

ATTENUATED CYCLOPHOSPHAMIDE, THALIDOMIDE & DEXAMETHASONE (CTDa)

INDICATIONS

First or subsequent-line chemotherapy for multiple myeloma

Note: For standard risk older MM patients not suitable for transplantation either as initial therapy or at relapse.

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
 - FBC & film
 - Clotting screen
 - U&Es
 - LFTs
 - Calcium
 - Albumin
 - Uric acid
 - CRP
 - 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
 - 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
 - Bone marrow aspirate and trephine and immunophenotype if appropriate

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

Additional investigations:

Plasma viscosity if hyperviscosity suspected

1. Fertility - all patients should be offered fertility advice, as appropriate.
2. Hydration - fluid intake of at least 3 litres /day should be attempted.
3. Document patient's height and weight, dose on actual body weight.
4. Treatment must be agreed at the relevant MDT.

This is a controlled document and therefore must not be changed

1 of 5

| | | | |
|--------------------------|---|-----------|--------|
| MM.9 CTD - attenuated | Authorised by Myeloma lead Dr. Karthik Ramasamy | July 2017 | V. 4.4 |
|--------------------------|---|-----------|--------|

5. Counselling - all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
6. 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 management programme forms.

REGIMEN SPECIFIC PRE-ASSESSMENT

The conditions of the Thalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients.

Clinical Assessment of thrombo-embolic risk.

DRUG REGIMEN

The optimum dose of thalidomide is unknown. 100 mg is a typical target dose.

| | | |
|-------------------------|---|------------------------------|
| Thalidomide | 50 - 100 mg po (preferably nocte) Start dosing at 50 mg/day, increase every 2-4 weeks dependent on side effects. | Nocte |
| Cyclophosphamide | Orally or intravenously either 500 mg once per week or orally 50-100 mg every day. | |
| Dexamethasone | 20 mg po daily for 4 days. | Days 1 to 4 Days 15 to 18 |

CYCLE FREQUENCY

The cycle is repeated every 4 weeks for a minimum of 4 cycles and usually for 6-8 cycles depending on response and toxicity.

DOSE MODIFICATIONS

Haematological toxicity:

Dose reductions of cyclophosphamide may be necessary. If the neutrophil count falls below $0.5 \times 10^9/L$ or platelets below $50 \times 10^9/L$ interrupt cyclophosphamide until blood counts recover to neutrophils $> 1.0 \times 10^9/L$ and platelets $> 50 \times 10^9/L$.

Peripheral Neuropathy:

Thalidomide should be stopped or dose reduced if there are symptoms of progressive peripheral or autonomic neuropathy causing functional disability (grade 2 or above). Consider cautious re-introduction of Thalidomide at 50 mg daily if neuropathy symptoms resolve to grade 1 or better. Alternatively consider second line treatment.

This is a controlled document and therefore must not be changed

2 of 5

| | | | |
|--------------------------|---|-----------|--------|
| MM.9 CTD - attenuated | Authorised by Myeloma lead Dr. Karthik Ramasamy | July 2017 | V. 4.4 |
|--------------------------|---|-----------|--------|

Hepatic/Renal impairment:

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 | |

Thalidomide:

| Renal | Hepatic |
|-----------------------------|-----------------------------|
| No dose reduction necessary | No dose reduction necessary |

INVESTIGATIONS during treatment

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTs, Ca⁺⁺, glucose – fortnightly.
- Ig's, paraprotein, usually monthly after first 2 months: Freelite assay if appropriate.
- Urinary light chain if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Random blood glucose/ blood sugar
-

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic laxatives to be taken if needed.
- Consider proton pump inhibitor or H2 antagonist at clinician's discretion.
- Prophylactic fluconazole.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Thromboprophylaxis/anticoagulation - see above.
- Prophylactic acyclovir 200 mg bd to tid (depending on renal function).
- Consider prophylactic co-trimoxazole if heavily pre-treated or previous autograft.

EMETIC RISK

Moderate emetic risk on weekly cyclophosphamide days, otherwise low risk.

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

- **Drowsiness, somnolence and sedation:** Prescribe as night time dose. Thalidomide may potentiate the drowsiness caused by alcohol & other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking thalidomide.
- **Peripheral neuropathy:** Patients should be advised to report prickling, numbness and paraesthesia.
- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis, and some form of prophylaxis is recommended as follows:
 1. Aspirin can be appropriate for patients with no additional risk factors for thrombosis

If additional risk factors consider:

2. Prophylactic low-molecular weight heparin OR
3. Vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3

Additionally:

4. Can consider use of a direct oral anticoagulant eg apixaban for thromboprophylaxis or treatment dose as indicated.

Aspirin is generally not preferred for higher risk patients with additional risk factors such as immobility. If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- **Teratogenicity:** A risk management programme should be observed. The concomitant use of 2 effective methods of contraception is mandatory in all female patients of childbearing potential. Male patients should also use a condom when having sexual intercourse with women of childbearing potential. **Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme.**
- **Dizziness and orthostatic hypotension:** Patients should be advised that thalidomide may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position.
- **Skin toxicity:** in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.
- **Cyclophosphamide related toxicities include:** leucopenia, haemorrhagic cystitis, hair loss, mucosal ulceration, anorexia, nausea and vomiting, pigmentation (typically affecting the palms and nails of the palms and the soles of the feet) pneumonitis and interstitial pulmonary fibrosis.
- **Dexamethasone related toxicities include:** mood changes, restlessness, withdrawal effects, glucose intolerance
- **Other warnings:** Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

REFERENCES

1. Bird J A, Owen R G, D'Sa S, Snowden J A, et al; 2014. Internet. Guidelines for the diagnosis and management of multiple myeloma. Online. Available at: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf (last accessed: 27/6/16)
2. Cavenagh JD, Oakervee H; UK Myeloma Forum and the BCSH Haematology/Oncology Task Forces. Thalidomide in multiple myeloma: current status and future prospects. Br J Haematol. 2003 Jan;120(1):18-26.
3. eMC UK Summary of Product Characteristics for Thalidomide, Celgene, last updated December 2015
4. Palumbo A et al. A Phase III Study of Enoxaparin vs Aspirin vs Low-Dose Warfarin as Thromboprophylaxis for Newly Diagnosed Myeloma Patients Treated with Thalidomide Based-Regimens. Blood (ASH Annual Meeting Abstracts) 2009 114: Abstract 492.
5. eMC UK Summary of Product Characteristics for cyclophosphamide 50 mg tablets, Baxter Healthcare, Last updated 1/04/2015

REVIEW

| Name | Revision | Date | Version | Review date |
|--|---|-----------|---------|-------------|
| Nadjoua Maouche Pharmacist | Formatting, adverse effects and pre assessment section, dose modification, contraindication section removed | May 2016 | 4.3 | May 2018 |
| Dr Jaimal Kothari Consultant | VTE, regimen specific pre assessment section included | May 2016 | 4.3 | May 2018 |
| Manuela Sultanova Service Coordinator | Formatting, general standardisation. | July 2017 | 4.4 | May 2018 |

| | | | |
|--------------------------|---|-----------|--------|
| MM.9 CTD - attenuated | Authorised by Myeloma lead Dr. Karthik Ramasamy | July 2017 | V. 4.4 |
|--------------------------|---|-----------|--------|