Bortezomib, Cyclophosphamide and Dexamethasone (VCD)

Indication

First line treatment of multiple myeloma in patients who are unable to tolerate thalidomide and are unsuitable for stem cell transplantation.

(NICE TA228)

ICD-10 codes

Codes with a pre-fix C90

Regimen details

21 day cycle – twice weekly bortezomib

Day	Drug	Dose	Route
1, 4, 8 and 11	Bortezomib	1.3 mg/m^2	SC
1, 8 and 15	Cyclophosphamide	500mg OM	PO
1 and 2, 4 and 5, 8 and 9, 11 and 12	Dexamethasone	20mg OM	PO

At least 72 hours must elapse between doses of bortezomib

35 day cycle – weekly bortezomib

Day	Drug	Dose	Route
1, 8, 15 and 22	Bortezomib	1.3 mg/m^2	SC
1, 8, 15 and 22	Cyclophosphamide	500mg OM	PO
1and 2, 8 and 9, 15 and 16, 22 and 23	Dexamethasone	20mg OM	PO

Cycle frequency

As above

Number of cycles

Maximum of 8 cycles

Administration

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

Cyclophosphamide is available as 50mg tablets. Tablets should be swallowed whole with a full glass of water. Cyclophosphamide should be taken early in the day and patients encouraged to maintain a good fluid intake. The aim is to reduce the amount of drug remaining in the bladder overnight.

Dexamethasone is available as 500microgram and 2mg tablets. The dose should be taken in the morning, with or after food.

Pre-medication

Nil

Emetogenicity

This regimen has low 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
Glucose	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 within 24 hours of each 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	≥ 75 x 10^9/L
Creatinine clearance	≥ 20mL/min
Bilirubin	< 1.0 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

- **Haematological toxicity**

Treatment on day 1 should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L.

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

On day of bortezomib administration, 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 neutropenia or thrombocytopenia omit cyclophosphamide and restart when neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L. Consider dose reduction to 80% dose.

- **Renal impairment**

Bortezomib:

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

Cyclophosphamide:

CrCl (mL/min)	**Cyclophosphamide dose**
>20	100%
10-20	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.

Cyclophosphamide:

Cyclophosphamide is not recommended if bilirubin > 1.0 x ULN or AST/ALT > 3 x ULN (consultant decision).

- **Other toxicities**

Bortezomib:

Toxicity	**Definition**	**Bortezomib dose**
Neuropathy	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 treatment until ≤ grade 1. Recommence with 1 level dose reduction of bortezomib and 80% dose cyclophosphamide.

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

- **Serious side effects**

Myelosuppression
Thromboembolism
Tumour lysis syndrome
Orthostatic hypotension
Cardiotoxicity
Psychosis

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Nausea and vomiting
Fatigue
Peripheral neuropathy
Autonomic neuropathy
Rash
Haemorrhagic cystitis
Insomnia
High blood sugars
Fluid retention
Dyspepsia
Blepharitis

- **Other side effects**

Altered LFTs
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 glycaemia 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.

Cyclophosphamide:
Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible – avoid
Itraconazole: may increase adverse effects of cyclophosphamide

Phenytoin: reduced absorption - may need to increase dose of phenytoin
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Additional comments

References

- Summary of Product Characteristics: Bortezomib (Janssen) accessed 20 July 2016 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide accessed 20 July 2016 via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
- National Institute for Clinical Excellence. Technology Appraisal Guidance 228. Accessed 20 July 2016 via www.nice.org.uk
- Hainsworth J. et al. Weekly Treatment with Bortezomib for patients with Recurrent or Refractory Multiple Myeloma. Cancer 2008; 113: 765 – 771
- Davies FE, Wu P, Jenner M, Srikanth M, Saso R, Morgan GJ. The combination of cyclophosphamide, velcade and dexamethasone induces high response rates with comparable toxicity to velcade alone and velcade plus dexamethasone. Haematologica 2007 Aug;92(8):1149-50.

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