BORTEZOMIB & DEXAMETHASONE +/- CYCLOPHOSPHAMIDE (CVD)

N.B. **See separate protocol** for bortezomib, dexamethasone +/- thalidomide in the 1st line setting for patients eligible for high dose chemotherapy with stem cell transplantation

Routinely funded for:

- Treatment of progressive multiple myeloma at first relapse after one prior therapy and who have undergone, or are unsuitable for, bone marrow transplantation (NICE 2007)
- First-line treatment of multiple myeloma in patients who are unable to tolerate, or have contraindications to, thalidomide and who are unsuitable for stem cell transplantation. (NICE 2011)
- An option for first-line treatment of multiple myeloma in patients unsuitable for stem cell transplantation and with advanced renal failure (dialysis either current or imminent) or with multisystem amyloidosis (on amyloid centre review)

~~**Individual funding must be obtained before treatment may start for:**~~

- ~~Bortezomib re-challenge for relapsed multiple myeloma, where PR or CR of ≥ 6 months achieved with a previous bortezomib course~~

Drugs/Dosage:

	Licensed frequency (3 weekly cycle) suggested starting schedule for fit patients; or as 2nd line treatment for bortezomib-naïve patients who relapsed before autograft or were refractory to 1st line treatment	**Once weekly dosing (5 week cycle)** a preferred option for patients aged > 70 years, or younger but with significant co-morbidities
Bortezomib (2.5mg/ml for subcut use)	1.3mg/m^2 s/c bolus on Day 1, Day 4, Day 8 and Day 11, every 21 days (at least 72 hours between doses)	1.3mg/m^2 s/c bolus on Days 1, 8, 15 and 22, every 35 days
Dexamethasone (unless contra-indicated)	20mg po once daily on each day of bortezomib, and the day after (Days 1+2, 4+5, 8+9, 11+12) to give a total of 160mg per cycle	20mg po once daily on day of bortezomib injection and day after (i.e. Days 1+2, 8+9, 15+16, 22+23)
+/- Cyclophosphamide (do not include in patients with cytopenias)	500mg po once weekly on Days 1, 8 & 15	500mg po once weekly on Days 1, 8, 15 & 22 (then 1 week rest)

Administration:

Bortezomib given by subcutaneous bolus injection into the thigh or abdomen.
Rotate sites: avoid injecting into the same site in the same cycle
e.g. alternate between right and left abdomen, and right and left thigh.
Patient should be encouraged to drink 2 – 3 litres over the 24 hours after each dose of bortezomib in the first cycle, to reduce the risk of tumour lysis syndrome.
Cyclophosphamide is available as 50mg tablets, to be swallowed whole with a full glass of water. Encourage 2 – 3 litres oral fluid intake over the 24 hours after each dose, to reduce the risk of haemorrhagic cystitis.
Dexamethasone is to be taken in the morning with or after food.

Reason for Update: general review / ~~added re-challenge indication;~~ updated renal function advice	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 10	Date: 12.12.14
Supersedes: Version 9	Review date: January 2017
Prepared by: S Taylor	Checked by: C Tucker

Other Drugs:	Allopurinol, dose according to renal function – review after 3 weeks. Consider PCP prophylaxis – prescribe according to unit practice/protocol. Fluconazole 50 – 150mg po od as antifungal prophylaxis Aciclovir 400mg po bd Use of PPI or H_2 receptor antagonist is recommended whilst treating with steroids.	
Frequency:	For responding patients (defined as 50% or greater reduction in paraprotein), continue until 2 cycles after CR, to a maximum of 8 cycles. For non-responders at 4 cycles, discontinue treatment. The manufacturer will be required to reimburse the full cost of bortezomib for these patients under the Velcade Response Scheme	
Main Toxicities:	myelosuppression (thrombocytopenia common but recovers rapidly; neutropenia usually less severe); postural hypotension; rash; GI toxicity; peripheral neuropathy (use with caution in patients with pre-existing neuropathy); exacerbation/development of heart failure (monitor patients with risk factors or pre-existing heart disease closely); steroid side effects; injection site reactions; haemorrhagic cystitis, if cyclophosphamide included;	
Anti- emetics:	moderately emetogenic (but anti-emetic doses of dexamethasone not required if dexamethasone included as part of treatment) For s/c route, avoid inserting a cannula: oral domperidone or metoclopramide to be taken before each bortezomib dose, and then as required.	
Extravasation:	bortezomib is a non-vesicant	
Regular Investigations:	FBC	Day 1
	U&Es	Day 1
	LFTs	Day 1
	MUGA/echo	only if concerned
	Blood pressure, lying and standing	Day 1 (and with every dose if sensori-motor problems)
	Serum and urine electrophoresis for para-protein quantification and Bence Jones protein	Day 1
	If on dexamethasone: Blood glucose and blood pressure	see Comments
Comments:	Blood glucose and blood pressure monitoring to be tailored according to individual patient needs, while on high dose dexamethasone. The IV route (IV bolus over 3 – 5 seconds) may be substituted if the s/c route is considered inappropriate (eg ITU patient), although note that this is associated with an increased incidence and severity of neuropathy-related toxicities. Also note that aseptics need to be informed of the change in route, as the formulation is different.	

Dose Modifications

Haematological Toxicity:	Withhold treatment if neutrophils < 0.5 x 10^9/L or platelets < 25 x 10^9/L. Once recovered, re-introduce with 25% bortezomib dose reduction (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). A reduced dose of cyclophosphamide should also be considered.

Renal Impairment: Consider a dose reduction of bortezomib if CrCl < 20ml/min.
For patients on dialysis, bortezomib should be given after the dialysis procedure, as dialysis may reduce bortezomib concentrations.

CrCl (ml/min)	Cyclophosphamide Dose
> 20	Give 100%
10 – 20	Omit cyclophosphamide until renal function improved, or give 75% dose
< 10	Omit cyclophosphamide until renal function improved, or give 50% dose

Hepatic Impairment: Use bortezomib with caution in mild to moderate hepatic impairment, and consider a dose reduction – clearance is mainly via hepatic metabolism.
If bilirubin > 1.5 x ULN, reduce bortezomib to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2, or further dose reduction to 0.5 mg/m^2, in subsequent cycles based on patient tolerability.

Sensory and Motor Neuropathy: Symptoms include numbness, tingling, burning, cramps, dysaesthesias.
This dose reduction schedule applies to new neuropathy symptoms (excludes pre-existing stable neuropathy):

Dose level	Dose of bortezomib (mg/m^2)
0	1.3
- 1	1.0
- 2	0.7

Severity of peripheral neuropathy	Modification of dose and regimen
Grade 1 (paraesthesia and/or loss of reflexes) with no pain or loss of function	For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule: no action, or reduce dose to 1.0mg/m^2
Grade 1 with pain or Grade 2 (interfering with function but not the activities of daily living)	Withhold bortezomib treatment until symptoms resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib treatment until symptoms resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule and maintain same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy which is life-threatening or leads to paralysis)	Discontinue bortezomib

Autonomic neuropathy, diarrhoea and hypotension:

This can come on insidiously and careful questioning of patients for symptoms of postural dizziness and unsteadiness is essential. The majority of patients on anti-hypertensive treatment will need their medication adjusting. Any patient who develops signs/symptoms of sensori-motor neuropathy should have lying and standing BP measurements at *each* dose of bortezomib, not just on day 1, even if asymptomatic.

Severity of autonomic neuropathy	**Modification of dose and regimen**
Grade 1: Occasional dizziness on standing (<3x/week)	No action
Grade 2: Regular dizziness on standing with no postural drop, or Grade 2 diarrhoea	Withhold bortezomib treatment until symptoms resolved to Grade 1. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 3: Postural drop of ≥20mm Hg with or without dizziness. Dizziness interfering with activities of daily living, or Grade 3 diarrhoea	Withhold bortezomib treatment until symptoms resolved to Grade 1. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 4: Syncopal episodes or other autonomic disturbance e.g. > Grade 3 diarrhoea	Discontinue bortezomib

Other Toxicities:

If any other Grade 3 or 4 non-haematological toxicity occurs, bortezomib should be withheld. Once recovered, bortezomib may be re-introduced with 25% dose reduction.

Injection site reactions (up to 5cm in diameter) are generally Grade 1 (red, dry or itchy) and last 3 – 5 days. Symptoms may be routinely managed with aloe vera gel, or other moisturisers.[1]

Patient Information:

Macmillan leaflets for Bortezomib, and Cyclophosphamide if included

References:

Richardson, PG et al; NEJM (2003); 348 (26): 2609 – 2617 (first relapse)
Evidence for 1st line use: San Miguel et al; NEJM 2008 ; 359 : 906 – 917
Kropff, M et al; Blood (ASH annual abstracts) 2005; 106: abs 2549 (cyclophos)
Bringhen, S et al ; Blood 2010 ; 116 : 4745 – 4753 (once weekly dosing)
Moreau, P et al ; Lancet 2011 ; 12 (5) : 431 – 440 (s/c route)
[1]No data, but information and advice from UCLH
Hainsworth, J et al; Cancer 2008; 113: 765 – 771 (once weekly)