

Chemotherapy Protocol

MULTIPLE MYELOMA

BORTEZOMIB (IV)-DEXAMETHASONE-PANOBINOSTAT

(21 day)

Regimen

- Multiple Myeloma – Bortezomib (IV)-Dexamethasone-Panobinostat (21 day)

Indication

- Panobinostat in combination with bortezomib and dexamethasone is recommended, within its marketing authorisation, as an option for treating multiple myeloma. That is, for adult patients with relapsed and/or refractory multiple myeloma who have received at least two prior regimens including bortezomib and an immunomodulatory agent, when the company provides panobinostat with the discount agreed in the patient access scheme.
- Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Bortezomib	GI disturbances, peripheral neuropathy, hypotension, dizziness, blurred vision, headache, musculoskeletal pain, pyrexia
Dexamethasone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Panobinostat	QT interval prolongation, diarrhoea, nausea, vomiting, thrombocytopenia, anaemia

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- FBC should be checked prior to each dose of bortezomib, that is on days 1 and 8. Consider before days 15 and / or 18 in patients who are 65 years or older or who have platelets less than $150 \times 10^9/L$.
- LFTs and U&Es prior to day 1 of each cycle.
- ECG prior to day 1
- Paraprotein or light chains every 3 weeks
- Regular monitoring of blood glucose is considered good practice but optional

- Women of childbearing potential must have a negative pregnancy test at screening and men who are sexually active with a woman of childbearing potential must agree to use barrier methods of contraception ☐ ☐
- Prior to starting treatment with panobinostat do an ECG. QTcF must be less than 480ms before initiation of treatment with panobinostat. This should be repeated on day one of cycle two, a single ECG is acceptable if no apparent QTcF prolongation is noted. In the following cycles no further ECG is required for patients with no apparent QTcF prolongation. Periodical ECGs are recommended as clinically indicated

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion or erythropoietin if the patient is symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Drug	Initial dose	Dose Level -1	Dose Level - 2	Action
Panobinostat	20mg	15mg	10mg	Discontinue
Bortezomib	1.3mg/m ²	1mg/m ²	0.7 mg/m ²	Discontinue

Drug	Neutrophils	Dose Modifications
Bortezomib	0.75 – 1x10 ⁹ /L	Maintain the same dose
	If the neutrophils are less than 1 with febrile neutropenia or less than 0.5x10 ⁹ /L	Interrupt treatment until febrile neutropenia resolves and the neutrophil count is greater than or equal to 1x10 ⁹ /L. If only 1 dose was omitted prior to correction to these levels, restart at same dose. If 2 or more doses were omitted consecutively, or within the same cycle, treatment should be restarted at a reduced dose
Panobinostat	0.75 – 1x10 ⁹ /L	Maintain the same dose
	0.5-0.75x10 ⁹ /L	If single occurrence within cycle then maintain the same dose level. If there are two or more episodes within cycle then interrupt treatment until levels are 1x10 ⁹ /L or above and then restart at same dose level
	less than 1x10 ⁹ /L with febrile neutropenia	Interrupt treatment until febrile neutropenia resolves and the neutrophils are equal to or greater than 1x10 ⁹ /L then restart at reduced dose level
	less than 0.5x10 ⁹ /L	Interrupt treatment until neutrophils are 1x10 ⁹ /L or greater, then restart at reduced dose level
Drug	Platelets	Dose Modifications
Bortezomib	25 – 50x10 ⁹ /L (grade 3)	Maintain the same dose
	25 – 50x10 ⁹ /L (grade 3 with haemorrhage) or platelets less than 25x10 ⁹ /L (grade 4)	Interrupt treatment until platelets are equal to or greater than 75x10 ⁹ /L. If only 1 dose was omitted prior to correction to these levels, restart at same dose level If 2 or more doses were omitted consecutively, or within the same cycle, treatment should be restarted at a reduced dose level

Panobinostat	25 – 50x10 ⁹ /L (grade 3)	Maintain the same dose, monitor platelet counts every seven days
	25 – 50x10 ⁹ /L (grade 3 with haemorrhage)	Interrupt treatment. Monitor platelet counts at least weekly until they are equal to or greater than 50x10 ⁹ /L, then restart at reduced dose level
	less than 25x10 ⁹ /L (grade 4)	Interrupt treatment. Monitor platelet counts at least weekly until they are equal to or greater than 50x10 ⁹ /L, then restart at reduced dose level

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin μmol/L		AST/ALT units/L	Dose (% of original dose)
Bortezomib	1.5xULN or below		N/A	100%
	greater than 1.5xULN		N/A	Initiate treatment at 0.7mg/m ² . The dose may be escalated to 1mg/m ² or reduced to 0.5mg/m ² in subsequent cycles based on patient tolerability.
Panobinostat	Bilirubin 1-1.5xULN and / or any abnormal AST			For the first treatment cycle start panobinostat at a reduced dose of 15mg and increase in subsequent cycles as tolerated. If this occurs during treatment then temporarily discontinue dosing until resolved to grade 2 or less or baseline and then restart treatment, reduced by one dose level
	Bilirubin between 1.5-3xULN and any abnormal AST			For the first treatment cycle start panobinostat at a reduced dose of 10mg and increase to 15mg in subsequent cycles as tolerated. If this occurs during treatment then temporarily discontinue dosing until resolved to grade 2 or less or baseline and then restart treatment, reduced by one dose level

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bortezomib	greater than 20	100%
	20 and below	Clinical decision
Panobinostat	No dose adjustments are necessary in those with mild to moderate renal impairment	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Gastrointestinal

Gastrointestinal toxicity is particularly problematic with panobinostat

Adverse drug reaction	Grade	Panobinostat Modifications	Bortezomib Modifications
Diarrhoea	2 despite anti-diarrhoeals	Omit dose until recovery to grade 1 or less then resume at the same dose	Omit dose until recovery to grade 1 or less then resume treatment at a reduced dose level or change to once weekly
	3 despite anti-diarrhoeals	Omit dose until recovery to grade 1 or less then resume treatment at a reduced dose	Omit dose until recovery to grade 1 or less then resume treatment with the same dose on a once weekly schedule
	4 despite anti-diarrhoeals	Permanently discontinue	Permanently discontinue

Bortezomib

Neuropathic pain and/or peripheral neuropathy

Subcutaneous administration should also be considered as the incidence and severity of peripheral neuropathy has been shown to be less when bortezomib is given by this route.

For patients experiencing NCI-CTC grade 1 neuropathy continue with full dose.

For NCI-CTC grade 1 with pain or grade 2 neuropathy reduce the dose of bortezomib to 1mg/m^2 or switch to a weekly bortezomib at the standard dose of 1.3mg/m^2

For NCI-CTC grade 2 with pain or grade 3 neuropathy discontinue treatment until symptoms have resolved to NCI-CTC grade 1 or less then reinstate bortezomib at a dose of 0.7mg/m^2

For NCI-CTC grade 4 neuropathy and/or severe autonomic neuropathy discontinue bortezomib.

For any other NCI-CTC grade 3 non haematological toxicity bortezomib should be discontinued until symptoms have resolved to NCI-CTC grade 1 or below. On the first occurrence treatment may be reinstated at a dose of 1mg/m^2 . Following second occurrence to dose should be further reduced to 0.7mg/m^2 once symptoms have resolved. If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of bortezomib must be considered unless the benefit of treatment clearly outweighs the risk.

Panobinostat

QTc Prolongation

If a prolonged QT interval is found on ECG prior to initiation of panobinostat (QTcF greater than or equal to 480ms or above 60ms from baseline), the start of therapy should be delayed until pre-dose average QTcF has returned to less than 480 ms and abnormal serum potassium, magnesium or phosphorus values corrected. In the event of QT prolongation during treatment:

- The dose should be omitted if the QTcF is greater than or equal to 480ms or above 60ms from baseline.
- If the QT prolongation is resolved within 7 days, resume treatment at prior dose for initial occurrence or at reduced dose if QT prolongation is recurrent
- If QT prolongation is unresolved within 7 days, treatment should be discontinued.
- If any QTcF value is above 500 ms, panobinostat should be permanently discontinued

[Regimen](#)

21 day cycle for cycle 1, 2, 3, 4, 5, 6, 7, 8

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m ²	1, 4, 8, 11	Intravenous injection
Dexamethasone	20mg	1, 2, 4, 5, 8, 9, 11, 12	Oral
Panobinostat	20mg	1, 3, 5, 8, 10, 12	Oral

21 day cycle for cycles 9, 10, 11, 12, 13, 14, 15, 16

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m ²	1, 8	Intravenous injection
Dexamethasone	20mg	1, 2, 8, 9	Oral
Panobinostat	20mg	1, 3, 5, 8, 10, 12	Oral

[Dose Information](#)

- Bortezomib will be dose rounded to the agreed bands
- At least 72 hours must elapse between bortezomib doses
- Dexamethasone is available as 500mcg and 2mg tablets
- Panobinostat is available as 10mg, 15mg and 20mg capsules

[Administration Information](#)

- Dexamethasone should be taken in the morning, with or after food
- Panobinostat should be administered orally once daily on scheduled days only, at the same time each day. The capsules should be swallowed whole with water, with or without food, and they should not be opened, crushed or chewed. If a dose is missed, it can be taken up to 12 hours after the specified dose time. If vomiting occurs the patient should not take an additional dose, but should take the next usual prescribed dose.

[Additional Therapy](#)

- Anti-emetics

As take home medication

- cyclizine 50mg three times a day oral when required
- Allopurinol 300mg once a day for seven days for cycle one only

- Anti-infective prophylaxis with
 - aciclovir 400mg twice a day oral
 - co-trimoxazole 960mg once day on Monday, Wednesday and Friday oral
- Loperamide 4mg after the first loose stool then 2mg after each loose stool thereafter to a maximum of 16mg/24hours oral
- Bisphosphonates in accordance with local policies
- Mouthwashes according to local or national policy on the treatment of mucositis.
- Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

[Additional Information](#)

- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.
- Panobinostat prolongs the QT interval. Agents that are also associated with this adverse effect should be used with caution. This includes many anti-emetics such as ondansetron, metoclopramide and domperidone

[Coding](#)

- Procurement – X70.8, X72.9
- Delivery – X72.4

[References](#)

1. San-Miguel JF, Hungria VTM, Yoon S-S et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicenter randomized double-blind phase 3 trial. *Lancet Oncol*, 2014; 15(11): 1195-1206.
2. National Institute for Health and Care Excellence. Panobinostat for treating multiple myeloma after at least two other treatments (TA 380). January 2016 DOH:London

REGIMEN SUMMARY

Bortezomib (IV)-Dexamethasone-Panobinostat (21 day)

Cycle 1

Day 1, 4, 8, 11

1. Bortezomib 1.3mg/m² intravenous injection

Take Home Medicines (day 1 only)

2. Dexamethasone 20mg once a day on days 1, 2, 4, 5, 8, 9, 11, 12 oral
Administration Instructions
Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle or individual bottles according to local practice.
3. Panobinostat 20mg once a day on days 1, 3, 5, 8, 10, 12 oral
Administration Instructions
Take in the morning, with or without food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle or individual bottles according to local practice. Oral chemotherapy.
4. Cyclizine 50mg up to three times a day when required oral
Administration Instructions
When required for the relief of nausea. Please dispense 28 tablets or nearest original pack size.
5. Aciclovir 400mg twice a day for 21 days oral
Administration Instructions
Please supply 21 days or an original pack if appropriate.
6. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 21 days oral
Administration Instructions
Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 21 days.
This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.
7. Allopurinol 300mg once a day for 7 days oral
Administration Instructions
Take with or after food with plenty of water. Please supply 7 days.
8. Gastric Protection
Administration Instructions
The choice of gastric protection is dependent on local formulary choice and may include;
 - esomeprazole 20mg once a day oral
 - omeprazole 20mg once a day oral
 - lansoprazole 15mg once a day oral
 - pantoprazole 20mg once a day oral
 - rabeprazole 20mg once a day oral
 - cimetidine 400mg twice a day oral
 - famotidine 20mg once a day oral
 - nizatidine 150mg twice a day oral
 - ranitidine 150mg twice a day oralPlease dispense 21 days or nearest original pack.
9. Loperamide capsules as directed
Administration Instructions
When required for the relief of diarrhoea. Take 4mg initially followed by 2mg after each loose stool. Maximum 16mg per day. Please supply 60 capsules or 2 original packs if appropriate.

Cycle 2, 3, 4, 5, 6, 7, 8

Day 1, 4, 8, 11

1. Bortezomib 1.3mg/m² intravenous injection

Take Home Medicines (day 1 only)

2. Dexamethasone 20mg once a day on days 1, 2, 4, 5, 8, 9, 11, 12 oral
Administration Instructions
Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle or individual bottles according to local practice.
3. Panobinostat 20mg once a day on days 1, 3, 5, 8, 10, 12 oral
Administration Instructions
Take in the morning, with or without food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle or individual bottles according to local practice. Oral chemotherapy.
4. Cyclizine 50mg up to three times a day when required oral
Administration Instructions
When required for the relief of nausea. Please dispense 28 tablets or nearest original pack size.
5. Aciclovir 400mg twice a day for 21 days oral
Administration Instructions
Please supply 21 days or an original pack if appropriate.
6. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 21 days oral
Administration Instructions
Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 21 days.
This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.
7. Gastric Protection
Administration Instructions
The choice of gastric protection is dependent on local formulary choice and may include;
 - a. esomeprazole 20mg once a day oral
 - b. omeprazole 20mg once a day oral
 - c. lansoprazole 15mg once a day oral
 - d. pantoprazole 20mg once a day oral
 - e. rabeprazole 20mg once a day oral
 - f. cimetidine 400mg twice a day oral
 - g. famotidine 20mg once a day oral
 - h. nizatidine 150mg twice a day oral
 - i. ranitidine 150mg twice a day oral

Please dispense 21 days or nearest original pack.

Cycles 9, 10, 11, 12, 13, 14, 15, 16

Day 1, 8

1. Bortezomib 1.3mg/m² intravenous injection

Take Home Medicines (day 1 only)

2. **Dexamethasone 20mg once a day on days 1, 2, 8, 9 oral**
Administration Instructions
Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle or individual bottles according to local practice.
3. **Panobinostat 20mg once a day on days 1, 3, 5, 8, 10, 12 oral**
Administration Instructions
Take in the morning, with or without food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle or individual bottles according to local practice. Oral chemotherapy.
4. **Cyclizine 50mg up to three times a day when required oral**
Administration Instructions
When required for the relief of nausea. Please dispense 28 tablets or nearest original pack size.
5. **Aciclovir 400mg twice a day for 21 days oral**
Administration Instructions
Please supply 21 days or an original pack if appropriate.
6. **Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 21 days oral**
Administration Instructions
Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 21 days.
This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.
7. **Gastric Protection**
Administration Instructions
The choice of gastric protection is dependent on local formulary choice and may include;
 - a. esomeprazole 20mg once a day oral
 - b. omeprazole 20mg once a day oral
 - c. lansoprazole 15mg once a day oral
 - d. pantoprazole 20mg once a day oral
 - e. rabeprazole 20mg once a day oral
 - f. cimetidine 400mg twice a day oral
 - g. famotidine 20mg once a day oral
 - h. nizatidine 150mg twice a day oral
 - i. ranitidine 150mg twice a day oral

Please dispense 21 days or nearest original pack.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	Dec 2016	"Oral chemotherapy" added to panobinostat admin instructions Quantity of cyclizine to be issued standardised to 28 tablets. Quantity of loperamide to be issued standardised to 60 capsules and admin instructions clarified.	Rebecca Wills Pharmacist	Dr Deborah Wright Pharmacist
1	Nov 2016	None	Dr Deborah Wright Pharmacist	Dr Mathew Jenner Consultant Haematologist Dr Helen Dignum Consultant Haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
 NHS Isle of Wight
 Portsmouth Hospitals NHS Trust
 Salisbury Hospital NHS Foundation Trust
 University Hospital Southampton NHS Foundation Trust
 Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.