Systemic Anti Cancer Therapy Protocol

VCD – Bortezomib, Cyclophosphamide & Dexamethasone Multiple Myeloma

PROTOCOL REF: MPHAVCDHA
(Version No: 1.0)

Approved for use in:

1. Bortezomib in combination with an alkylating agent (cyclophosphamide) and a corticosteroid is recommended as an option for the first-line treatment of multiple myeloma if:
    - high-dose chemotherapy with stem cell transplantation is considered inappropriate **and**
    - the person is unable to tolerate or has contraindications to thalidomide.
2. Relapsed or refractory multiple myeloma in patients who are at first relapse having received one prior line of therapy and who have undergone, or are unsuitable for, bone marrow transplantation

No blueteq registration is required for these indications

3. Relapsed or refractory multiple myeloma in patients who are at second or more relapse and who have not received prior bortezomib based therapy.

Blueteq registration is required for this indication

Twice Weekly Bortezomib Dosage:

Drug	Dose	Route	Frequency
Bortezomib	**1.3mg/m^2**	S/C	Days 1, 4, 8 and 11
Cyclophosphamide	**500mg**	Oral	Days 1, 8 and 15
Dexamethasone	**20mg**	Oral	Days 1, 4, 8 and 11

Maximum of 8 cycles (21 day cycle)

Once Weekly Bortezomib Dosage (for frailer patients):

Drug	Dose	Route	Frequency
Bortezomib	**1.6mg/m^2**	S/C	Days 1 and 8
Cyclophosphamide	**500mg**	Oral	Days 1, 8 and 15
Dexamethasone	**20mg**	Oral	Days 1, 8 and 15

Maximum of 8 cycles (21 day cycle).

Administration:

- There must be a gap of at least 72 hours between bortezomib doses.
- Cyclophosphamide should be taken on an empty stomach; that is an hour before food or two hours after food.

Anti-emetic risk:

Moderately emetogenic.

Supportive treatments:

- Allopurinol 300mg daily (first cycle only)
- Aciclovir PO 400mg twice daily
- Co-trimoxazole PO 480mg daily
- Nystatin 1ml topically four times a day **or** fluconazole PO 50mg daily
- Omeprazole 20mg daily

Extravasation risk:

Bortezomib – non-vesicant

Refer to the network guidance for the prevention and management of extravasation

Interactions:

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% ($CI_{90\%}$ [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.

Cyclophosphamide

Substances that reduce the efficacy of cyclophosphamide include:
aprepitant, bupropion, busulfan,ciprofloxacin, chloramphenicol, azole-antimycotics (e.g, fluconazole and itraconazole, CYP2B6 and CYP3A4 inhibitors (e.g. nevirapin and ritonavir): co-administration may reduce the efficacy of cyclophosphamide, prasugrel, sulfonamides, e.g. sulfadiazine, sulfamethoxazoel and sulfapyridine, thiotepa, grapefruit (fruit or juice), rifampicin, St. John’s wort.

An increased risk of side-effects may occur with:
Azathioprine: increased risk of hepatotoxicity (liver necrosis), chloral hydrate, cimetidine, disulfiram, glyceraldehyde, protease inhibitors, saquinavir, rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, corticosteroids and dabrafenib.

There is an increased risk of cardiotoxicity when cyclophosphamide is co-administered with: Anthracyclines, mitomycin, cytarabine, pentostatin and radiation therapy.

Twice Weekly Bortezomib Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Bortezomib**	**1.3mg/m²**	**S/C**	
	Cyclophosphamide	**500mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	
4	**Bortezomib**	**1.3mg/m²**	**S/C**	
	Dexamethasone	**20mg**	**PO**	
8	**Bortezomib**	**1.3mg/m²**	**S/C**	

	Cyclophosphamide	**500mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	
11	**Bortezomib**	**1.3mg/m^2**	**S/C**	
	Dexamethasone	**20mg**	**PO**	
15	**Cyclophosphamide**	**500mg**	**PO**	

Once Weekly Bortezomib Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Bortezomib**	**1.6mg/m^2**	**S/C**	
	Cyclophosphamide	**500mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	
8	**Bortezomib**	**1.6mg/m^2**	**S/C**	
	Cyclophosphamide	**500mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	
15	**Cyclophosphamide**	**500mg**	**PO**	
	Dexamethasone	**20mg**	**PO**	

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea and peripheral neuropathy.

Investigations and treatment plan:

	Pre	Cycle 1+ D1	Cycle 1 D2	Cycle 1+ D4	Cycle 1+ D8	Cycle 1+ D11	Ongoing
Informed consent	X						
Clinical Assessment	X	X					
SACT Assessment (including performance status toxicity assessment)		X		X	X	X	
FBC	X	X					
U&E, LFTs and calcium profile	X	X					
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X						
Dental Assessment	X						If clinically indicated
HbA1c and glucose	X						Repeat if clinically indicated
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X					
Neurological assessment (for neuropathy) – performed at medical review	X	X					
Blood pressure	X	X		X	X	X	
Cardiac monitoring		X	X				To be considered, discuss with consultant. Would need in patient admission
Weight	X	X					
Height	X						
Pregnancy test	X						If clinically indicated
Imaging as per NICE/network guidance and clinical indication	X						To restage as indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Neutrophils ($x10^9$/L)		Platelets ($x10^9$/L)	Recommendation
≥ 1.0	and	≥ 70	Proceed
0.75 – 1.0	or	30 to 70	Delay cyclophosphamide 1 week (continue dexamethasone and bortezomib). Restart at same dose when neutrophils and platelets recovered as above. If recurrent, i.e. if neutrophils <$1.0x10^9$/L and platelets < $50x10^9$/L on day 1 of subsequent cycles (when previously > than these levels), delay cyclophosphamide and consider dose reduction of cyclophosphamide. If the patient was receiving 500 mg weekly, reduce to 400 mg, if 400 mg reduce to 300 mg, if 300 mg reduce to 200 mg. Consider adding G-CSF weekly if neutropenia
<0.75	or	<30	Withhold chemotherapy until recovery. Once recovered, reduce bortezomib dose by one level and consider reducing cyclophosphamide dose as above. (1.6mg/m^2 dose reduced to 1.3mg/m2, 1.3mg/m2 dose reduced to 1.0mg/m2, 1.0mg/m2 dose reduced to 0.7mg/m2 Discontinue treatment if still cytopenias on lowest possible dose.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Dosing in renal and hepatic impairment:

Bortezomib	
Renal	
No dose adjustments required but bortezomib should be administered after dialysis.	
Hepatic	
Liver function	Dose adjustment
Moderate to severe impairment	Reduce to 0.7mg/m^2

Cyclophosphamide	
Renal	
CrCl (ml/min)	Dose
10-29	Consider 75% of dose
<10 or haemodialysis	Not recommended. If unavoidable consider 50% of dose.
Liver	
Severe liver dysfunction	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	Dose adjustment
Grade 1 with pain or grade 2	Reduce to 1.0mg/m^2 or reduce to 1.3mg/m^2 weekly (day 1 and 8)
Grade 2 with pain of 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 March 2020)
2. https://www.medicines.org.uk/emc cyclophosphamide (accessed March 2020)
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. Cheshire and Merseyside Strategic Clinical Network VCD Protocol
5. NICE. Bortezomib and thalidomide for the first-line treatment of multiple myeloma. TA228. July 2011.