

## Bortezomib, Thalidomide and Dexamethasone (VTD) – 28 day

### Indication

First line treatment of multiple myeloma in patients who are eligible for stem cell transplantation.

(NICE TA311)

### 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 <sup>2</sup>	SC
1-28 (continuously)	Thalidomide	50mg ON*	PO
1,2 and 8,9 and 15,16 and 22,23	Dexamethasone	20mg OM	PO

\*Thalidomide may be increased to 100mg ON during cycle 1 if tolerated and to 200mg ON for subsequent cycles.

**At least 72 hours must elapse between doses of bortezomib**

### Cycle frequency

28 days

### Number of cycles

Maximum of 6 cycles (response should be assessed after 4 cycles and an additional 2 cycles may be given)

### Administration

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

Thalidomide is available as 50mg capsules. The capsules should be swallowed whole in the evening.

Women of child bearing potential must have a **NEGATIVE PREGNANCY TEST** within 72 hours before starting thalidomide therapy, and then once a month during treatment continuing until one month after stopping treatment (every 2 weeks if irregular periods). If a woman thinks she may be pregnant she must stop taking thalidomide immediately.

Dexamethasone is available as 500 microgram 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<sub>2</sub> 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.

Thromboprophylaxis is required – risk assess patient and consider prophylactic LMWH as per local policy (unless platelet count < 30 x 10<sup>9</sup>/L, then withhold until recovered). If patient is already taking warfarin consider switch to treatment dose LMWH or DOAC (as applicable within NICE guidance).

### 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
HIV, hepatitis B and C status	7 days
Blood pressure (lying and standing)	On day 1
Pregnancy test (women of childbearing potential)	3 days

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

Bone marrow aspirate and trephine, including FISH

Assessment of venous thromboembolic risk

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
Pregnancy test (women of child bearing potential)	3 days

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

Assessment for neuropathy

\* Additional FBC monitoring is required as below:

For patients with platelet count at cycle pre-assessment > 70x10<sup>9</sup>/L the risk of severe thrombocytopenia is low. Check FBC before each dose but administer the drug without waiting for the result. If the platelets are subsequently found to be low, then consider a repeat FBC 48 hours later and the need for platelet transfusion. In patients with platelet count < 70x10<sup>9</sup>/L at cycle pre-assessment, the drug should be withheld until the FBC is known and the dose omitted if the platelets are < 25 x10<sup>9</sup>/L. Unless the thrombocytopenia is due to marrow infiltration by myeloma; consider proceeding with treatment with platelet transfusion support.

### 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	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 70 \times 10^9/L$
Creatinine clearance	$\geq 50\text{mL/min}$
Bilirubin	$< 1.5 \times \text{ULN}$

### Dose modifications

Doses of bortezomib are modified according to the following table:

Full dose	$1.3\text{mg/m}^2$
First dose reduction	$1.0\text{mg/m}^2$
Second dose reduction	$0.7\text{mg/m}^2$
Third dose reduction	$0.5\text{mg/m}^2$

- Haematological toxicity**

Treatment on day 1 should only be initiated if neutrophils  $\geq 1.0 \times 10^9/L$  and platelets  $\geq 70 \times 10^9/L$ .

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

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

See above for FBC monitoring requirements.

- Renal impairment**

**Bortezomib:**

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

- Hepatic impairment**

**Bortezomib:**

If bilirubin  $> 1.5 \times \text{ULN}$  consider starting dose of  $0.7\text{mg/m}^2$  for cycle 1. For subsequent cycles consider increasing dose to  $1\text{mg/m}^2$  or reducing dose to  $0.5\text{mg/m}^2$  according to tolerability.

- 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	$1.0\text{mg/m}^2$
	Grade 2 with pain or grade 3	Withhold until symptoms resolved Restart at dose of $0.7\text{mg/m}^2$
	Grade 4	Discontinue

Any other  $\geq$  grade 3 non-haematological toxicity: withhold bortezomib until  $\leq$  grade 1. Recommence with 1 level dose reduction.

**Thalidomide:**

Toxicity	Definition	Thalidomide dose
Peripheral neuropathy	Grade 1-2	Reduce thalidomide dose by 50% and consider discontinuing.
	Grade 3-4	Stop thalidomide (usually permanently). If symptoms resolve consider starting at 50mg for subsequent cycles (dose may be escalated in 50mg increments)
Sedation, constipation, rash, fatigue, tremor, oedema	Grade 3-4	Stop thalidomide for remainder of cycle. Consider restarting at 50mg for subsequent cycles (dose may be escalated in 50mg increments).

Thalidomide – MHRA alert: viral reactivation and pulmonary hypertension :

- Cases of viral reactivation have been reported in patients previously infected with varicella-zoster and Hepatitis B. Previously infected patients should be closely monitored for signs and symptoms or reactivation throughout treatment.
- Cases of pulmonary hypertension have been reported following thalidomide treatment. Patients should be closely monitored for signs and symptoms of cardiopulmonary disease.

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

- **Serious side effects**

Thromboembolism  
 Tumour lysis syndrome  
 Orthostatic hypotension  
 Painful peripheral neuropathy  
 Cardiac toxicity  
 Stevens-Johnson syndrome  
 Myelosuppression  
 Teratogenicity

- **Frequently occurring side effects**

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

- **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 glycaemia has been reported. Close monitoring of blood glucose is required.

**Ciclosporin:** increased risk of severe neuropathy: avoid concomitant use.

**High dose 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.

**Thalidomide:**

**Hormonal contraceptives:** may increase risk of thrombo-embolic disease – not recommended

**Sedative medication:** may enhance sedative effect

### Additional comments

Women of child bearing potential and males must use contraception as outlined by a MHRA approved Risk Management Program.

---

### References

- Summary of Product Characteristics: Bortezomib (Janssen) accessed 11 Nov 2015 via [www.medicines.org.uk](http://www.medicines.org.uk)
- Summary of Product Characteristics Thalidomide (Celgene) accessed 11 Nov 2015 via [www.medicines.org.uk](http://www.medicines.org.uk)
- National Institute for Clinical Excellence. Technology Appraisal Guidance 311. Accessed 11 Nov 2015 via [www.nice.org.uk](http://www.nice.org.uk)
- Nooka A, Kastritis E, Dimopoulos M, Lonial S. Treatment options for relapsed and refractory multiple myeloma. Blood. 2015 May;125 (20):3085-3099
- Rosinol L et al. Superiority of bortezomib, thalidomide and dexamethasone (VTD) as induction pre-transplantation therapy in multiple myeloma: a randomized phase III PETHEMA/GEM study. Blood. 2012. July 12
- MHRA alert accessed 27 July 2016 via <https://www.gov.uk/drug-safety-update/letters-sent-to-healthcare-professionals-in-june-2016>

---

Written/reviewed by: Dr J Griffin (Consultant Haematologist, UHBristol NHS Trust), Dr A Whiteway (Consultant Haematologist, North Bristol NHS Trust), Becky Bagnall (Haematology Pharmacist, North Bristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

Date: December 2016

---