Cyclophosphamide, Bortezomib (subcutaneous) and Dexamethasone (CyBorDex)

INDICATION: Multiple Myeloma

Prior to a course of treatment

- Check creatinine clearance – see dose modification.
- 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, platelets >25 unless due to marrow infiltration
- Check LFTs – see dose modification.
- 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
- With severe renal failure consideration should be given to using other bortezomib combinations. Consultant medical decision.

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

Drug	Dose	Route	Frequency
Bortezomib days	**1.3mg/m^2**	**subcutaneous injection**	**days 1, 8 and 15 (allow at least 72hrs between each dose) (state dates on prescription)**
Dexamethasone	**20mg od**	**PO**	**On the day of and day after each Bortezomib dose (days 1, 2, 8, 9, 15 & 16)**
Cyclophosphamide (Route/Frequency is a clinical decision)	**50mg**	**PO**	**daily for 21 days**
	OR		
	500mg	**PO**	**once a week for 3 weeks**
	OR		
	500mg	**IV**	**once a week for 3 weeks**
Repeat cycle every 21 days for up to 8 cycles			

Other medications	Allopurinol 300mg od (100mg if Cr.Cl<20ml/min) for cycle 1 only
	Aciclovir 400mg bd prophylactically
	Proton Pump Inhibitor or H2 antagonist at clinicians discretion

Dose modification for haematological toxicity (unless due to disease)	
If prolonged G4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Omit cyclophosphamide 1 week (continue dexamethasone). Restart at same dose when neutrophils and platelets recovered as above. If recurrent, i.e. if neutrophils < 1.0 x 109 /L and platelets < 50 x 109 /L on day 1 of subsequent cycles (when previously > than these levels), omit cyclophosphamide and consider dose reduction of cyclophosphamide for subsequent doses. If the patient was receiving 500 mg weekly, reduce to 400 mg, if 400 mg reduce to 300 mg, if 300 mg reduce to 200 mg. If patients receiving 50mg daily omit for a week and consider reduced frequency.
• If platelet ≤ 30 x 109 /L or ANC ≤ 0.75 x 109 /l on a bortezomib dosing day (other than Day 1)	Withhold bortezomib
• If several bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	bortezomib reduced by 1 dose level (from 1.3 mg/m2 to 1 mg/m2 , or from 1 mg/m2 to 0.7 mg/m2)
G ≥ 3 non-haem toxicities (see above for neuropathic pain and/or peripheral neuropathy)	bortezomib withheld until symptoms resolved to G1 or baseline. bortezomib reinitiated with one dose level reduction (from 1.3 mg/m2 to 1 mg/m2 , or from 1 mg/m2 to 0.7 mg/m2)

Dose modifications 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/m2
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/m2 at once a week
Grade 4, i.e permanent sensory loss that interferes with function	Discontinue bortezomib

Dose 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
- If <30ml/min consider alternative less renal toxic regime. Consultant clinical decision.

Dose modification for hepatotoxicity (unless due to lymphoma)

- 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/m2 , then 0.7mg/m2 if symptoms persist

Bortezomib Toxicities	
Thrombocytopenia	Nausea
Neutropenic Sepsis	Fatigue
Fluid retention & cardiac failure	Diarrhoea, constipation & Ileus
Peripheral neuropathy (may be painful)	Hopotension
Fatigue, malaise, weekness	Injection site reaction

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Reference:
Thames Valley Strategic Clinical Networks CyBorDex protocol version 1.6 (June 2016) accessed from http://nssg.oxford-haematology.org.uk/myeloma/pdf-protocols/mm-12-cy-bor-dex.pdf on 11/08/2016.

Velcade SmPC Updated 26 Jan 2016