Bortezomib, Thalidomide and Dexamethasone (VTD) – 21 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 prefix C90

Regimen details

Day	Drug	Dose	Route
1, 4, 8 and 11	Bortezomib	1.3 mg/m^2	SC
1-21 (continuously)	Thalidomide	50mg ON*	PO
1,2 and 4,5 and 8,9 and 11,12	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
21 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_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
Thromboprophylaxis is required – risk assess patient and consider prophylactic LMWH as per local policy (unless platelet count < 30 x 10^9/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 > 70x10^9/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 < 70x10^9/L at cycle pre-assessment, the drug should be withheld until the FBC is known and the dose omitted if the platelets are < 25 x10^9/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	≥ 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 4, 8 and 11 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.

See above for FBC monitoring requirements.

- **Renal impairment**

Bortezomib:

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

- **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.

- **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 bortezomib until ≤ 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.
Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

References

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