Thames Valley
Strategic Clinical Network

ATTENUATED CYCLOPHOSPHAMIDE, THALIDOMIDE & DEXAMETHASONE (CTDa)

INDICATIONS

First or subsequent-line chemotherapy for multiple myeloma

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
   - Baseline random blood glucose level
   - 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
   - Bone marrow aspirate and trephine and immunophenotype if appropriate

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

Additional Investigations

- Plasma viscosity if hyperviscosity suspected

2. Hydration - fluid intake of at least 3 litres /day should be attempted
3. Fertility - all patients should be offered fertility advice, as appropriate.
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 recommendation and chemotherapy measure.
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 Pregnancy Prevention Programme forms.

REGIMEN SPECIFIC PRE-ASSESSMENT

1. The conditions of the Thalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the Celgene Pregnancy Prevention Programme.
2. Clinical Assessment of thrombo-embolic risk
3. Evaluate for and document presence of neuropathy. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with thalidomide.

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 x 10^9/L or platelets below 50 x 10^9/L interrupt cyclophosphamide until blood counts recover to neutrophils > 1.0 x 10^9/L and platelets > 50 x 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.

Hepatic/Renal impairment:

Cyclophosphamide:

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

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.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days 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
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Consider prophylactic levofloxacin 500mg od for 12 weeks (cycles 1-3)

- Consider proton pump inhibitor or H2 antagonist at clinician's discretion.
- Thromboprophylaxis/anticoagulation – see VTE section below.
- Bone protection as per NSSG Bone Protection protocol MM.3

EMETIC RISK

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

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

- **Teratogenic:** The Thalidomide Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme

- **Peripheral neuropathy**: Patients should be advised to report prickling, numbness and paraesthesia.

- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with thalidomide. 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, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **Drowsiness, somnolence and sedation**: Take thalidomide dose at 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

- **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

REFERENCES

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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. Thalidomide, Celgene® eMC UK Summary of Product Characteristics for, last updated March 2018 4.
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. Cyclophosphamide 50 mg tablets, Baxter Healthcare eMC UK Summary of Product Characteristics for, Last updated December 2016.

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
Network Protocol Review	VTE information. Standardise assessment, investigations. concurrent medication, adverse effects sections.	June 2018	4.5	June 2020
NSSG Myeloma Group	2021 Annual Protocol Review	June 2021	4.6	June 2022