Bortezomib, Melphalan and Prednisolone (VMP)

Indication

First line treatment of multiple myeloma in patients who are intolerant of or have contraindications to thalidomide, and are unsuitable for bone marrow transplantation.

(NICE TA228)

ICD-10 codes

Codes with a pre-fix C90

Regimen details

Day	Drug	Dose	Route
1,8,15 and 22	Bortezomib	1.3 mg/m^2	SC
1-4	Melphalan	9 mg/m^2	PO
1-4	Prednisolone	60 mg/m^2 OM	PO

* Consider reducing melphalan to 7mg/m^2 if significant co-morbidities, poor performance status.

At least 72 hours must elapse between doses of bortezomib

Cycle frequency

35 days

Number of cycles

Maximum of 8 cycles

Administration

Bortezomib is administered by SC injection. At least 72 hours must elapse between doses of bortezomib.

Melphalan is available as 2mg tablets. Melphalan tablets are cytotoxic. Tablets should be swallowed whole with a glass of water and should not be broken, crushed or chewed.

Prednisolone is available as 5mg and 25mg tablets. The dose should be taken once a day in the morning, with or after food.

Pre-medication

Nil

Emetogenicity

This regimen has moderate emetogenic potential.

Additional supportive medication

H_2 antagonist or proton pump inhibitor
Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for the first cycle only
Bisphosphonates as per local policy
Antifungal, antiviral and PCP prophylaxis as per local policy
Loperamide if required.

Extravasation

Bortezomib is neutral (group 1).

Investigations – pre first cycle

Investigation	Validity period
FBC and film	7 days
Clotting screen	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Blood pressure (lying and standing)	On day 1

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)
Bone marrow aspirate and trephine
Consider baseline echocardiogram (risk of bortezomib-induced cardiomyopathy)

Investigations – pre subsequent cycles

Investigation	Validity period
FBC*	96 hours
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Blood pressure	On day 1

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)

* In addition FBC is required on days 8, 15 and 22 within 24 hours of bortezomib administration.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 70 x 10^9/L
Creatinine clearance	≥ 50mL/min
Bilirubin	< 1.5 x ULN

Dose modifications

Doses of bortezomib are modified according to the following table:

Full dose	1.3mg/m^2
First dose reduction	1.0mg/m^2
Second dose reduction	0.7mg/m^2
Third dose reduction	0.5 mg/m^2

- **Haematological toxicity**

Treatment on day 1 should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 70 x 10^9/L.

If cytopenia considered to be disease related, treatment may be given at consultant discretion.

On days 8, 15 and 22 if neutrophils ≤ 0.75 x 10^9/L **or** platelets ≤ 30 x 10^9/L withhold bortezomib. If several doses within a cycle are withheld, consider dose reduction of bortezomib for subsequent cycles.

If prolonged grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding, reduce melphalan dose to 75% for subsequent cycles.

- **Renal impairment**

Bortezomib:
If CrCl < 20mL/min use with caution. If patient is on dialysis, bortezomib should be administered after dialysis.

Melphalan:

CrCl (mL/min)	**Melphalan dose**
> 50	100%
10-50	75%
< 10	50%

- **Hepatic impairment**

Bortezomib:
If bilirubin > 1.5 x ULN consider starting dose of 0.7mg/m^2 for cycle 1. For subsequent cycles consider increasing dose to 1mg/m^2 or reducing dose to 0.5mg/m^2 according to tolerability.

There are no dose modification recommendations for melphalan in hepatic impairment, however, if excess toxicity experienced, consider dose reduction for subsequent cycles.

- **Other toxicities**

Neuropathy:

Grade	**Bortezomib dose**
Grade 1 with no pain	100%
Grade 1 with pain or grade 2 but not interfering with daily living	1.0mg/m^2
Grade 2 with pain or grade 3	Withhold until symptoms resolved Restart at dose of 0.7mg/m^2
Grade 4	Discontinue

Any other ≥ grade 3 non-haematological toxicity: withhold bortezomib until ≤ grade 1. Recommence with 1 level dose reduction.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Tumour lysis syndrome
Cardiac failure
Pulmonary hypotension
Acute respiratory distress syndrome

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Nausea and vomiting
Fatigue
Peripheral neuropathy
Headache
Rash

- **Other side effects**

Altered LFTs
Decreased appetite
Confusion
Depression

Significant drug interactions – for full details consult product literature/ reference texts

Bortezomib:

Antihypertensives: Risk of additive hypotensive effect. Close monitoring of BP is required.
Oral anti diabetic agents: Hyper and hypo glycermia has been reported. Close monitoring of blood glucose is required.
Ciclosporin: increased risk of severe neuropathy: avoid concomitant use.
Vitamin C: reduced efficacy of bortezomib: avoid concomitant use.
Cytochrome P34A inhibitors (ketoconazole and other azole antifungals, clarithromycin, erythromycin) may increase bortezomib levels: avoid concomitant use.
Cytochrome P34A inducers (rifampicin, carbamazepine, phenytoin, St Johns Wort) may reduce bortezomib levels: avoid concomitant use.

Additional comments

References

- Summary of Product Characteristics: Bortezomib (Janssen) accessed 21 September 2015 via www.medicines.org.uk
- Summary of Product Characteristics: Melphalan (Aspen) accessed 21 September 2015 via www.medicines.org.uk
- National Institute for Clinical Excellence. Technology Appraisal Guidance 228. Accessed 21 September 2015 via www.nice.org.uk
- Morabito et al. Bortezomib, melphalan, prednisone (VMP) versus melphalan, prednisone, thalidomide (MPT) in elderly newly diagnosed multiple myeloma patients: a retrospective case-matched study/ Am J Hematology. 2014: 89 (4); 355-362
- Petrucci et al. Bortezomib, melphalan and prednisone in elderly patients with relapsed/refractory multiple myeloma. Cancer. 2012: 119 (5); 971-977

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