PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Bortezomib, Thalidomide and Dexamethasone (VTD) MYELOMA

PROTOCOL REF: MPHAVTDHA
(Version No. 1.1)

Approved for use in:

Induction treatment of untreated multiple myeloma in patients who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Blueteq submission is not required

Dosage:

Drug	Dosage	Route	Frequency
Bortezomib	**1.3mg/m^2**	S/C	Day 1, 4, 8 and 11*
Thalidomide	**50mg once daily at night**** Titrate up to max daily dose of 200mg nocte	Oral	Days 1 to 28 (continuous)
Dexamethasone	**40mg*****	Oral	Days 1 to 4 and days 8 to 11

*Bortezomib can be administered weekly on days 1, 8, 15 and 22 of a 28 day cycle if they cannot tolerate twice weekly dosing above.

** Thalidomide should be initiated at 50mg for the first 2 weeks and can be titrated to 100mg from day 15 to 28 of cycle 1 if appropriate. Thereafter this can be titrated to 200mg if appropriate at clinician discretion.

*** Dexamethasone dose may be reduced if appropriate at clinician discretion.

Cycle length 28 days. Max 6 cycles

Administration and counselling points:

- VTE prophylaxis is required throughout treatment due to thrombotic effect of thalidomide.
- Dexamethasone tablets should be taken in the morning after food.
- At least 72 hours should elapse between bortezomib administrations.
- Bortezomib should be administered subcutaneously through the thighs (right or left) or abdomen (right or left). The solution should be injected subcutaneously, at a 45-90° angle. Injection sites should be rotated for successive injections.
- Thalidomide should be taken as a single dose at bedtime, to reduce the impact of somnolence. Capsules should not be opened or crushed.
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the pregnancy prevention programme (PPP) and provide patients with appropriate patient educational brochure and patient card.

Pregnancy Prevention Programme (PPP):

Due to the increased risk of birth defects associated fetal exposure to thalidomide the following should be adhered to:

- A Treatment Initiation Form (TIF) must be completed prior to treatment initiation (cycle 1) with thalidomide
- A Prescription Authorisation Form (PAF) must be completed by the prescriber for each supply of thalidomide. This must be approved by a pharmacist when verifying each prescription and confirmation of dispensing completed by the relevant dispensing pharmacy. Supply must be completed within 7 days of the prescription generation.
- A maximum of 3 months can be supplied for men or women of non-child bearing potential
- A maximum of 1 month can be supplied for women of child bearing potential. A negative pregnancy test must be confirmed within 3 days of prescription generation.

Emetogenic risk:

Mildly emetogenic.

Supportive Medication:

- Allopurinol 300mg PO once daily (cycle 1 only)
- Aciclovir oral 400mg PO twice a day
- Co-trimoxazole 480mg PO once daily
- Metoclopramide 10mg PO three times a day when required for up to 7 days
- Nystatin oral suspension 1mL four times daily or fluconazole 50mg PO once daily (higher risk patients only)
- Omeprazole 20mg PO once daily
- VTE prophylaxis:
    - Dalteparin 5,000 units subcutaneous injection daily (or alternative prophylactic low molecular weight heparin (LMWH))
    - Therapeutic dose LMWH in high risk patients. Patients may continue previously established DOAC treatment or be switched to a LMWH.
    - Aspirin oral 75mg daily (for those patients who decline LMWHs or for those deemed to be low risk on long term treatment)

Dosing in renal and hepatic impairment:

Thalidomide
Thalidomide Celgene has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.

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

Extravasation Risk:

Bortezomib – non-vesicant

Interactions:

Thalidomide

- Thalidomide has sedative properties, thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H_1antihistamines, opiate derivatives, barbiturates and alcohol. Use with caution.
- Thalidomide may cause bradycardia. Use with caution alongside other medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.
- Use with caution alongside other medicinal products known to be associated with peripheral neuropathy (e.g. vincristine and bortezomib).

Bortezomib

- Monitor closely for side effects when giving bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) due to potential for increased exposure to bortezomib.
- 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

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**40mg**	**PO**	Mane **days 1 to 4** and **days 8 to 11** (Administer on day 1 and give remainder as TTO)
	Thalidomide	**50 to 200mg**	**PO**	Nocte days 1 to 28 (give as TTO)
	Bortezomib	**1.3mg/m^2**	**S/C**	
4	**Bortezomib**	**1.3mg/m^2**	**S/C**	
8	**Bortezomib**	**1.3mg/m^2**	**S/C**	
11	**Bortezomib**	**1.3mg/m^2**	**S/C**	

Main toxicities:

Bortezomib
Infections, herpes zoster reactivation, herpes simplex, pneumonia, thrombocytopenia, neutropenia, anaemia, leukopenia, lymphopenia, reduced appetite, hypokalaemia, hyponatraemia, dehydration, hypocalcaemia, mood disturbance, sleep disturbance, anxiety, neuropathies, peripheral sensory neuropathy, fatigue, eye swelling, conjunctivitis, vertigo, hypo/hyper-tension, nausea, vomiting, constipation, diarrhoea, abnormal hepatic enzymes, rash, pruritus, muscle pain/weakness, weight loss, hepatitis B reactivation. Rare – seizures (review if additional risk factors for seizures)
Thalidomide
Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, drowsiness, venous thromboembolism, peripheral neuropathy, injection site reactions, infusion related reactions, high blood sugars, teratogenicity

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					Every cycle
Thalidomide prescription authorization form		X					Every cycle
SACT Assessment (including performance status toxicity assessment)		X		X	X	X	Every cycle
FBC, U&E, LFTs and calcium profile	X	X					Every cycle
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					Every cycle
Neurological assessment (for neuropathy) – performed at medical review	X	X					Every cycle
Blood pressure	X	X		X	X	X	
Weight	X	X					Every cycle
Height	X						
Pregnancy test	X						If clinically indicated. Repeat each cycle if women of childbearing potential
Imaging as per NICE/network guidance and clinical indication	X						To restage as indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 0.5 x 10^9/L	Platelets ≥ 25 x 10^9/L

Once the symptoms of the toxicity have resolved, bortezomib treatment may be re-initiated at a 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/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.

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:

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 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

Thalidomide	
Severity of neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no loss of function	Consider reducing dose if symptoms worsen. Dose reduction is not necessarily followed by improvement of symptoms.
Grade 2 (interfering with function but not with activities of daily living)	Reduce dose / interrupt treatment and continue to monitor. Discontinue if no improvement or continued worsening of the neuropathy. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted.
Grade 3 (interfering with activities of daily living) or Grade 4 (disabling neuropathy)	Discontinue treatment

References:

1. https://www.medicines.org.uk/emc Bortezomib (updated Aug 2022, accessed July 2023)
2. https://www.medicines.org.uk/emc Thalidomide (updated March 2022, accessed July 2023)
3. Supplement to: 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. NICE: TA311: Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplant. Published April 2014.

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

		Author name and designation	Summary of main changes
June 2020	1.0	**Aileen McCaughey – Advanced Pharmacist HO**	**New protocol**
Aug 2023	1.1	**Jennifer Gibson – Principal Pharmacist HO**	**3 yearly review.** **Transferred to new template.** **Added PPP section.** **Added administration detail re thalidomide and bortezomib. Added thalidomide dose titration information.**