Thames Valley
Strategic Clinical Network

PANOBINOSTAT WITH BORTEZOMIB AND DEXAMETHASONE (PanBorDex)

INDICATION

Relapsed or relapsed and refractory multiple myeloma in patients who have received at least 2 prior lines of therapy including bortezomib and an immunomodulatory agent (NICE TA380).

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay (Freelite)
   - Hevylite analysis (if paraprotein level difficult to quantify)
   - β_2 microglobulin
   - LDH
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   - Group and save
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital
Salisbury
Wiltshire
SP2 8B

Additional Investigations

- Plasma viscosity if hyperviscosity suspected.
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.

2. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
3. Fertility - all patients should be offered fertility advice, as appropriate.
4. Hydration - fluid intake of at least 3 litres /day should be attempted.
5. Document patient's height and weight, dose on actual body weight.
6. Document patient's performance status.
7. Treatment must be agreed at the relevant MDT.

REGIMENT SPECIFIC PRE-ASSESMENT

1. Evaluate for presence of neuropathy. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with bortezomib. Baseline clinical assessment must be documented in the notes before the first dose of bortezomib is prescribed.
2. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1.
3. ECG must be performed prior to the start of therapy and repeated periodically every cycle during treatment as clinically indicated. QTcF must be <480 msec prior to initiation of treatment with panobinostat.

DRUG REGIMEN:

Full-twice weekly bortezomib schedule in the first table can be used for patients with good tolerability to treatment. Consider using the once-weekly schedule (in the second table) in selected patients.

Full twice-weekly bortezomib schedule:

Bortezomib	1.3 mg/m^2 given as SC bolus	**Cycles 1-8:** Days 1, 4, 8 and 11 **Cycle 9 onwards: Days 1 and 8 only.**
WITH		
Dexamethasone	20 mg PO once daily	**Cycles 1-8:** On the day of and day after each Bortezomib dose. This will usually be days 1, 2, 4, 5, 8, 9, 11 & 12 **Cycle 9 onwards: Days 1, 2, 8, and 9.**
WITH		
Panobinostat	20 mg PO	Days 1, 3, 5, 8, 10 and 12. Consider reducing frequency to twice a week on days 1,5,8 and 12, depending on tolerability **Or** Consider reducing dose to 10mg on Days 1,

		3, 5, 8, 10 and 12, depending on tolerability

At least 72 hours should elapse between consecutive doses of Bortezomib.
Panobinostat is available as 10mg, 15mg and 20mg strength capsules.

Attenuated once-weekly bortezomib schedule

Bortezomib	1.3 mg/m^2 given as SC bolus	**Cycles 1-8:** Days 1, 8, 15 **Cycle 9 onwards:** Days 1 and 8 only.
WITH		
Dexamethasone	20 mg PO once daily	**Cycles 1-8:** on the day of and day after each bortezomib dose. This will be on days 1, 2, 8, 9, 15 and 16. **Cycle 9 onwards:** Days 1, 2, 8, and 9.
WITH		
Panobinostat	20 mg PO	Days 1, 3, 5, 8, 10 and 12. Consider reduce frequency to twice a week on days 1, 5, 8 and 12, depending on tolerability. **Or** Consider reducing dose to 10mg on Days 1, 3, 5, 8, 10 and 12, depending on tolerability.

CYCLE FREQUENCY

Repeat every 21 days for up to 8 treatment cycles. In patients showing clinical benefit, treatment can continue for an additional 8 cycles (total 16 cycles).

DOSE MODIFICATIONS

Haematological toxicity

Baseline platelet count must be at least 100x 10^9/L and baseline absolute neutrophil count (ANC) must be at least 1.0 x 10^9/L. If the counts are lower due to heavy marrow burden patient can be started on this protocol but FBC should be monitored weekly (or more often as clinically indicated) during treatment.

Dosing levels of panobinostat and bortezomib:

	Initial dose	Dose Level -1	Dose Level - 2	Then

Panobinostat	20mg	15mg	10mg	discontinue
Bortezomib	1.3mg/m^2	1.0mg/m^2	0.7 mg/m^2	discontinue

Thrombocytopenia:

Thrombocytopenia grade on day of treatment	**Modification of panobinostat starting dose**	**Panobinostat dose on recovery to grade 2 thrombocytopenia (≥50 x 10^9/l)**	**Modification of bortezomib starting dose**	**Bortezomib dose on recovery to grade 2 thrombocytopenia (≥50 x 10^9/l)**	
				1 dose omitted	**More than 1 dose omitted**
Grade 3 Platelets <50 x 10^9/l with bleeding	Omit dose	Resume at reduced dose	Omit dose	Resume at same dose	Resume at reduced dose
Grade 4 Platelets <25 x 10^9/l	Omit dose	Resume at reduced dose	Omit dose	Resume at same dose	Resume at reduced dose

Neutropenia:

Support with GCSF can be considered as per local policy

Neutropenia grade on day of treatment	**Modification of panobinostat starting dose**	**Panobinostat dose on recovery to grade 2 neutropenia (<1.5-1.0 x 10^9/l)**	**Modification of bortezomib starting dose**	**Bortezomib dose on recovery to grade 2 neutropenia (<1.5-1.0 x 10^9/l)**
Grade 3 neutropenia (<1.0-0.5 x 10^9/l)	Omit dose	Resume at same dose	Omit dose	Resume at same dose
Grade 4 neutropenia (<0.5 x 10^9/l) or febrile neutropenia (<1.0 x 10^9/l and fever ≥38.5°C)	Omit dose	Resume at reduced dose	Omit dose	Resume at same dose

Diarrhoea: At the first sign of abdominal cramping, loose stools or onset of diarrhoea, it is recommended that the patient be treated with an anti-diarrhoeal medicinal product (e.g. loperamide).

Adverse drug reaction	**Grade on day of treatment**	**Modification of panobinostat starting dose**	**Panobinostat dose on recovery to ≤ grade 1**	**Modification of bortezomib starting dose**	**Bortezomib dose on recovery to ≤ grade 1**
Diarrhoea	Grade 2 despite anti-diarrhoeal medicinal product	Omit dose	Resume at the same dose	Omit dose	Resume at reduced dose or change to once weekly
	Grade 3 despite anti-diarrhoeal medicinal product	Omit dose	Resume at reduced dose	Omit dose	Resume at reduced dose or with the same dose but with a once-weekly schedule
	Grade 4 despite anti-diarrhoeal medicinal product	Permanently discontinue		Permanently discontinue	

Nausea and vomiting:

Drug	Grade 1 & 2	Grade 3 or 4
Panobinostat	Maintain dose level	Discontinue until resolves to ≤ grade 1 then restart reduced by one dose level

Bortezomib-related neuropathy:

Severity of neuropathy	Posology modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m^2 or reduce treatment schedule to 1.3 mg/m^2 once per week if patient on the twice-weekly schedule
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Renal and hepatic impairment:

Panobinostat:

Renal	Hepatic
-No dose reductions are required in mild to severe renal impairment. -No studies were conducted in end stage renal failure patients. Avoid use in these patients	**Mild** (Bili ≤1.0 x ULN and ALT/AST >ULN) or (Bili >1.0 x ULN and ≤1.5 x ULN and any ALT/AST)**:** Start at reduced dose 15 mg in 1st cycle. Consider dose escalation up to 20 mg in subsequent cycles if tolerated. **Moderate** (Bili >1.5 x ULN and ≤3.0 x ULN and any ALT/AST): Start at reduced dose 10 mg in the 1st cycle. Consider dose escalation up to 15 mg in subsequent cycles if tolerated

Bortezomib:

Renal	Hepatic
Clinical decision if GFR < 20ml/min In dialysis patients, give after dialysis	Bili > 1.5x ULN Reduce 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.

QTc prolongation

Patients must have QTcF < 480 msec prior to initiating treatment with panobinostat. If during treatment, the QTcF increases to ≥480 msec, treatment must be interrupted and any electrolyte abnormalities must be corrected, adjust dosing as follows:

- Omit, if QTcF is ≥480 msec or above 60 msec from baseline.
- If resolved within 7 days, resume at prior dose if first occurrence or at reduced dose if QT prolongation is recurrent.
- If unresolved within 7 days, treatment should be discontinued.
- If any QTcF value is above 500 msec, permanently discontinue panobinostat.

INVESTIGATIONS (prior to the beginning of each treatment cycle)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC (weekly)
- Creatinine, U&E, LFTs, adjusted calcium, and magnesium and phosphate. Correct any electrolyte abnormalities
- ECG must be performed prior to the start of therapy and repeated periodically every cycle during treatment as clinically indicated. QTcF must be <480 msec prior to initiation of treatment with panobinostat.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib.
- Blood pressure (consider checking for postural drop if symptomatic).
- Ig's, paraprotein, Freelite assay.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

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CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and 3 months post therapy.
- Prophylactic fluconazole 50mg OD
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton Pump Inhibitor or H2 antagonist at clinician's discretion.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Loperamide 4mg stat then 2mg prn every 4 hours up to maximum of 16mg in 24 hours should be prescribed readily available for patient to start at the first episode of diarrhoea.
- Antiemetic: cyclizine, prochlorperazine. Avoid drugs which can cause QTc prolongation or with prokinetic properties that can worsen diarrhoea
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DRUG INTERACTIONS

(Consult pharmacist or Refer to SmPC for further details on drug interactions)

Panobinostat Interactions:

- **CYP3A4 Inhibitors:** In patients who take concomitant medicinal products which are strong CYP3A and/or P-gp inhibitors, including, but not limited to, ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole and nefazodone, the dose of panobinostat should be reduced Patients should be instructed to avoid star fruit, grapefruit, grapefruit juice, pomegranates and pomegranate juice.
- **CYP3A4 inducers: s**trong CYP3A inducers including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort should be avoided with Panobinostat
- Drugs that may cause QTc prolongation or induce torsades de pointes should be avoided.

Bortezomib Interactions:

- Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

EMETIC RISK

Moderately emetogenic.

Avoid/use with caution anti-emetics which cause QTC prolongation e.g. ondansetron, domperidone and those with prokinetic properties that can worsen diarrhoea metoclopramide. Cyclizine, prochlorperazine may be considered.

ADVERSE EFFECTS/REGIMEN COMPLICATIONS

WARNING ABOUT PANOBINOSTAT: FATAL AND SERIOUS TOXICITIES: SEVERE DIARRHEA AND CARDIAC TOXICITIES

Severe diarrhoea occurred in 25% of panobinostat treated patients. Monitor for symptoms, institute anti-diarrheal treatment, interrupt panobinostat and then reduce dose or discontinue it.

Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving panobinostat. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.

- **Diarrhoea:** Severe diarrhoea occurred in 25% of treated patients. Monitor for symptoms, institute anti-diarrheal treatment, interrupt panobinostat and then reduce dose or discontinue it.
- **Peripheral neuropathy**: Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia. If these occur see above dose reductions and consider use of Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU. Caution in patients with existing peripheral neuropathy.
- **Cardiac adverse effects**: Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving panobinostat. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.
- **Dizziness and orthostatic hypotension:** Patients should be advised that bortezomib may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position**.** Caution in patients with history of syncope, receiving medications associated with hypotension and patients who are dehydrated. Patients who experience dizziness or low blood pressure may benefit from 500 ml intravenous 0.9% sodium chloride with each bortezomib dose.

TREATMENT RELATED MORTALITY

5%

REFERENCES

1. 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,* published online 19.09.2014.
2. Panobinostat (Farydak®) Summary Of Product Characteristics. Online. Available on http://www.medicines.org.uk/emc/medicine/31545 (Last updated may 2018).
3. eMC UK Summary of Product Characteristics for Velcade, Janssen, February 2019
4. National institute for Health and Care Excellence. 2016. Internet. Panobinostat for treating multiple myeloma after at least 2 previous treatments.Online. Available at: https://www.nice.org.uk/guidance/ta380 (last accessed on19.06.2016)

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Indication, Drug regime, Investigations, Dose modification, Adverse effects, contraindication removed	May 2016	2.0	May 2018
Faouzi Djebbari	Updated dose modifications, renal	July 2017	2.1	May 2018

(Haematology Pharmacist)	and hepatic impairment, concurrent medication, drug interactions and references			
Network Protocol Review	Dosing schedule. Concurrent medication. Pre-assessment. Adverse events.	June 2018	2.2	June 2020
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	2.3	June 2021
Quality Manager	Nursing care plan added	April 2021	2.4	June 2021
Faouzi Djebbari (Haematology Pharmacist)	Updated list of concurrent meds	Aug 2021	2.5	Aug 2021

Nursing Care Plan:
Panobinostat Bortezomib Dexamethasone

Indication: Relapsed or refractory Myeloma in patients who have received at least 2 prior lines of therapy.
Frequency: Repeat every 21 days, continue until signs of disease progression or unacceptable toxicity for up to 8 treatment cycles. In patients showing clinical benefit, treatment can continue for an additional 8 cycles (maximum 16 cycles).
Alopecia: No

PANOBINOSTAT: Histone deacetylase (HDAC) inhibitor.
Administered **orally** on days 1, 3, 5, 8, 10 and 12.
Emetic Risk: Moderate risk. Avoid anti-emetics which cause QTC prolongation e.g. ondansetron, metoclopramide.
Side effects: Diarrhoea, cardiac adverse events (arrhythmias/ischaemic events), electrolyte imbalances, bone marrow depression.
WARNING ABOUT PANOBINOSTAT:
FATAL AND SEVERE DIARRHOEA AND CARDIAC TOXICITIES.
Monitor for symptoms of diarrhoea and start treatment for this promptly.
An ECG must be performed on day 1 of each cycle seen by registrar before treatment is given.

BORTEZOMIB (VELCADE): Proteasome inhibitor.
Administered subcutaneously **on days 1, 8, 15 cycles 1-8 (can be given on days 1, 4, 8 and 11 if required but this is rare)**. Minimum of 72 hours required between doses.
Cycles 9-16 bortezomib is given on days 1 and 8.
Emetic risk: low
Classification of extravasation: irritant
Side effects: tachycardia, diarrhoea, constipation, anorexia, nausea/vomiting, thrombocytopenia, neutropenia, peripheral neuropathy (sensory and motor), headache, rash, fatigue, postural hypotension, dizziness, shingles, inflammation at injection site, infections, bone marrow depression.

DEXAMETHASONE: corticosteroid tablets
Administered orally on the day of each bortezomib dose and the day after. Taken with or after food preferably at breakfast
Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations

- Lying and standing blood pressure to be recorded pre cycle 1, advise patients that velcade can cause orthostatic hypotension and counsel them to sit upright for a moment before standing from a sitting/lying position.
- Advise patients to maintain a fluid intake of 2-3 litres and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- Assess for presence of peripheral neuropathy before starting treatment and **prior to the start of each cycle.**
- Bloods are required at the start of each cycle and **FBC must be repeated weekly**. Random blood glucose monitoring is recommended. Biochemistry may need to be repeated more frequently if diarrhoea occurs as electrolyte imbalance can increase severity/occurrence of cardiac arrhythmias.

- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle.
- Perform ECG on day 1 of each cycle.