsequent line treatment of multiple myeloma where transplantation is not considered appropriate
- Relapsed or progressive multiple myeloma following high dose melphalan and PBSCT

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrragic cystitis (rare), taste disturbances
Dexamethasone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Thalidomide	Drowsiness, constipation, dizziness, increased risk of thromboembolic events, dry skin/rash, peripheral neuropathy, teratogenicity, syncope, bradycardia

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
- Pregnancy testing in women of childbearing potential. A negative pregnancy test must be obtained within 3 days of starting thalidomide the test must be repeated every 4 weeks (every 2 weeks in women with irregular menstrual cycles) with the final test 4 weeks after the last dose of thalidomide.
- 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 is 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.

Neutrophils ($x10^9$/L)	Dose Modifications (cyclophosphamide)
1 or greater	100%
less than 1	Reduce, delay or omit cyclophosphamide treatment until the neutrophils are $1x10^9$/L or above and then either continue at full dose with growth factor support or give reduced dose and seek consultant advice
Platelets ($x10^9$/L)	**Dose Modifications (cyclophosphamide)**
75 or above	100%
less than 75 or bleeding	Reduce, delay or omit cyclophosphamide treatment until the platelets are $75x10^9$/L or above and then either continue at full dose or give reduced dose and seek consultant advice

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin µmol/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.
Thalidomide	N/A		N/A	No dose modification required

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
Thalidomide	N/A	No dose modification required

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.

Thalidomide

Peripheral Neuropathy

If NCI-CTC grade 1 neurological toxicity occurs treatment may be continued, if symptoms worsen consider dose reduction or interruption. Treatment may be reintroduced at a reduced dose if symptoms resolve.

If NCI-CTC grade 2 neurological toxicity occurs suspend treatment or reduce the dose by at least 50%. Treatment may be reintroduced at a reduced dose if symptoms resolve to grade 1 or below.

For NCI-CTC neurological toxicity grade 3 or above or toxicity that does not resolve despite treatment interruption / dose reduction thalidomide treatment should be stopped.

Thromboembolism

The thrombotic risk for patients commencing on thalidomide must be assessed. Appropriate thromboprophylaxis must be prescribed according to local policies. Thromboprophylaxis is generally recommended for at least the first 5 months of thalidomide treatment, especially in patients with additional thrombotic risk factors. Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.

The occurrence of a thromboembolic event such as a DVT or thromboembolism, notably pulmonary embolism, is an indication for full anticoagulation following standard treatment guidelines. Thalidomide may be stopped, but can be re-introduced, initially at 50mg daily with escalation at subsequent cycles to 100mg, assuming good anticoagulant control and no other untoward side effects.

All patients should be initially prescribed a low molecular weight heparin at the appropriate prophylactic dose. Therapeutic warfarin is an alternative to low molecular heparin. Aspirin 75mg each morning is an alternative in very low risk patients once a response has been obtained.

Teratogenicity

Thalidomide is highly teratogenic.

All prescribers, patients and pharmacy staff must comply with the manufacturer's Pregnancy Prevention Programme.

Women of child-bearing potential taking thalidomide must use one agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on thalidomide and for one month after. They must have a negative pregnancy test within 3 days prior to starting treatment. Pregnancy testing should be repeated monthly thereafter until one month after stopping thalidomide (or every 2 weeks in women with irregular menstrual cycles).
If a woman taking thalidomide thinks she may be pregnant she must stop the drug immediately and seek medical advice.

Men taking thalidomide must use a barrier method of contraception throughout treatment and for one week after stopping, if their partner is capable of bearing children.

Other

For other thalidomide related toxicities of NCI-CTC grade 3 or above. Stop thalidomide until recovery to NCI-CTC grade 1 or below. Cautious reintroduction of thalidomide at a dose of 50mg a day may be considered with dose escalation if tolerated.

Dexamethasone

For patients who are elderly or unable to tolerate the standard dose of dexamethasone the dose may be reduced or days 15-18 omitted.

Regimen

28 day cycle continued until maximal response (minimum 6 cycles) and continue until plateau plus two cycles (8 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Cyclophosphamide	500mg	1, 8, 15, 22	Oral
Dexamethasone	20mg	1, 2, 3, 4 15, 16, 17, 18	Oral
Thalidomide*	50mg	1-28	Oral

*This dose may be increased to 200mg at night depending on tolerance.

Dose Information

- Cyclophosphamide is available as 50mg tablets
- Dexamethasone is available as 500microgram and 2mg tablets
- Thalidomide is available as 50mg capsules

Administration Information

- Cyclophosphamide tablets should be swallowed whole with a full glass of water
- Dexamethasone should be taken in the morning, with or after food
- Thalidomide should be taken at night to avoid daytime drowsiness
- Thalidomide prescriptions must be accompanied by a completed Prescription Authorisation Form

Additional Therapy

- Anti-emetics

  As take home medication

  - metoclopramide 10mg three times a day oral when required oral

- ondansetron 8mg once a day on days 1, 8, 15, 22 oral

- Thromboprophylaxis according to local formulary choice. For example;

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

- Consider allopurinol 300mg once a day for seven days for the first cycle only oral

- 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

- Laxatives as required for thalidomide-induced constipation.

- Bisphosphonates in accordance with local policies

- Mouthwashes according to local or national policy on the treatment of mucositis.

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- 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.

- For all patients taking thalidomide; the patient, prescriber and supplying pharmacy must comply with an appropriate pregnancy prevention programme.

Coding

- Procurement – X70.4(CTa50/100D), X71.1(CTa150D), X71.3 (CTa200D)

- Delivery – X73.1

References
1. Morgan G, Davies F, Gregory W et al. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematol 2012; 97; 3: 442-450
2. BCSH and UKMF Guidelines on the Management and Diagnosis of Multiple Myeloma Sept 2010

REGIMEN SUMMARY

CTDa (28)-Cyclophosphamide-Dexamethasone-Thalidomide Attenuated (CTDa)

Cycle 1

Take Home Medicines (day 1 only)

1. Warning – Pregnancy Prevention Programme
   Administration Instructions
   Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy.

2. Cyclophosphamide 500mg oral once a day on days 1, 8, 15, 22
   Administration Instructions
   Please supply four doses of cyclophosphamide; ONE dose to be taken on days 1, 8, 15 and 22..
   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 20mg oral once a day in the morning on days 1, 2, 3 & 4 and 15, 16, 17 & 18
   Administration Instructions
   Please supply eight doses of dexamethasone; ONE dose to be taken on days 1, 2, 3 & 4 and 15, 16, 17 & 18.
   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. Thalidomide 50mg oral once a day for 28 day
   Administration Instructions
   Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. The dose of thalidomide may be increased to 200mg at night if tolerated at not more than 50mg every 14 days. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg.
   Take at night to avoid daytime drowsiness.

5. Metoclopramide 10mg up to three times a day when required for the relief of nausea 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 days 1, 8, 15 and 22 oral
   Administration Instructions
   Please supply four doses of ondansetron; ONE dose to be taken on days 1, 8, 15 and 22.
   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 administration.

7. Allopurinol 300mg once a day for 7 days 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

Take Home Medicines

12. Warning – Pregnancy Prevention Programme
    Administration Instructions
    Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

13. Cyclophosphamide 500mg oral once a day on days 1, 8, 15, 22
    Administration Instructions
    Please supply four doses of cyclophosphamide; ONE dose to be taken on days 1, 8, 15 and 22..
    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 20mg oral once a day in the morning on days 1, 2, 3, 4 and 15, 16, 17, 18 inclusive
    Administration Instructions
    Please supply eight doses of dexamethasone; ONE dose to be taken on days 1, 2, 3 & 4 and 15, 16, 17 & 18.
    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. Thalidomide 50mg oral once a day for 28 days
    Administration Instructions
    Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. The dose of thalidomide may be increased to 200mg at night if tolerated at not more than 50mg every 14 days. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg.
    Take at night to avoid daytime drowsiness.

16. Metoclopramide 10mg oral up to three times a day when required for the relief of 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 days 1, 8, 15 and 22 oral
    Administration Instructions
    Please supply four doses of ondansetron; ONE dose to be taken on days 1, 8, 15 and 22.
    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 administration.

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.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 2016	None	Rebecca Wills Pharmacist Dr Debbie 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.