Thames Valley
Strategic Clinical Network

BORTEZOMIB THALIDOMIDE AND DEXAMETHASONE (VTD21) 21 day cycle

INDICATIONS

Induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation [NICE TA311].

Appropriate therapy for relapsed or refractory multiple myeloma in patients who are at second or more relapse and who have not received prior bortezomib based therapy.

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 (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust

Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ

Additional Investigations
- Plasma viscosity if hyperviscosity suspected
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology

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

REGIMEN SPECIFIC PRE -ASSESMENT

1. Evaluate for 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 bortezomib
2. 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 Pregnancy Prevention Programme
3. Clinical assessment of thrombo-embolic risk
4. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1

DRUG REGIMEN

Bortezomib	1.3 mg/m^2 given S/C bolus	Days 1, 4, 8 and 11
Thalidomide	50 -100 mg PO (preferably nocte) Start at 50mg and consider increasing the dose as tolerated	Daily on days 1 to 21
Dexamethasone	20 mg PO once daily	Days 1, 2, 4, 5, 8, 9, 11 and 12 - i.e. day of and day after each bortezomib dose

At least 72 hours should elapse between consecutive doses of bortezomib.

Bortezomib can also be administered weekly on days 1, 8 and 15 in a 21 days cycle in selected patients.

If neurotoxicity precludes completing planned therapy, consider completing the intended number of VTD cycles after the autologous transplant.

CYCLE FREQUENCY

Repeat every 21 days.

Allowable number of doses is as follows
- 24 doses for transplant eligible patients (first line therapy)
- 32 doses at (first) relapse

DOSE MODIFICATIONS

Haematological toxicity

BORTEZOMIB:
Thrombocytopenia due to bortezomib is transient and very rarely causes significant bleeding. If baseline platelet count is > 70, then the risk of severe thrombocytopenia is very low

In such patients, FBC should be checked only at the start of the cycle and does not need to be repeated before each dose.

In patients with platelets < 70 at the start of each cycle, FBC should be checked before each dose, bortezomib should be withheld until FBC is through and the dose omitted if the platelets are < 25 unless thrombocytopenia is thought to be mainly due to marrow infiltration by myeloma. In that scenario, consider proceeding with treatment along with platelet transfusion support.

In all other circumstances, if these levels are not reached, then treatment should be withheld and subsequent doses reduced by 25% (i.e. from 1.3 mg/m^2 to 1.0 mg/m^2 or from 1.0 mg/m^2 to 0.7 mg/m^2).

Peripheral neuropathy

BORTEZOMIB:
If there are symptoms of peripheral neuropathy, the dose reduction schedule must be invoked (see below). The drug should be stopped if symptoms or signs progress despite this.

Severity of neuropathy	Dose modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m^2 or reduce treatment schedule to 1.3 mg/m^2 once per week if currently is twice per week
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

THALIDOMIDE:
Thalidomide should be stopped or dose reduced if there are symptoms of progressive peripheral neuropathy causing functional disability (grade 2 or above). Consider cautious re-introduction of thalidomide at a dose of 50mg daily if symptoms resolve to grade 1 or better after a two-week gap Subsequent cautious dose escalation should be considered if symptoms permit. Switching to CyBorDex is a reasonable alternative.

Renal & Hepatic impairment:
BORTEZOMIB:

Renal	Hepatic
. Clinical decision if GFR < 20ml/min In dialysis patients, give after dialysis	Bili > 1.5 x ULN: reduce to 0.7 mg/m^2 in the first treatment cycle. Consider a dose escalation to 1.0 mg/m^2, or a further dose reduction to 0.5 mg/m^2 in subsequent cycles, based on patient tolerability.

THALIDOMIDE:

Renal	Hepatic
No dose reduction necessary	No dose reduction necessary

INVESTIGATIONS (at the beginning of each cycle)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTs, Ca^{2+}
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle.
- Blood pressure (consider checking for postural drop if symptomatic)
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

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CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and 3 months post therapy.
- Consider prophylactic fluconazole 50mg OD
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.

- Consider levofloxacin prophylaxis at 500mg od for 12 weeks (i.e. cycles 1-4) for all newly diagnosed myeloma patients. If this regimen is used in the relapsed setting, consider levofloxacin at clinician discretion, only in patients deemed at high risk of infections. Adjust dose for renal function

- 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

Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin,

carabamazepine, phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

Extravasation risk:
Irritant: bortezomib

EMETIC RISK

Low

ADVERSE EFFECTS/REGIEMN 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 pain hypersensitivity prickling, numbness and paraesthesia. If these occur see above dose reductions and consider use of Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU. Caution in patients with existing peripheral neuropathy

- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with thalidomide. Unless the patient is thought to be at high-risk of bleeding (and this risk exceeds the risk of VTE), 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 (preferred)

  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

- **Dizziness and orthostatic hypotension**: Patients should be advised that Bortezomib may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position. Caution in patients with history of syncope, receiving medications associated with hypotension and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells. Patients who experience dizziness or low blood pressure may benefit from 500ml intravenous 0.9% sodium chloride with each dose of bortezomib.
- **Gastrointestinal**: Nausea, diarrhoea, vomiting and constipation are very common and ileus has been reported.
- **Drowsiness, somnolence and sedation**: Take the thalidomide dose at night time. 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.

- **Skin toxicity**: in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.
- **Other warnings**: Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

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5. Heher EC, Goes NB, Spitzer TR, Raje NS, Humphreys BD, Anderson KC, Richardson PG. Kidney disease associated with plasma cell dyscrasias. Blood. 2010 Sep 2;116(9):1397-404.
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REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, adverse effects and pre assessment section, dose modification, contraindication section removed	May 2016	1.3	May 2018
Dr J. Kothari Consultant	Regimen specific pre assessment included	May 2016	1.3	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated haematological toxicity, renal and hepatic impairment, concurrent medications, adverse effects and references	July 2017	1.4	June 2018
Nadjoua Maouche	Indications. Standardise assessment, investigations, concurrent medication, VTE assessment, adverse effects.	June 2018	1.5	June 2019
Myeloma Protocol Review 2019	Update of indication, addition of allowable number of doses per treatment line, clarification of dosing in hepatic impairment, extravasation risk, update of references	June 2019	1.6	June 2020
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	1.7	June 2021
Quality manager	Nursing care plan added	April 2021	1.8	June 2021
NSSG Myeloma Group	2021 Annual myeloma protocol review	June 2021	1.9	June 2022
NSSG Myeloma Group	Updated concurrent medication section	Dec 2022	2.0	June 2023

Nursing Care Plan:
Bortezomib Thalidomide Dexamethasone (VTD) – 21 day cycle

Indication: newly diagnosed Myeloma patients or relapsed or those with refractory disease.

Frequency: 6-8 cycles of 21 days.

Alopecia: No

BORTEZOMIB (VELCADE): Proteasome inhibitor

Administered subcutaneously on **days 1, 4, 8, 11 (can also be given on days 1, 8 and 15 of a 21 day cycle)**. Minimum of 72 hours required between doses.

Emetic risk: Low.

Classification of extravasation: irritant

Side effects: tachycardia, diarrhoea, constipation, anorexia, nausea/vomiting, thrombocytopenia, neutropenia, peripheral neuropathy (sensory and motor), headache, rash, fatigue, postural hypotension, dizziness, shingles, inflammation at injection site, infections, bone marrow depression.

THALIDOMIDE: Immunomodulator and angiogenesis inhibitor.

Administered orally **daily.**

Emetic risk: minimal.

Side effects: sedation (thalidomide is to be taken at night), constipation, dry mouth, dyspnoea, venous thromboembolism, bone marrow depression, peripheral neuropathy, confusion, depression, fatigue, rash, tinnitus.

DEXAMETHASONE: corticosteroid tablets

Administered orally on the day of each bortezomib dose and the day after. Taken with or after food preferably at breakfast.

Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations

- Lying and standing Blood pressure to be recorded pre cycle 1, advise patients that velcade can cause orthostatic hypotension and counsel them to sit upright for a moment before standing from a sitting/lying position.
- Bloods are required at the start of each cycle. Patients with unstable blood counts (specifically low platelets, see protocol) may require more frequent monitoring.
- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle (due to the teratogenic effect of thalidomide).
- Advise patients to maintain a fluid intake of 2-3 litres and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.

Assess for presence of peripheral neuropathy before starting treatment and **prior to the start of each cycle.**