PAD (Bortezomib, Doxorubicin and Dexamethasone)

An option for multiple myeloma patients, in the first-line setting, or in relapsed or primary refractory disease (bortezomib-naïve only), if suitable for bone marrow transplantation and require rapid cytoreduction e.g. plasma cell leukaemia

Drugs/Dosage:	**Bortezomib** (2.5mg/ml)	1.3mg/m^2	s/c bolus on Day 1, Day 4, Day 8 and Day 11
	Doxorubicin	9mg/m^2	IV on Day 1, Day 2, Day 3 and Day 4
	Dexamethasone	20 mg	po once daily on Days 1+2, 4+5, 8+9, 11+12

Administration:
Bortezomib given by subcutaneous bolus injection into the thigh or abdomen.
There must be a minimum of 72 hours between bortezomib doses.
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.
Doxorubicin IV bolus via fast-running infusion of sodium chloride 0.9%
Dexamethasone is to be taken in the morning with or after food.

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:
21 day cycle, usually for up to 4 cycles

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); alopecia; mucositis; cardiomyopathy (see Comments)
steroid side effects; injection site reactions; ovarian failure; infertility

Anti- emetics:
bortezomib 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.
Doxorubicin; ondansetron before each daily dose

Extravasation:
doxorubicin is a vesicant

Regular Investigations:	FBC	Day 1
	U&Es & LFTs	Day 1
	Serum sample for protein electrophoresis, paraprotein and serum free light chains	Day 1
	MUGA/echo	see Comments
	Blood pressure, lying and standing	Day 1 (and with every dose if sensori-motor problems)
	Blood glucose and blood pressure	see Comments

Reason for Update: repeated off-protocol usage	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 1	Date: 5.8.15
Supersedes: None	Review date: Sept 2017
Prepared by: S Taylor	Checked by: C Tucker

Comments: Blood glucose and blood pressure monitoring to be tailored according to individual patient needs, while on high dose dexamethasone.

Maximum cumulative dose of doxorubicin = 450 - 550mg/m^2
A baseline MUGA scan should be performed where the patient is considered at risk of having significantly impaired cardiac contractility. If ejection fraction is less than 50%, an alternative regimen should be given. MUGA scan should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

The IV route (IV bolus over 3 – 5 seconds) for bortezomib 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: Delay the next cycle if neutrophils < 1.0 x 10^9/L or platelets < 75 x 10^9/L.
Once recovered to above these levels, reduce bortezomib to 1.0 mg/m^2 and doxorubicin to 6mg/m^2/day for all subsequent cycles.
If further toxicity occurs where neutrophils < 1.0 x 10^9/L and platelets < 75 x 10^9/L on day 1, delay until as above, and then reduce bortezomib to 0.7mg/m^2 and doxorubicin to 4.5mg/m^2/day for all further cycles.

Renal Impairment: Consider a dose reduction of bortezomib if CrCl < 20ml/min.
For patients on dialysis, a reduced bortezomib dose may be required (monitor patients carefully). With regards to timing of doses, bortezomib is unlikely to be dialysed, and doxorubicin is not dialysed. However, ideally administer the cytotoxics on non-dialysis days, or after the dialysis procedure on dialysis days.
For patients on continuous renal replacement therapies (e.g. CVVH); bortezomib is unlikely to be dialysed and no dose reduction is required; doxorubicin has unknown dialysability. (St Helier NHS Trust advise that they do not stop filtration when administering these drugs)

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.

Bilirubin (µmol/l)	Doxorubicin Dose
20 – 50	Give 50%
51 – 85	Give 25%
> 85	Omit

Sensory and Motor Neuropathy: Symptoms include numbness, tingling, burning, cramps, dysaesthesias.
This bortezomib 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 bortezomib 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	Withhold bortezomib treatment until symptoms resolved

Hg with or without dizziness. Dizziness interfering with activities of daily living, or Grade 3 diarrhoea	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) to s/c bortezomib 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 Doxorubicin

References: Oakervee, H et al ; Br J Haem 2005 ; 129 : 755 – 762