BORTEZOMIB-THALIDOMIDE-DEXAMETHASONE (VTD) for patients with NEWLY DIAGNOSED myeloma eligible for PBSCT, 21 day cycle

INDICATION:

1. Induction treatment of adults with previously untreated multiple myeloma, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.
   More appropriate for high-risk MM patients. High risk (unknown risk, cytogenetics failed) Patients can be switched from CTD to this regimen.
2. Appropriate therapy for relapsed or refractory multiple myeloma in bortezomib naïve patients. Funding may be required depending on line of therapy

Prior to a course of treatment

- Assess cardiac function by history and exam with ECG, CXR. Consider MUGA scan if abnormal. Note bortezomib is contraindicated if severe cardiac impairment.
- Assess for peripheral neuropathy – may worsen on therapy; contraindicated if Grade 3 sensory
- Check FBC – neutrophils must be >0.5 and platelets must be >25 unless due to marrow infiltration
- Check renal function and LFTs – see dose modification.
- Patients must be counselled about the risk of birth defects with foetal exposure to thalidomide. Prescription must be accompanied by a completed thalidomide prescription authorization form.
- If appropriate discuss possibility of pregnancy with female patients and need for contraception with both male and female patients. Discuss potential for infertility - offer semen cryopreservation to male patients
- Written consent for course

Prior to each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function.
- Check FBC, U&Es, creat, LFTs – *see dose modification*. *Discuss with consultant* if renal or hepatic function have changed change significantly.
- Encourage patient to drink 3 L fluid daily

Prior to each dose

- Reassess for peripheral neuropathy – *see dose modifications*
- Check FBC - give blood product and GCSF support as necessary during the cycle.

Bortezomib	1.3mg/m^2	SC Bolus	days 1, 4, 8 and 11
Thalidomide	50mg for 2 weeks then increase to 100mg if tolerated	PO (preferably nocte)	Daily
Dexamethasone	20mg od	PO	Days 1, 2, 4, 5, 8, 9, 11 and 12 – (i.e. day of and day after each Bortezomib dose)

Repeat cycle every 21 days

- It is recommended that patients with a confirmed maximal response receive 2 additional cycles of treatment beyond confirmation of this status to a maximum of 8 treatment cycles.

Anti-emetic prophylaxis	Low emetic Risk
Other medications	Allopurinol 300mg od (100mg if Cr.Cl <20ml/min) for cycle 1 Prophylactic acyclovir 400mg bd recommended Prophylactic dose LMWH – e.g. dalteparin 5000 units sc daily (when platelets > 50 x 109/l). Aspirin can also be considered for VTE prophylaxis. Consider a PPI such as omeprazole.

Dose modification for haematological toxicity (unless due to disease)

Neutropenia:

• Neutrophils <0.5 or platelets <25 on day of bortezomib	Stop until recovery then restart with 25% dose reduction i.e 1.3mg/m^2 reduce to 1.0 mg/m^2, 1.0mg/m^2 reduce to 0.7 mg/m^2 **OR** GCSF prophylaxis(discuss with consultant)
• No resolution of cytopaenia or they recur at 0.7mg/m^2	If no resolution or recurs at lowest dose, consider stopping treatment – *discuss with consultant*

Thrombocytopenia:

• Platelets <25 on day of bortezomib	Stop until >25 then restart at 1.0 mg/m^2 if initially 1.3mg/m^2 or 0.7 mg/m^2 if initially 1.0mg/m^2 **OR** Support with platelet transfusion
No resolution of thrombocytopenia or recurs at 0.7mg/m^2	Consider stopping treatment – *discuss with consultant*

Dose modifications to Bortezomib for peripheral neuropathy

• Grade 1 (but no pain) i.e loss of tendon reflexes or paraesthesiae but not interfering with function	No change
• Grade 1 with pain or Grade 2, i.e objective sensory loss or paraesthesia interfering with function but not activities of daily living	Reduce to 1.0mg/m^2
• Grade 2 with pain or Grade 3, i.e sensory loss or paraesthesia interfering with activities of daily living	Withhold until symptoms resolve, then restart at 0.7mg/m^2 at once a week
• Grade 4, i.e permanent sensory loss that interferes with function	Discontinue bortezomib

Management of neuropathy secondary to Thalidomide

Sensory Motor Loss of deep tendon reflexes, mild paraesthesias but not interfering with function	Asymptomatic weakness on exam only
Sensory alteration or paraesthesias interfering with function but not ADLs	Symptomatic weakness interfering with function but not ADLs
Severe sensory loss or paraesthesias interfering with ADLs	Weakness interfering with ADLs; bracing or assisitance to walk required
Disability	Severe weakness/disability e.g paralysis
Grade 3 or 4 toxicity	Stop thalidomide until symptoms resolve; consider reintroducing at 50mg od and escalation up to 100mg if tolerated
Grade 2 toxicity	Stop thalidomide until toxicity resolves to less than grade 1 then restart at 50% dose
Grade 1 toxicity	Reduce dose by 50%

Modification for renal dysfunction (Bortezomib)

- If < 30ml/min *discuss with consultant*. Note that the incidence of serious adverse effects increases with mild-moderate renal impairment. Patients have been treated safely when the creatinine clearance is<30ml/min and on dialysis but monitor carefully for toxicities if renal function is impaired
- If <30ml/min consider alternative less renal toxic regime. Consultant clinical decision.

Modification for liver dysfunction

- The major route of bortezomib excretion is hepatic and there is limited on the use of bortezomib in patients with hepatic impairment. If bilirubin >30μmol/L use with caution, monitor closely for toxicity and consider dose reduction – *discuss with consultant*

Dose modification for diarrhoea

• If ≥ grade 3 diarrhoea, i.e increase of ≥ 7 stools/day over baseline, incontinence, hospitalization with >24 hrs IV fluids	Reduce dose to 1.0mg/m^2, then 0.7mg/m^2 if symptoms persist

Dexamethasone dose modification

- If dexamethasone poorly tolerated reduce dose to 10mg.
- If still poorly tolerated consider weekly dosing.
- No dose modification needed in renal failure

Bortezomib Toxicities

Thrombocytopenia	Nausea
Neutropenic sepsis	Fatigue
Fluid retention & cardiac failure	Diarrhoea, constipation & ileus
Peripheral neuropathy (may be painful)	Hypotension
Fatigue, malaise, weakness	

Thalidomide Toxicities

Nausea (none-mild)	Sedation, somnolence
Constipation Peripheral	Neuropathy
Tremor	Venous thromboembolism
Foetal abnormalities in pregnancy (phocomelia)	

Dexamethasone Toxicities

Agitation,	Confusion
Depression	Insomnia
Oedema, fluid retention	Peptic ulceration
Proximal myopathy	

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