

BORTEZOMIB & DEXAMETHASONE +/- THALIDOMIDE

The preferred 1st-line option for induction treatment of patients with previously untreated multiple myeloma who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation (NICE approved April 2014)

N.B. **See separate protocol** for bortezomib use in patients unsuitable for stem cell transplantation

Drugs/Dosage:

Bortezomib + Dexamethasone + Thalidomide (VTD)

*If patient immobile or has advanced renal failure, delay introduction of thalidomide until cycle 2 or 3, and instead use the 2-drug combination (3-weekly cycle) as below, until patient's kidney function has improved, or they are no longer immobile.

**if quick response needed, see regimen below

Bortezomib	1.3mg/m ² (2.5mg/ml)	s/c bolus on Day 1, Day 8, Day 15 and Day 22
Dexamethasone	20mg	po once daily on Days 1+2, 8+9, 15+16, 22+23
Thalidomide	50mg	po once daily initially, then titrating upwards every 2 weeks to a maximum of 200mg daily, depending on tolerability (unusual to increase beyond 100mg od)
4 weekly cycle for 4 cycles		
A further 2 cycles may be given to patients with at least a partial response after 4 cycles		

Bortezomib + Dexamethasone +/- Thalidomide

*2-drug regimen (no thalidomide) to be followed if patient not suitable for thalidomide

or

**if quick response wanted, all 3 drugs may be given, as this more intensive 3-weekly regimen.

Bortezomib (2.5mg/ml)	1.3mg/m ²	s/c bolus on Day 1, Day 4, Day 8 and Day 11 (at least 72 hours between doses)
+		
Dexamethasone	20mg	po once daily on Days 1+2, 4+5, 8+9, 11+12
+/-		
Thalidomide	50mg	po once daily initially, then titrating upwards every 2 weeks to a maximum of 200mg daily, depending on tolerability (unusual to increase beyond 100mg od)
3 weekly cycle		
*The 2-drug schedule may be used until the patient is suitable for introduction of thalidomide, then switch to the 3-drug schedule (4 weekly cycle), as above, for remaining cycles.		
**Where a quick response is wanted, usually 1 – 2 cycles administered, then switch to the 4 weekly cycle as above.		

Other Drugs:

Allopurinol, dose according to renal function – review after the 1st cycle.

Consider PCP prophylaxis – prescribe according to unit practice/protocol.

Fluconazole 100mg po od as antifungal prophylaxis

Aciclovir 400mg po bd

Omeprazole 20mg od is recommended whilst treating with steroids.

Laxative as required for thalidomide-induced constipation.

Thromboprophylaxis for patients on thalidomide, according to unit practice, is recommended in the absence of specific contraindication.

Reason for Update: 3-drug combination every 3 weeks added as an option; general review	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 2	Date: 31.1.18
Supersedes: Version 1	Review date: Feb 2020
Prepared by: S Taylor	Checked by: M Chow

Administration: **Bortezomib** given by subcutaneous bolus injection into the thigh or abdomen.
 Rotate sites: avoid injecting into the same site in the same cycle, e.g. alternate between right and left abdomen, and right and left thigh.
 Patient should be encouraged to drink 2 – 3 litres over the 24 hours after each dose of bortezomib in the first cycle, to reduce the risk of tumour lysis syndrome.
Dexamethasone is to be taken in the morning with or after food.
Thalidomide is available as 50mg capsules. The daily dose should be taken at bedtime to avoid problems with day-time sedation. Patients should be advised not to drive or operate machinery for 8 hours after each dose.

Main Toxicities: *bortezomib side effects:* myelosuppression (thrombocytopenia common but recovers rapidly; neutropenia usually less severe); postural hypotension; rash; GI toxicity; peripheral neuropathy (use with caution in patients with pre-existing neuropathy); exacerbation/development of heart failure (monitor patients with risk factors or pre-existing heart disease closely); injection site reactions; *steroid side effects*
thalidomide side effects: teratogenicity (see Comments); sedation (take at bedtime); constipation (often requiring laxatives); peripheral neuropathy; bradycardia and syncope; dizziness; dry skin or rash; increased risk of thromboembolic events

Anti- emetics: moderately emetogenic (but anti-emetic doses of dexamethasone not required)
 For s/c route, avoid inserting a cannula: oral domperidone or metoclopramide to be taken before each bortezomib dose, and then tds as required.

Extravasation: bortezomib is a non-vesicant

Regular Investigations:

FBC	Day 1
U&Es & LFTs	Day 1
MUGA/echo	only if concerned
Blood pressure, lying and standing	Day 1 (with every dose if sensori-motor problems)
Paraprotein and/or serum free light chains	every 4 weeks
<i>If on dexamethasone:</i>	
Blood glucose and blood pressure	see Comments

Comments: Blood glucose and blood pressure monitoring to be tailored according to individual patient needs, while on high dose dexamethasone.

The IV route (IV bolus over 3 – 5 seconds) for bortezomib may be substituted if the s/c route is considered inappropriate (eg ITU patient), although note that this is associated with an increased incidence and severity of neuropathy-related toxicities. Also note that aseptics need to be informed of the change in route, as the formulation is different.

Thalidomide is highly teratogenic:

- women of child bearing potential must have a negative pregnancy test within 3 days prior to starting treatment. Pregnancy testing should be repeated monthly thereafter until one month after stopping thalidomide (every 2 weeks in women with irregular menstrual cycles)
 If a woman taking thalidomide thinks she may be pregnant she must stop the drug immediately.
- women of child-bearing potential must use one agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on thalidomide and for one month after. (The combined oral contraceptive pill is not recommended due to the increased risk of thromboembolism)
- men taking thalidomide must use a barrier method of contraception throughout treatment and for one week after stopping, if their partner is capable of bearing children.

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Thalidomide is supplied through the Celgene Pregnancy Prevention Programme. All aspects of the programme should be followed, including completion of an authorisation form by both doctor and pharmacist with every cycle.

Dose Modifications

Haematological Toxicity:	Withhold treatment if neutrophils < 0.5 x 10 ⁹ /L or platelets < 25 x 10 ⁹ /L. Once recovered, re-introduce with 25% bortezomib dose reduction (1.3 mg/m ² reduced to 1.0 mg/m ² ; 1.0 mg/m ² reduced to 0.7 mg/m ²).
Renal Impairment:	Consider a dose reduction of bortezomib if CrCl < 20ml/min. For patients on dialysis, bortezomib should be given after the dialysis procedure, as dialysis may reduce bortezomib concentrations.
Hepatic Impairment:	Use bortezomib with caution in mild to moderate hepatic impairment, and consider a dose reduction – clearance is mainly via hepatic metabolism. If bilirubin > 1.5 x ULN, reduce bortezomib to 0.7 mg/m ² in the first treatment cycle. Consider dose escalation to 1.0 mg/m ² , or further dose reduction to 0.5 mg/m ² , in subsequent cycles based on patient tolerability.
Sensory and Motor Neuropathy:	Symptoms include numbness, tingling, burning, cramps, dysaesthesias. This dose reduction schedule applies to new neuropathy symptoms (excludes pre-existing stable neuropathy):

Dose level	Dose of bortezomib (mg/m ²)
0	1.3
- 1	1.0
- 2	0.7

Severity of peripheral neuropathy	Modification of dose and regimen
Grade 1 (paraesthesia and/or loss of reflexes) with no pain or loss of function	For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule: no action, or reduce dose to 1.0mg/m ²
Grade 1 with pain or Grade 2 (interfering with function but not the activities of daily living)	Withhold bortezomib treatment until symptoms resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib treatment until symptoms resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule and maintain same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy which is life-threatening or leads to paralysis)	Discontinue bortezomib

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Autonomic neuropathy, diarrhoea and hypotension: This can come on insidiously and careful questioning of patients for symptoms of postural dizziness and unsteadiness is essential. The majority of patients on anti-hypertensive treatment will need their medication adjusting. Any patient who develops signs/symptoms of sensori-motor neuropathy should have lying and standing BP measurements at *each* dose of bortezomib, not just on day 1, even if asymptomatic.

Severity of autonomic neuropathy	Modification of dose and regimen
Grade 1: Occasional dizziness on standing (<3x/week)	No action
Grade 2: Regular dizziness on standing with no postural drop, or Grade 2 diarrhoea	Withhold bortezomib treatment until symptoms resolved to Grade 1. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down (1.3mg/m ² to 1.0mg/m ² ; 1.0mg/m ² to 0.7mg/m ²)
Grade 3: Postural drop of ≥20mm Hg with or without dizziness. Dizziness interfering with activities of daily living, or Grade 3 diarrhoea	Withhold bortezomib treatment until symptoms resolved to Grade 1. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down (1.3mg/m ² to 1.0mg/m ² ; 1.0mg/m ² to 0.7mg/m ²)
Grade 4: Syncopal episodes or other autonomic disturbance e.g. > Grade 3 diarrhoea	Discontinue bortezomib

Thalidomide-related peripheral neuropathy: Grade 2: reduce the dose of thalidomide by 50%
Grade 3: discontinue thalidomide until recovered to Grade ≤ 1, and then restart with a 50% dose reduction.

Steroid Side Effects: If severe steroid-related side effects develop, withhold further dexamethasone until resolved to Grade 2 or less. Then re-start with a 50% dose reduction.

Other Toxicities: If any other Grade 3 or 4 non-haematological toxicities due to bortezomib occur, bortezomib should be withheld.
Once recovered, bortezomib may be re-introduced with 25% dose reduction.

Injection site reactions (up to 5cm in diameter) are generally Grade 1 (red, dry or itchy) and last 3 – 5 days. Symptoms may be routinely managed with aloe vera gel, or other moisturisers.

Patient Information: Macmillan leaflets for Bortezomib and Thalidomide
Celgene Pregnancy Prevention Programme Booklet

References: Harousseau, J-L et al ; JCO 2010 ; 28 (30) : 4621 – 4629
Rosinol, L et al ; Blood 2012 ; 120 (8)

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