PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

BORTEZOMIB, MELPHALAN & PREDNISOLONE (VMP) MULTIPLE MYELOMA

PROTOCOL REF: MPHABMPMM
(Version No. 1.0)

Approved for use in:

The following patients with multiple myeloma:

- Patients who have received one prior line of therapy and have undergone, or are unsuitable for, a bone marrow transplant **(NICE TA129)**.Treatment should only be continued after 4 cycles if there is a complete or partial response (ie reduction in serum M protein of ≥50% or if not measurable then an appropriate alternative biochemical measure of response)..
- Patients with untreated myeloma if high dose chemotherapy with stem cell transplant is considered inappropriate and thalidomide is contraindicated or not tolerated **(NICE TA228)**.

Blueteq submission is not required

Dosage:

Drug	Dosage	Route	Frequency
Bortezomib	**1.3mg/m^2**	S/C	Day 1, 8, 15, 22
Melphalan	***7mg/m^2**	PO	Days 1 to 4
Prednisolone	****60mg/m^2**	PO	Days 1 to 4

*Can be increased to 9mg/m2 at clinician discretion.

**Prednisolone dose can be adjusted at clinician discretion. Consider capping at 100mg.

Cycle length every 35 days. Max 8 cycles.

Administration and counselling points:

- Prednisolone should be taken in the morning with food to avoid sleep disturbance and gastric irritation.
- 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.

Emetogenic risk:

Mildly emetogenic.

Supportive Medication:

- Allopurinol 300mg oral once daily (cycle 1 only)
- Aciclovir oral 400mg oral twice a day
- Co-trimoxazole 480mg oral once daily
- Metoclopramide 10mg oral three times a day when required for up to 7 days
- Nystatin oral suspension 1mL four times daily or fluconazole 50mg oral once daily (higher risk patients only)
- Omeprazole 20mg oral once daily

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
Bortezomib	No dose adjustments required but bortezomib should be administered after dialysis.	
Melphalan	**Creatinine Clearance (mL/min)**	**Dose Adjustment**
	30 to 50	Consider 75% dose at clinician discretion
	<30	Clinician discretion

	Hepatic Dose Modifications	
Bortezomib	**Liver function**	**Dose adjustment**
	Moderate to severe impairment (bilirubin >1.5xULN)	Reduce to 0.7mg/m^2
Melphalan	No recommendations, if excess toxicity reduce dose for subsequent cycles	

Extravasation Risk:

Bortezomib – non-vesicant

Interactions:

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

Melphalan

No interactions of note with low dose oral melphalan.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Prednisolone**	**60mg/m^2**	**PO**	Mane day 1 to 4 (TTO)
	Melphalan	**7mg/m^2**	**PO**	Daily days 1 to 4 (TTO)
	Bortezomib	**1.3mg/m^2**	**S/C**	
8	**Bortezomib**	**1.3mg/m^2**	**S/C**	
15	**Bortezomib**	**1.3mg/m^2**	**S/C**	
22	**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)
Melphalan
Bone marrow suppression, anaemia, thrombocytopenia, neutropenia, nausea, vomiting, diarrhoea, fatigue, raised urea

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
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 ≥ 1.0 x 10^9/L	Platelets ≥ 70 x 10^9/L

Toxicity	Posology modification or delay
Haematological toxicity during a cycle • If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle.
• If platelet counts ≤ 30 x 10^9/L or ANC ≤ 0.75 x 10^9/L on a bortezomib dosing day (other than day 1)	Bortezomib therapy should be withheld
• If several bortezomib doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	Bortezomib dose should be reduced by 1 dose level (from 1.3 mg/$m^2$to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2)
Grade ≥ 3 non-haematological toxicities	Bortezomib therapy should be withheld until symptoms of the toxicity have resolved to Grade 1 or baseline. Then, bortezomib may be reinitiated with one dose level reduction (from 1.3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0.7 mg/m^2). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify

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:

Non haematological toxicities should have resolved to Grade 1 or baseline.

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

References:

1. https://www.medicines.org.uk/emc Bortezomib (updated Aug 2022, accessed Aug2023)
2. 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.
3. NICE: TA311: Bortezomib for induction therapy in multiple myeloma before high dose chemotherapy and autologous stem cell transplant. Published April 2014.
4. NICE TA288. Bortezomib and Thalidomide for the first line treatment of multiple myeloma. July 2011.
5. Melphalan, Bortezomib, Prednisolone v2.1. Thames Valley Strategic Clinical Network. June 2020. https://nssg.oxford-haematology.org.uk/myeloma/pdf-protocols/MM-19-mel-bor-pred.pdf

Circulation/Dissemination

Date added into Q-Pulse	1st February 2024
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
Oct 2023	1.0	**Jennifer Gibson Principal Pharmacist HO**	**New protocol**