Chemotherapy Protocol

MULTIPLE MYELOMA

BORTEZOMIB (SC)-DEXAMETHASONE-PANOBINOSTAT-THALIDOMIDE

(21 day)

Regimen

- Multiple Myeloma – Bortezomib (SC)-Dexamethasone-Panobinostat-Thalidomide (21 day)

Indication

- Panobinostat in combination with bortezomib, dexamethasone and thalidomide 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
Thalidomide	Drowsiness, constipation, dizziness, increased risk of thromboembolic events, dry skin/rash, peripheral neuropathy, teratogenicity, syncope, bradycardia

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.

- LFTs and U&Es prior to day 1 of each cycle.

- 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 / or 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
Thalidomide	No adjustments necessary			

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	
Thalidomide	No adjustments necessary	

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

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 reinitiate 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 resolve to NCI-CTC grade 1 or below. On the first occurrence treatment may be reinitiated 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 msec 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 msec, panobinstat should be permanently discontinued

Thalidomide

Peripheral Neuropathy

If NCI-CTC grade 1 neurological toxicity occurs treatment may be continued, if symptoms worsen consider dose reduction or interruption. Treatment may be reintroduced at a reduced dose if symptoms resolve.

If NCI-CTC grade 2 neurological toxicity occurs suspend treatment or reduce the dose by at least 50%. Treatment may be reintroduced at a reduced dose if symptoms resolve to grade 1 or below.

For NCI-CTC neurological toxicity grade 3 or above or toxicity that does not resolve despite treatment interruption / dose reduction thalidomide treatment should be stopped.

Thromboembolism

The thrombotic risk for patients commencing on thalidomide must be assessed. Appropriate thromboprophylaxis must be prescribed according to local policies. Thromboprophylaxis is generally recommended for at least the first 5 months of thalidomide treatment, especially in patients with additional thrombotic risk factors. Patients and their carers should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness, chest pain, or swelling of a limb.

The occurrence of a thromboembolic event such as a DVT or thromboembolism, notably pulmonary embolism, is an indication for full anticoagulation following standard treatment guidelines. Thalidomide may be stopped, but can be re-introduced, initially at 50mg daily with escalation at subsequent cycles to 100mg, assuming good anticoagulant control and no other untoward side effects.

All patients should be initially prescribed a low molecular weight heparin at the appropriate prophylactic dose. Therapeutic warfarin is an alternative to low molecular heparin.

Teratogenicity

Thalidomide is highly teratogenic.

All prescribers, patients and pharmacy staff must comply with the manufacturer's Pregnancy Prevention Programme.

Women of child-bearing potential taking thalidomide must use one agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on thalidomide and for one month after. They 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 (or 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 and seek medical advice.

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.

Other

For other thalidomide related toxicities of NCI-CTC grade 3 or above. Stop thalidomide until recovery to NCI-CTC grade 1 or below. Cautious reintroduction of thalidomide at a dose of 50mg a day may be considered with dose escalation if tolerated.

Regimen

21 day cycle for up to 16 cycles

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1, 8	Subcutaneous injection
Dexamethasone	20mg	1, 2, 8, 9	Oral
Panobinostat	20mg	1, 3, 5, 8, 10, 12	Oral
Thalidomide	50mg – 100mg once a day at night	1-21 inclusive	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
- Thalidomide dose is started at 50mg. This may be increased to 100mg if well tolerated during the first cycle.
- Thalidomide is available as 50mg 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.
- Thalidomide should be taken at night to avoid daytime drowsiness.
- Thalidomide prescriptions must be accompanied by a completed Prescription Authorisation Form.

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
- Thromboprophylaxis according to local formulary choices. For example;

  - dalteparin 5000units subcutaneous injection once a day
  - enoxaparin 40mg subcutaneous injection once a day
  - heparin 5000units subcutaneous injection twice a day
- 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 H_2 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.
- For all patients taking thalidomide the patient, prescriber and supplying pharmacy must comply with an appropriate pregnancy prevention programme.
- 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 (SC)-Dexamethasone-Panobinostat-Thalidomide (21day)

Cycle 1

Day 1, 8

1. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

2. Warning – Pregnancy Prevention Programme
   Administration Instructions
   Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy.

3. 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.

4. 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.

5. Thalidomide 50mg once a day at night for 21 days
   Administration Instructions
   Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy.

6. 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.

7. Aciclovir 400mg twice a day for 21 days oral
   Administration Instructions
   Please supply 21 days or nearest original pack size

8. 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.

9. Allopurinol 300mg once a day for 7 days oral
   Administration Instructions
   Take with or after food with plenty of water. Please supply 7 days.

10. 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.

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11. 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 oral

Please dispense 21 days or nearest original pack.

10. Thromboprophylaxis according to local formulary choice;

Administration Instructions

The choice of thromboprophylaxis is dependent on local formularly choice and may include;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 21 days or nearest equivalent original pack size.

Cycle 2 onwards

Day 1, 8

1. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

2. Warning – Pregnancy Prevention Programme

Administration Instructions

Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy.

3. 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.

4. 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.

5. Thalidomide 50mg once a day at night for 21 days

Administration Instructions

Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy.

6. 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.

7. Aciclovir 400mg twice a day for 21 days oral

Administration Instructions

Please supply 21 days or nearest original pack size

8. 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.

9. 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 oral

Please dispense 21 days or nearest original pack.

10. Thromboprophylaxis according to local formulary choice;

Administration Instructions
The choice of thromboprophylaxis is dependent on local formularly choice and may include;

- dalteparin 5000units once a day subcutaneous injection
- enoxaparin 40mg once a day subcutaneous injection
- heparin 5000units twice a day subcutaneous injection

Please supply 21 days or nearest equivalent original pack size.

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.