PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

CVD – Cyclophosphamide, Bortezomib and Dexamethasone Low Dose Protocol AMYLOIDOSIS

PROTOCOL REF: MPHACVDLHA
(Version No. 1.1)

Approved for use in:

- This is the ***low dose*** *CVD* protocol; please ensure you have the correct protocol before proceeding.
- This protocol is for patients with advanced Mayo Stage III Amyloidosis (defined as NTproBNP >1000 pMol/L and some patients with SBP <100mm of Hg) as per recommendation from the National Amyloidosis Centre (NAC).

This protocol should be initiated under cardiac monitoring for the first dose of bortezomib (24-48 hours from day 1)

Blueteq registration is not required

Dosage:

Drug	Dose	Route	Frequency
Bortezomib	**1mg/m^2***	S/C	Days 1, 8, 15 and 22
Cyclophosphamide	**350mg/m^2 (max 500mg)**	Oral	Days 1, 8, 15 and 22
Dexamethasone	**20mg**	Oral	**Cycle 1:** Days 1 and 8 only **Subsequent cycles (if tolerated):** Days 1, 2, 8, 9, 15, 16, 22 and 23.

*Consider increasing bortezomib to 1.3mg/m^2 from cycle 1 day 8 if day 1 was well tolerated. In selected patients, depending on tolerance, if there is less than a partial response by end of cycle 1 or less than a very good partial response by end of cycle 2, bortezomib dose can be further increased to 1.6mg/m^2.

Maximum of 8 cycles (35 day cycle).

Administration and counselling points:

- There must be a gap of at least 72 hours between bortezomib doses.
- Cyclophosphamide should be taken on an empty stomach, an hour before food or two hours after food.
- If SBP <90mmHg, please consider addition of oral midodrine 2.5 mg BD (increase as needed to maximum of 20 mg TDS) to support the blood pressure before commencing therapy and to allow for adequate diuresis.
- All patients will receive a minimum of three cycles of CVD in the absence of unacceptable toxicity or poor tolerability.
- Patients who achieve a complete response (CR) or a very good partial response (VGPR) will continue for one more cycle after achieving response (e.g. if patient has achieved CR or VGPR at cycle 1 or 2, they will finish three cycles and stop. If they achieve CR or plateau after cycle 3, they will receive one more cycle after achieving CR or plateau).
- Patients with ongoing reduction in dFLC should continue until they achieve VGPR or complete response or to a maximum of 8 cycles. Note: dLFC is blood test which show the difference between the involved and uninvolved free light chains.
- Patients who have not responded to treatment by end of cycle 2 will need regime modification after discussion with the National Amyloid Centre or as per local practice.
- **Sudden Cardiac Death:** patients with proven/suspected cardiac amyloid have a risk of fatal arrhythmias in the early days/weeks of treatment. Patients should be counselled appropriately for this and considered for telemetry at treatment initiation.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

- Allopurinol 300mg PO daily (first cycle only)
- Aciclovir PO 400mg twice daily
- Co-trimoxazole PO 480mg daily
- Nystatin 1mL oral suspension four times a day **or** fluconazole PO 50mg daily

- Omeprazole 20mg PO daily
- Metoclopramide 10mg PO three times a day if needed
- Doxycycline 100mg PO twice daily at clinician discretion if cardiac amyloid

Extravasation Risk:

Bortezomib: Non vesicant

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

Interactions:

Bortezomib

- Strong CYP3A4 inhibitors (ketoconazole, ritonavir) – monitor closely as potential increase exposure to bortezomib
- Strong CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) – not recommended as efficacy of bortezomib 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, sulfamethoxazole 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.
For more detailed interactions please refer to the SPC.

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
	Creatinine Clearance (mL/min)	**Modification**
Cyclophosphamide	10 - 29	Consider 75% dose ie 250mg/m^2
	<10 or haemodialysis	Not recommended. If unavoidable consider 50% of dose.
Bortezomib	No dose adjustments required but bortezomib should be administered after dialysis.	

Hepatic Dose Modifications		
	Impairment	**Modification**
Cyclophosphamide	Severe	Not recommended
Bortezomib	Bilirubin >1.5xULN	Reduce to 0.7mg/m^2. Consider dose escalation or further reduction in subsequent cycles

Treatment schedule Cycle 1:

Day	Drug	Dose	Route
1	**Bortezomib**	**1mg/m^2**	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**
	Dexamethasone	**20mg**	**PO**
8	**Bortezomib**	**1mg/m^2***	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**
	Dexamethasone	**20mg**	**PO**
15	**Bortezomib**	**1mg/m^2***	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**
22	**Bortezomib**	**1mg/m^2***	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**

Treatment schedule Cycle 2+ (if tolerated dexamethasone):

Day	Drug	Dose	Route

1	**Bortezomib**	**1mg/m^2****	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**
	Dexamethasone	**20mg**	**PO**
2	**Dexamethasone**	**20mg**	**PO**
8	**Bortezomib**	**1mg/m^2***	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**
	Dexamethasone	**20mg**	**PO**
9	**Dexamethasone**	**20mg**	**PO**
15	**Bortezomib**	**1mg/m^2***	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**
	Dexamethasone	**20mg**	**PO**
16	**Dexamethasone**	**20mg**	**PO**
22	**Bortezomib**	**1mg/m^2***	**S/C**
	Cyclophosphamide	**350mg/m^2 (max 500mg)**	**PO**
	Dexamethasone	**20mg**	**PO**
23	**Dexamethasone**	**20mg**	**PO**

Main toxicities:

Bortezomib
Bone marrow suppression (anaemia, thrombocytopenia, neutropenia), herpes zoster, herpes simplex, hepatitis B reactivation, pneumonia, fungal infection, leukopenia, lymphopenia, reduced appetite, dehydration, hypokalaemia, hyponatraemia, hypocalcaemia, dehydration, mood disorder, anxiety, sleep disorders, neuropathy, peripheral neuropathy, neuralgia, dysaesthesia, lethargy, syncope, conjunctivitis, eye swelling, vertigo, hypotension, hypertension, epistaxis, nausea, vomiting, diarrhoea, constipation, rash, dry skin, renal impairment, fatigue, seizures (very rare), progressive multifocal leukoencephalopathy (PML)
Cyclophosphamide
Infection, myelosuppression, immunosuppression, haemolytic uraemic syndrome, abnormal hepatic function, alopecia, cystitis, haemhorragic cystitis, haematuria, impairment of spermatogenesis, fever, asthenia, mucosal inflammation

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 (including performance status toxicity assessment)	X	X					
SACT Assessment (including 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						
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:

Cycle can proceed if:

ANC ≥ 1.0 x10^9/L	Platelets ≥ 70 x10^9/L

Neutrophils (x10^9/L)		Platelets (x10^9/L)	Recommendation
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 cytopenic 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.

Non- Haematological toxicity:

Bortezomib treatment must be withheld at the onset of any Grade 3 non-haematological excluding neuropathy as (further information on management of neuropathy below). Once the symptoms of the toxicity have resolved, bortezomib treatment may be re-

initiated at a 25% reduced dose (1.3 mg/m2 reduced to 1.0 mg/m2; 1.0 mg/m2 reduced to 0.7 mg/m2). 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.

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 June 2023)
2. https://www.medicines.org.uk/emc cyclophosphamide (accessed June 2023)
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. National Amyloid Centre. Low dose Cyclophosphamide-Bortezomib-Dexamethasone protocol (35 day cycle). https://www.ucl.ac.uk/drupal/site_amyloidosis/sites/amyloidosis/files/low_dose_CVD_protocol.pdf Accessed June 2023.

Circulation/Dissemination

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Version History

		Author name and designation	Summary of main changes
July 2020	V1.0	**Aileen McCaughey – Haematology Pharmacist**	**New protocol**
July 2023	V1.1	**Jennifer Gibson – Principal Pharmacist Haematology**	**Three yearly review – transferred to new template,**