PAD (bolus doxorubicin)

Indication: Myeloma

Prior to a course of treatment:

- Check calculated creatinine clearance – *see dose modification*.
- If there is a clinical suspicion of impaired cardiac check MUGA scan or echocardiogram. Note bortezomib and doxorubicin are contraindicated if severe cardiac impairment.
- Assess for peripheral neuropathy – may worsen on therapy; contraindicated if ≥ Grade 3 sensory
- Check FBC – neuts must be >1.0 , plats >75 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

On day 1 of each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function.
- Check FBC, U&Es, creat, LFTs – neuts must be > 1.0 and plats > 75 unless due to disease (*see dose modifications)*.
- Advise patient to drink 3 L fluid daily

On each day when bortezomib due

- Reassess for peripheral neuropathy – *see dose modifications*
- Check FBC – plats must be > 30 and neuts > 0.75. Give platelet transfusion and GCSF support as necessary during the cycle.

Cycle 1			
Bortezomib	1.3mg/m^2	SC	days 1, 4, 8, 11 *
Doxorubicin	9mg/m^2/day	IV bolus	days 1 – 4
Dexamethasone	40mg/day	PO	days 1, 4, 8, 11
Repeat cycle every 21 days for up to 4 cycles			

Antiemetic prophylaxis	Metoclopramide
Other medications	Allopurinol 300mg od (100mg if Cr.Cl <20ml/min) for cycle 1 Acyclovir 400mg bd

Dose modifications for neutropenia (unless due to disease)	
If neuts < 1.0 on day 1 of a cycle	Reduce to bortezomib 1.0mg/m^2 and doxorubicin 6mg/m^2 for all future cycles *
If further neuts < 1.0 on day 1 of cycle despite dose reduction	Reduce to bortezomib 0.7mg/m^2 and doxorubicin 4.5mg/m^2 for all future cycles *
If further neuts < 1.0 on day 1 of cycle despite dose reduction and/or GCSF	Further PAD may not be appropriate – discuss with consultant

* or give GCSF prophylaxis with all future cycles

Dose modifications due to thrombocytopenia (unless due to disease)

Plats < 30 when bortezomib due	Defer bortezomib or give platelet transfusion
If further plats < 50 on day 1 of cycle	Reduce to bortezomib 1.0mg/m^2 and doxorubicin 6mg/m^2 for all future cycles *
If further plats < 50 on day 1 of cycle despite dose reduction	Reduce to bortezomib 0.7mg/m^2 and doxorubicin 4.5mg/m^2 for all future cycles *
If further plats < 50 on day 1 of cycle despite dose reduction	Further PAD may not be appropriate – discuss with consultant

* or support with platelet transfusions

Bortezomib dose modifications for neurological toxicity

• 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/m^2
• 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 at <u>once</u> a week. If symptoms fail to resolve within 2 weeks – stop treatment
• 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 bortezomib 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.

Dose modifications for hepatic dysfunction

• Bilirubin 20 - 50μmol/l	Give 50% dose doxorubicin
• Bilirubin >50μmol/l	Give 25% doxorubicin
• Bilirubin > 85μmol/l	Omit doxorubicin

- 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

PAD toxicities

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

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