Panobinostat, Bortezomib and Dexamethasone

Indication

Treatment of relapsed/refractory multiple myeloma in patients who have received at least 2 prior regimens, including bortezomib and an immunomodulatory agent.

(NICE TA380)

ICD-10 codes

Codes with a pre-fix C90

Regimen details

Cycles 1-8:

Day	Drug	Dose	Route
1, 4, 8, 11	Bortezomib	1.3 mg/m^2	SC
1,2 and 4,5 and 8,9 and 11,12	Dexamethasone	20mg OM	PO
1, 3, 5, 8, 10, 12	Panobinostat*	20mg*	PO

At least 72 hours must elapse between doses of bortezomib

*For patients >75 years of age, depending on the patient's general condition and concomitant diseases, an adjustment of the starting doses or schedule may be considered as follows:
- Panobinostat dose reduced to 15 mg (if tolerated this may be escalated to 20 mg for subsequent cycles).
- Bortezomib 1.3 mg/m^2 once weekly on days 1 and 8 and dexamethasone given on days 1,2 and 8,9 only.
NOTE this dosing is unlicensed.

If clinical benefit is demonstrated, an additional 8 cycles may be given as below:

Cycles 9-16:

Day	Drug	Dose	Route
1, 8	Bortezomib	1.3 mg/m^2	SC
1, 2, and 8, 9	Dexamethasone	20mg OM	PO
1, 3, 5, 8, 10, 12	Panobinostat	20mg	PO

Cycle frequency

21 days

Number of cycles

As above. Treatment is continued as long as the patient continues to benefit or until a maximum of 16 cycles are completed.

Administration

Bortezomib is administered by SC injection.

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

Panobinostat is available as 10mg, 15mg and 20mg capsules. It should be taken once daily, at the same time of day, on the scheduled days only. Capsules should be swallowed whole with water, with or without food. They should not be opened, crushed or chewed. If a dose is missed it can be taken within 12 hours of the scheduled time, otherwise that dose is omitted and the patient should take the next scheduled dose. If a patient vomits they should not take an additional dose.
Missed doses must not be taken on days outside of the scheduled dose days as detailed above.
Patients should be advised to avoid star fruit, grapefruit and pomegranate and their juices.

Pre-medication

Nil

Emetogenicity

This regimen has mild-moderate emetogenic potential.

Additional supportive medication

H_2 antagonist or proton pump inhibitor
Antiemetics as per local policy
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 – patients should be advised to take at first onset of loose stools.

Extravasation

Bortezomib is neutral (group 1).

Investigations – pre first cycle

Investigation	**Validity period**
FBC and film	On day 1
Clotting screen	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days
Phosphate	7 days
Blood glucose	7 days
Blood pressure (lying and standing)	On day 1
Pregnancy test (women of child bearing potential)	3 days
Thyroid function	Baseline
ECG	On day 1

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)
Bone marrow aspirate and trephine
ECG must be performed at the start of treatment and then as clinically indicated. QTcF must be <480msec prior to commencing panobinostat.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC*	Weekly (or more often if clinically indicated) and within 24 hours of each bortezomib administration
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days
Phosphate	7 days
Blood glucose	As clinically indicated
Blood pressure	On day 1
Pregnancy test (if applicable)	3 days
Thyroid function	As clinically indicated
ECG	As clinically indicated

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

* For patients > 65 years of age, it is recommended that FBC is monitored more frequently and during the rest period, especially in those with a baseline platelet count < 150 x 10^9/L.

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	≥ 100 x 10^9/L
Haemoglobin	≥ 80g/L
Creatinine clearance	≥ 50mL/min
Bilirubin	< ULN
AST/ALT	< ULN

Dose modifications

Funding is approved for combination treatment. If one agent is permanently discontinued the other agent should also be discontinued.

Doses of bortezomib and panobinostat are modified according to the following table:

Dose level	Bortezomib dose	Panobinostat dose
Full dose	1.3mg/m^2	20mg
First dose reduction	1.0mg/m^2	15mg
Second dose reduction	0.7mg/m^2	10mg
Third dose reduction	Discontinue	Discontinue

- **Haematological toxicity**

Prior to commencing treatment, baseline neutrophils must be ≥ 1.0 x 10^9/L and platelets ≥ 100 x 10^9/L.

FBC should be monitored prior to each bortezomib dose.

Thrombocytopenia
If platelet count < 50 x 10^9/L monitor FBC twice weekly until ≥ 50 x 10^9/L.

Platelets (x 10^9/L)	**Bortezomib dose**	**Panobinostat dose**
25-50 with bleeding or <25	Omit until recovery ≥ 50 x 10^9/L If one dose omitted: resume at same dose If more than one dose omitted: resume at reduced dose	Omit until recovery ≥ 50 x 10^9/L Resume at reduced dose

Neutropenia

Neutrophils (x 10^9/L)	**Bortezomib dose**	**Panobinostat dose**
0.5 - <1.0 (no fever)	Omit until recovery > 1.0 x 10^9/L Resume at same dose	Omit until recovery > 1.0 x 10^9/L Resume at same dose
<0.5 (or <1.0 with fever)	Omit until recovery > 1.0 x 10^9/L Resume at same dose	Omit until recovery > 1.0 x 10^9/L Resume at reduced dose

If thrombocytopenia or neutropenia persist despite dose modifications treatment may need to be discontinued.

- **Renal impairment**

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

Panobinostat:
No starting dose reduction in mild-severe renal impairment. Panobinostat has not been studied in end stage renal disease or in patients undergoing dialysis.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Bortezomib dose**	**Panobinostat dose**
< ULN	and	< ULN	100%	100%
< ULN	and	> ULN	100%	15mg starting dose Consider escalating to 20mg for subsequent cycles if tolerated
1.0-1.5	and	Any	100%	15mg starting dose Consider escalating to 20mg for subsequent cycles if tolerated
1.5-3.0	and	Any	Consider 0.7mg/m^2 starting dose. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on tolerability.	10mg starting dose Consider escalating to 15mg for subsequent cycles if tolerated
> 3.0	and	Any	Do not administer	

- **Other toxicities**

Toxicity	Definition	Bortezomib dose	Panobinostat dose
Neuropathy	Grade 1 with no pain	100%. If bi-weekly schedule, consider changing to weekly.	No dose modifications required
	Grade 1 with pain or grade 2 but not interfering with daily living	Omit until symptoms resolve. If bi-weekly reduce to weekly. If weekly reduce one dose level.	
	Grade 2 with pain or grade 3	Omit until symptoms resolve. If bi-weekly reduce to weekly. If weekly reduce one dose level.	
	Grade 4	Discontinue	
Diarrhoea	Grade 2 (despite antidiarrhoeal treatment)	Omit until symptoms resolved to ≤grade 1 Resume at reduced dose or change to weekly dosing.	Omit until symptoms resolved to ≤grade 1 Resume at same dose
	Grade 3 (despite antidiarrhoeal treatment)	Omit until symptoms resolved to ≤grade 1 Resume at reduced dose or change to weekly dosing.	Omit until symptoms resolved to ≤grade 1 Resume at reduced dose level
	Grade 4 (despite antidiarrhoeal treatment)	Discontinue	Discontinue
Nausea and vomiting	Grade 1 and 2	No dose modifications required	Symptomatic control Maintain dose level
	Grade 3 and 4		Withhold until symptoms resolved to ≤grade 1 Restart at reduced dose level

QTC prolongation - panobinostat:
ECG and electrolytes (particularly potassium, magnesium and phosphate) should be monitored prior to commencing panobinostat and periodically every cycle as clinically indicated. Any electrolyte abnormalities must be corrected. QTc must be <480msec prior to commencing treatment.

If, during treatment, the QTcF increases to ≥480 msec or above 60 msec from baseline, treatment must be interrupted. Any electrolyte abnormalities must be corrected.

- If resolves within 7 days, resume at same dose (first occurrence) or reduced dose (repeat occurrence).
- If QT prolongation does not resolve within 7 days or QTcF > 500 msec, treatment must be permanently discontinued.

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

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

- **Serious side effects**

Myelosuppression
Thromboembolism
Pulmonary hypotension
Cardiac toxicity
QT prolongation
Psychosis

- **Frequently occurring side effects**

Myelosuppression
Severe diarrhoea
Abdominal cramping
Nausea and vomiting
Fatigue
Peripheral neuropathy
Headache
Rash
Hypothyroidism
Insomnia
High blood sugars
Fluid retention
Dyspepsia
Blepharitis

- **Other side effects**

Altered LFTs
Decreased appetite
Confusion
Depression

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

Cytochrome P3A4 inhibitors (ketoconazole and other azole antifungals, clarithromycin, erythromycin) may increase bortezomib and panobinostat levels: avoid concomitant use. If essential reduce panobinostat dose to 10mg. Consider dose escalation to 15mg based on tolerability.
Cytochrome P3A4 inducers (rifampicin, carbamazepine, phenytoin, St Johns Wort) may reduce bortezomib and panobinostat levels: avoid concomitant use.

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.

Panobinostat:
Avoid all medication which have the potential to prolong QT interval.
Avoid star fruit, grapefruit and pomegranate as may reduce the bioavailability of panobinostat.
Effect on hormonal contraception is unknown so patients should be advised to use barrier contraception where appropriate.

Additional comments

Women of childbearing potential taking panobinostat in combination with bortezomib and dexamethasone must use highly effective contraception for three months after stopping treatment.

References

- Summary of Product Characteristics: Bortezomib (Janssen) accessed 4 May 2016 via www.medicines.org.uk
- Summary of Product Characteristics Panobinostat (Novartis) accessed 4 May 2016 via www.medicines.org.uk
- National Institute for Clinical Excellence. Technology Appraisal Guidance 380. Accessed 4 May 2016 via www.nice.org.uk
- Jesús F San-Miguel, Vânia T M Hungria, et al. (2014). Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncology

Written/reviewed by: Dr A Whiteway (Consultant Haematologist, North Bristol NHS Trust), Dr S Moore (Consultant Haematologist, Royal United Bath NHS Trust)

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

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

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