PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti-Cancer Therapy Protocol

Modified PAD (Bortezomib, Doxorubicin & Dexamethasone) Relapsed / Refractory Multiple Myeloma

PROTOCOL REF: MPHAPADR
(Version No. 1.0)

Approved for use in:

- For patients previously receiving this protocol at Aintree University Hospitals prior to Feb 2022
- Second or subsequent line treatment for transplant eligible multiple myeloma
- Extraosseous plasmacytoma, plasma cell leukaemia, plasma cell myeloma or solitary plasmacytoma of bone

Dosage:

Drug	Dose	Route	Frequency
Bortezomib	**1.3mg/m^2**	S/C injection	Days 1, 4, 8 & 11.
Doxorubicin	**36mg/m^2**	IV infusion	Day 1
Dexamethasone	**40mg**	Oral	**Cycle 1:** Day 1 to 4, 8 to 11 & 15 to18. **Cycle 2+:** Day 1 to 4 only

Cycle frequency of 21 days with a maximum of 6 cycles.

Administration:

- There must be a gap of at least 72 hours between bortezomib doses.

Emetogenic risk (if applicable):

moderately emetogenic.

Supportive treatments:

- Allopurinol 300mg daily *(first cycle only)*

- Dalteparin 5,000units SC daily *(first cycle only if high risk)*
- Ciprofloxacin 500mg BD *(first cycle only if high risk)*
- Aciclovir PO 400mg twice daily
- Chlorhexidine 0.2% mouthwash 10mL QDS
- Co-trimoxazole PO 480mg daily
- Fluconazole PO 50mg daily
- Omeprazole 20mg daily

Extravasation risk:

- Doxorubicin: vesicant
- Bortezomib: non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Interactions:

Doxorubicin

Care required with drugs that cause cardiotoxicity or that affect cardiac function (e.g. trastuzumab or felodipine). Also care required with drugs that cause hepatotoxicity. Doxorubicin undergoes metabolism via CYP450 so concomitant use of inhibitors may increase toxicity and inducers may reduce efficacy. Ciclosporin and cimetidine increase the AUC of doxorubicin; dose adjustments may be required. Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels. Doxorubicin is a potent, radio sensitising agent.

Bortezomib

A drug-drug interaction study assessing the effect of ketoconazole, a potent CYP3A4 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC increase of 35% (CI90% [1.032 to 1.772]) based on data from 12 patients. Therefore, patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir). A drug-drug interaction study assessing the effect of rifampicin, a potent CYP3A4 inducer, on the pharmacokinetics of bortezomib (injected intravenously), showed a mean bortezomib AUC reduction of 45% based on data from 6 patients. Therefore, the concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

For more detailed interactions please refer to the SPC and add a link to the appropriate SPC

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate

1	**Doxorubicin**	**36mg/m^2**	**IV**	100mL Sodium Chloride 0.9% IV over 30 minutes
	Bortezomib	**1.3mg/m^2**	**SC**	Subcutaneous bolus
1 to 4	**Dexamethasone**	**40mg**	**PO**	Mane
4	**Bortezomib**	**1.3mg/m^2**	**SC**	Subcutaneous bolus
8	**Bortezomib**	**1.3mg/m^2**	**SC**	Subcutaneous bolus
8 to11	**Dexamethasone**	**40mg**	**PO**	Mane
11	**Bortezomib**	**1.3mg/m^2**	**SC**	Subcutaneous bolus
15 to 18	**Dexamethasone**	**40mg**	**PO**	Mane

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, neuropathy, cardiotoxicity, nephrotoxicity.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Informed Consent	X							
Clinical Assessment	X	X	X	X	X	X	X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	X	X	X	Every cycle
Neurology Score	X	X	X	X	X	X	X	Every Cycle
CT scan	X							At the end of treatment and if clinically indicated
Imaging as per NICE/ network guidance	X							Repeat as clinically indicated
Dental assessment	X							
Serum Ig/ electrophoresis/ serum light chains (if indicated)	X	X	X	X	X	X	X	If clinically indicated
ECG	X							If clinically indicated
Blood pressure measurement	X							Repeat if clinically indicated
Respiratory Rate	X							If clinically indicated
Weight recorded	X	X	X	X	X	X	X	Every cycle
HbA1C & Blood glucose	X							Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L	Haemoglobin >80g/L

If cytopenias are thought to be caused by disease, then treatment delay may not be indicated – clinical decision

	ANC (x10^9/L)	Platelets (x10^9/L)	Dose adjustment
Doxorubicin	≥1.0	≥75	100% dose
	-	50-74	75% dose
	<1.0	<50	Delay 1 week and review

Bortezomib	Once the symptoms of the toxicity have resolved, bortezomib treatment may be reinitiated at a 25% reduced dose (1.3mg/m^2 reduced to 1.0mg/m^2; 1.0 mg/m^2 reduced to 0.7mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk

In the event of a patient experiencing haematological toxicity >Grade 3 (neutrophil <1 x10^9/L and platelets <75 x10^9/L) ON DAY 1 OF A CYCLE, the following dose reductions should be applied to all further cycles:

- Bortezomib: 1mg/m^2
- Doxorubicin: 24mg/m^2 total
- Dexamethasone: no reduction

If FURTHER haematological toxicity >Grade 3 (neutrophil <1 x10^9/L and platelets <50 x10^9/L) OCCURS ON DAY 1, then the following dose reduction should be applied to all further cycles:

- Bortezomib: 0.7mg/m^2
- Doxorubicin: 18mg/m^2 total)
- Dexamethasone: no reduction.

Dosing in renal and hepatic impairment:

Renal	Bortezomib	No dose adjustments required but bortezomib should be administered after dialysis.
	Doxorubicin	If patient having haemodialysis reduce to 75% dosing and increase if tolerated.

Hepatic	Bortezomib	Reduce to 0.7mg/m^2 if moderate to severe liver impairment present.
	Doxorubicin	• If bilirubin 20-50micromol/L: Reduce dose to 50% • If bilirubin 51-85micromol/L: Reduce dose to 25% • If bilirubin >85micromol/L: Doxorubicin not recommended • If AST 2-3 x ULN: Reduce dose to 75% • If AST >3 x ULN: Reduce dose to 50% • If Child-Pugh C: Doxorubicin not recommended

Peripheral Neuropathy:

Bortezomib	If there are symptoms of peripheral neuropathy the dose reduction schedule below must be invoked. Bortezomib should be stopped if symptoms or signs progress despite this	
	Grade 1 with no pain or loss of function	No dose adjustment
	Grade 1 with pain or grade 2	Reduce to 1.0mg/m2 or reduce to 1.3mg/m2 weekly (day 1 and 8)
	Grade 2 with pain or grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7mg/m^2 weekly (day 1 and 8)
	Grade 4 and/or severe autonomic neuropathy	Discontinue

References:

1. https://www.medicines.org.uk/emc bortezomib (accessed January 2022)
2. https://www.medicines.org.uk/emc Doxorubicin (accessed January 2022)

3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20: e201–08
4. BNF available via: https://bnf.nice.org.uk/
5. Aintree University Teaching Hospitals Modified PAD protocol

Circulation/Dissemination

Date added into Q-Pulse	22nd June 2022
Date document posted on the Intranet	N/A

Version History

		Author name and designation	Summary of main changes
Version 1.0	January 2022	**Daniel Dutton:** **Advanced Pharmacist Haemato-oncology**	New protocol created in preparation for Aintree HO merger.