Subcutaneous Bortezomib (Velcade®), Cyclophosphamide & Dexamethasone (VCD) for Multiple Myeloma

Indication: Bortezomib is indicated for:
Newly diagnosed Multiple Myeloma as per SELCN Guidelines.
Relapsed Multiple Myeloma.

Regimen details:

Twice weekly protocol:

Bortezomib	1.3 mg/m^2	SC	Days 1, 4, 8 and 11
Cyclophosphamide	500mg	orally	Days 1, 8 and 15
Dexamethasone	20mg od	orally	Days 1, 4, 8 and 11

Weekly protocol:

Bortezomib	1.6 mg/m^2	SC	Days 1 and 8
Cyclophosphamide	500mg	orally	Days 1, 8 and 15
Dexamethasone	20mg od	orally	Days 1, 8 and 15

For patients undergoing haemodialysis, bortezomib should be given on the day of, but after, dialysis.

Administration: Bortezomib subcutaneous bolus over 3 to 5 seconds
The site of subcutaneous injection should be rotated between the thighs and abdomen.
Cyclophosphamide and dexamethasone orally.

Premedication: None required

Frequency: Twice weekly and weekly protocol: 21 day (3 week) cycle, maximum of 8 cycles
Assess response after each cycle (by EBMT criteria)
If complete response (CR) is achieved, give another 2 cycles and stop.
If partial response (PR) or PR plateau is achieved, give another 2 cycles. These responding patients who do not achieve a CR can receive up to 8 cycles.
Minimal response (MR), no change (NC) or progressive disease at 4 cycles, stop treatment.
Progressive disease at any point, stop treatment.

Extravasation: Non-vesicant

Anti- emetics: Mild emetogenicity

Supportive Care: Antiviral prophylaxis as per local policy e.g. aciclovir 200mg bd
PCP prophylaxis as per local policy e.g. co-trimoxazole 960mg od Monday, Wednesday, Friday each week.

Reason for Update: SC route licensed , include twice weekly protocol	Approved by Consultant: M Streetly 05/12/2012
Version: 2	Approved by Chair Haem TWG: M Kazmi
Supersedes: All other versions	Date: 17/12/2012
Prepared by: Laura Cameron	Checked by (Network Pharmacist): J Turner 12/12/2012

Consider antifungal prophylaxis as per local policy if the patient is also receiving dexamethasone
PPI or H_2 receptor antagonist e.g. omeprazole 20mg od, if receiving dexamethasone
Allopurinol 300mg od (or 100mg od for renal impairment) for first cycle only
500ml oral hydration prior to the bortezomib dose

To manage peripheral neuropathy:
Consider Vitamin B and folic acid supplementation
Topical cocoa butter (not supplied by NHS) applied to affected areas twice a day may be beneficial to some patients.
Gabapentin up to 300mg tds for neuropathic pain
Further details as per SELCN Guidelines for the Management of Multiple Myeloma and Related Plasma Cell Disorders

Regular investigations:

FBC	D1 and prior to each bortezomib dose
LFTs	D1
U&Es	D1

Serum paraprotein and serum free light chains at the start of each cycle.
Baseline neurological examination.
Baseline vitamin B_{12} and folate.

Toxicities: Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation. Hepatobiliary disorders. The most common haematological toxicity is thrombocytopenia. Peripheral neuropathy. Orthostatic/postural hypotension. Cardiotoxicity – patients with a known history of heart disease, should have an Echo prior to commencing treatment. Fatigue. Tumour lysis syndrome. Rash.

Dose Modifications

Haematological Toxicity

Prior to every cycle of bortezomib:

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Bortezomib
≥1.0 x 10^9/L	&	≥ 75 x 10^9/L	100% dose
<1.0 x 10^9/L	or	< 75 x 10^9/L	Delay on a weekly basis, until recovery of toxicity.

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the, day 1 dose will go ahead even if neutrophils <1.0 x 10^9/L and platelets < 75 x 10^9/L. This should be confirmed with a Consultant.

If neutrophils < 1.0 x 10^9/L and platelets < 75 x 10^9/L on day 1 of subsequent cycles (when previously > than these levels), delay until as above, and reduce the bortezomib dose for all further cycles.

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Prior to any day of bortezomib during a cycle (other than D1):

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Bortezomib
≥ 0.5 x 10^9/L	&	≥ 30 x 10^9/L	100% dose
< 0.5 x 10^9/L	or	< 30 x 10^9/L	With hold until recovery of toxicity. Re-initiate treatment at a reduced dose.

NB. In the presence of cytopenias due to marrow involvement with myeloma, it is possible that the doses will go ahead even if neutrophils < 0. 5 x 10^9/L and platelets < 30 x 10^9/L. This should be confirmed with a Consultant. Doses not given in a cycle are not made up later.

Consideration should be given to platelet transfusion and GCSF support for haematological toxicity. This must be on the recommendation of a Consultant Haematologist.

Renal Impairment — Bortezomib should be used with caution in patients with CrCl < 20ml/min not undergoing dialysis; however, no specific dosing recommendations have been made.
Since dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure.

Hepatic Impairment — There is very limited information available regarding the use of bortezomib in patients with hepatic insufficiency and it should therefore be used with caution.

Non-Haematological toxicities

Severity of neuropathy	Bortezomib
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce dose: discuss with Consultant
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate bortezomib treatment and reduce dose as per Consultant
Grade 4 (sensory neuropathy which is disabling or motor neuropathy that is life threatening or leads to paralysis) and/or severe autonomic neuropathy	Discontinue bortezomib

Doses reduced for toxicity should not be re-escalated

Drug interactions: Bortezomib may increase the levels/effects of citalopram, phenytoin and other CYP2C19 substrates. Levels/effects of bortezomib may be increased by azole antifungals, ciprofloxacin, clarithromycin, erythromycin, verapamil and other CYP3A4 inhibitors.

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References:

www.medicines.org.uk
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