CYCLOPHOSPHAMIDE, THALIDOMIDE & DEXAMETHASONE (CTD)

INDICATION

First or subsequent-line chemotherapy for multiple myeloma

Note: oral option for standard risk myeloma, outside of a clinical trial for younger patients who are eligible for autograft.

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
   - Creatinine clearance (CrCl), urine/ creatinine ratio, light chain (Bence Jones)
   - 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
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Additional Investigations
- o Plasma viscosity if hyperviscosity suspected
- o Tissue type patient, siblings and check CMV serology if eligible for allogeneic transplantation

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. Document patient's performance status.
6. Treatment must be agreed at the relevant MDT.
7. Counselling - all patients should receive verbal and written information on oral chemotherapy. Ensure pre-chemotherapy counselling in line with NPSA 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 the Pregnancy Prevention Programme forms.

REGIMEN SPECIFIC PRE- ASSESSMENT

1. The conditions of the Thalidomide Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the 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. 200 mg is the recommended target dose but is rarely achievable.

Thalidomide	100-200 mg po (preferably nocte) Start dosing at 50-100 mg/day, increase every 2-4 weeks dependent on side effects.	ONCE daily at NIGHT
Cyclophosphamide	orally **either** 500 mg once per week **or** orally 50-100 mg every day	Days 1,8,15 if weekly dosing is used
Dexamethasone	40 mg po daily for 4 days*	Days 1 to 4 Days 12 to 15

***Consider dose reducing to 20mg in elderly patients (≥75 years) or frail patients**

CYCLE FREQUENCY

The cycle is repeated every 3 weeks for a minimum of 4 cycles and usually 6-8 cycles depending on response (and timing of any harvest). At this time continuous thalidomide is stopped.

DOSE MODIFICATIONS

Haematological toxicity:

Myelosuppression: 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 and above). Consider cautious re-introduction of Thalidomide at 50 mg daily if symptoms resolve to grade 1 or better. Alternatively consider second line treatment.

Renal/Hepatic impairment

Cyclophosphamide:

Renal	Hepatic
According to GFR (mL/min): ≥30: 100% dose 10-29: 75% dose <10: Not recommended, if unavoidable consider 50% dose Hemodialysis: Not recommended, if unavoidable consider 50% dose	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy. Discuss with Consultant

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 – every 3-4 weeks.
- 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)
- Prophylactic fluconazole 50mg OD.
- Consider prophylactic co-trimoxazole 480mg to 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Consider levofloxacin prophylaxis at 500mg od for 12 weeks, particularly if the protocol is used to treat a newly diagnosed patient.
- 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/REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic:** The 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**: Prescribe thalidomide as night time dose. Thalidomide 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 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.

- **Cyclophosphamide related toxicities include:** leukopenia, 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

- **Skin toxicity**: in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.

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. Thalidomide, Celgene ® eMC UK Summary of Product Characteristics for, last updated March 2018
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. Baxter Healthcare, Last updated December 2016
6. Lancet Oncology Supplementary document: Dose recommendations for anticancer drugs in patients with renal or hepatic impairment
7. University College London Hospitals NHS Foundation Trust. 2009. Internet. Dose Adjustment for Cytotoxics in Renal Impairment.
8. University College London Hospitals NHS Foundation Trust. 2009. Internet. Dose Adjustment for Cytotoxic in hepatic impairment.

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, Standardisation of VTE, pre-assessment and address	July 2017	4.4	May 2018
Network Protocol Review	VTE information. Standardise assessment, investigation, concurrent medication, adverse effects sections.	June 2018	4.5	June 2020
NSSG Myeloma Group	Annual protocol review, updated sections for drug regimen, and renal/hepatic impairment	June 2022	4.6	June 2023