BORTEZOMIB-THALIDOMIDE-DEXAMETHASONE (VTD) for patients with NEWLY DIAGNOSED myeloma eligible for PBSCT **OFF TRIAL**

INDICATION : Newly diagnosed myeloma eligible for PBSCT as per NICE technology appraisal TA 311 April 2014

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.
- 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 (Velcade®)	1.3mg/m^2	SC	on days 1, 4, 8, 11
Thalidomide	Cycle 1 = 50mg nocte day 1 - 14, 100mg nocte day 15 - 28 Cycle 2 and thereafter if tolerating give 200mg nocte	PO	
Dexamethasone	40mg od	PO	days 1-4, 8-11

Bortezomib may be administered intravenously if localized reactions occur

Repeat cycle every 28 days

- Plan to give at least 4 cycles to assess response
- If PR or better is achieved, give an additional 2 cycles up to a maximum of 6 cycles
- If patient fails to reach at least a minimal response after 4 cycles consider stopping bortezomib - *discuss with consultant*

Anti-emetic prophylaxis	Metoclopramide
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 10^9/l). Aspirin can also be considered for VTE prophylaxis. Consider a PPI such as omeprazole.

Bortezomib dose modifications:

Dose modification for neutropenia (unless due to disease)

• Neutrophils <0.5 or platelets <25 on day 1 of cycle	Stop until > 1.0 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** GCSF prophylaxis
• No resolution of neutropenia or recurs at 0.7mg/m^2	Consider stopping treatment – *discuss with consultant*

Dose modification for thrombocytopenia (unless due to disease)

• Platelets <25 on day 1 of cycle	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 for peripheral neuropathy

• Grade 1 (but no pain) i.e loss of tendon reflexes or paraesthesiae but not interfering with function	Reduce to 1.3mg/m^2 weekly
• 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 weekly
• 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 weekly. If symptoms fail to resolve within 2 weeks – stop treatment
• Grade 4, i.e permanent sensory loss that interferes with function	Discontinue bortezomib

Modification for renal dysfunction

- 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.

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

Bortezomib Toxicities

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

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 200mg if tolerated
Grade 2 toxicity	Stop thalidomide until toxicity resolves to less than grade 1then restart at 50% dose
Grade 1 toxicity	Reduce dose by 50%

Thalidomide Toxicities

Nausea (none-mild)	Sedation, somnolence
Constipation	Peripheral neuropathy
Tremor	Venous thromboembolism

Foetal abnormalities in pregnancy (phocomelia)

Dexamethasone dose modification

If dexamethasone poorly tolerated reduce dose to 20mg. If still poorly tolerated consider weekly dosing.

No dose modification needed in renal failure

Dexamethasone Toxicities

Agitation, confusion, depression	Insomnia
Oedema, fluid retention	Peptic ulceration
Proximal myopathy	

References: Superiority of bortezomib, thalidomide and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study, Blood, 23 Aug 2012, vol 120, number 8.

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