Chemotherapy Protocol

MULTIPLE MYELOMA

PAD (SC)-BORTEZOMIB (SC)-DEXAMETHASONE-DOXORUBICIN

Regimen

- Multiple Myeloma – PAD (SC)-Bortezomib (SC)-Dexamethasone-Doxorubicin

Indication

- Second or subsequent line treatment of transplant eligible multiple myeloma.

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
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red)

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

Monitoring

- FBC prior to day 1. Days 4, 8, 11 are optional.
- LFTs and U&Es on day 1
- Paraprotein or light chains every 3-6 weeks
- Regular monitoring of blood glucose is considered good practice
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems, cardiac risk factors or in the elderly. Discontinue doxorubicin if cardiac failure develops

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.

Dose modifications based on haematological parameters apply to bortezomib and doxorubicin only. In the presence of cytopenias due to bone marrow involvement with myeloma, it is possible that the day 1 dose will go ahead even if the neutrophils are less than $1x10^9$/L and platelets less than $75x10^9$/L.

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

Neutrophils ($x10^9$/L)		**Platelets ($x10^9$/L)**	**Dose (bortezomib and doxorubicin)**
1 or greater	and	75 or greater	100%
less than 1	or	less than 75	Delay on a weekly basis until recovery

If the neutrophil count is less than $1x10^9$/L and platelets less than $75x10^9$/L on day 1 of subsequent cycles (when previously greater than these levels) delay on a weekly basis until recovery and then decrease the bortezomib dose to 1mg/m^2 and the doxorubicin dose to 6mg/m^2 per day (24mg/m^2 in total).

If further toxicity occurs where neutrophils are less than $1x10^9$/L and platelets less than $75x10^9$/L on day 1, delay weekly until recovery and reduce the dose of bortezomib to 0.7mg/m2 and doxorubicin to 4.5mg/m^2 per day (18mg/m^2 in total).

Neutrophils ($x10^9$/L)		**Platelets ($x10^9$/L)**	**Dose (bortezomib and doxorubicin)**
0.75 or greater	and	30 or greater	100%
less than 0.75	or	less than 30	Delay on a weekly basis until recovery and re-initiate at a reduced dose

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.
Doxorubicin	less than 30	and	2-3xULN	75%
	30-50	and/or	More than 3xULN	50%
	51-85		N/A	25%
	more than 85		N/A	omit

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bortezomib	greater than 20	100%
	20 and below	Clinical decision
Doxorubicin	less than 10	Consider dose reduction in severe renal failure

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.

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.

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 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.

Dexamethasone

For patients who are elderly or unable to tolerate the standard dose of dexamethasone the dose given the day after bortezomib may be omitted or the dose reduced to avoid omission.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops

Regimen

21 day cycle continued to plateau plus two cycles (6 cycles will be set in Aria)

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1, 4, 8, 11	Subcutaneous injection
Dexamethasone	40mg once a day	1, 2, 3, 4	Oral
Doxorubicin	9mg/m^2	1, 2, 3, 4	Intravenous infusion over 96 hours (36mg/m^2 in total) via a portable infusion device

Dose Information

- Bortezomib will be dose banded according to the agreed bands
- Dexamethasone is available as 2mg and 500mcg tablets
- Doxorubicin will be dose banded according to the agreed bands

- The maximum lifetime cumulative dose of doxorubicin is 450mg/m². However prior radiotherapy to mediastinal/pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m²

Administration Information

Extravasation

- Bortezomib – neutral
- Doxorubicin - vesicant

Other

- At least 72 hours should elapse between consecutive doses of bortezomib.
- Dexamethasone should be taken in the morning, with or after food
- The doxorubicin dose can be administered as a daily intravenous bolus injection if there is no portable pump available

Additional Therapy

- Anti-emetics

  15-30 minutes prior to chemotherapy on day 1

  - ondansetron 8mg oral or intravenous

  As take home medication

  - metoclopramide 10mg three times a day oral when required
  - ondansetron 8mg twice a day for 5 days starting on the evening of day 1

- Consider allopurinol 300mg once a day for seven days for the first cycle only oral
- Anti-infective prophylaxis with;

  - aciclovir 400mg twice a day a day oral
  - co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only

- Bisphosphonates in accordance with local policies
- Mouthwashes according to local or national policy on the treatment of mucositis
- Laxatives may be considered if ondansetron is taken for 5 days
- 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.

Coding

- Procurement – X71.5
- Delivery – X72.3, X72.4

References
1. Oakervee HE et al. PAD combination therapy (PS-341/bortezomib, doxorubicin and dexamethasone) for previously untreated patients with multiple myeloma. Br J Haem 2005; 129: 755-762.

REGIMEN SUMMARY

PAD (SC)-Bortezomib (SC)-Dexamethasone-Doxorubicin

Cycle 1

Day 1

1. Ondansetron 8mg oral or intravenous

2. Bortezomib 1.3mg/m^2 subcutaneous injection

3. Doxorubicin 36mg/m^2 over 96 hours via a portable infusion device

Day 4, 8, 11

4. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

5. Dexamethasone 40mg oral once a day in the morning on days on day 1, 2, 3, 4
   Administration Instructions
   Take in the morning with or after food.

6. Metoclopramide 10mg oral up to three times a day when required for the relief of nausea
   Administration Instructions
   When required for the relief of nausea. Please supply 28 tablets or nearest original pack size

7. Ondansetron 8mg twice a day starting on the evening of day 1 for 5 days

8. Aciclovir 400mg twice times a day for 21 days
   Administration Instructions
   Please supply 21 days or an original pack if appropriate.

9. 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.

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

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 size.

Cycle 2, 3, 4, 5, 6

Day 1

12. Ondansetron 8mg oral or intravenous

13. Bortezomib 1.3mg/m^2 subcutaneous injection

14. Doxorubicin 36mg/m^2 over 96 hours via a portable infusion device

Day 4, 8, 11

15. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

16. Dexamethasone 40mg oral once a day in the morning on days on day 1, 2, 3, 4
    Administration Instructions
    Take in the morning with or after food.

17. Metoclopramide 10mg oral up to three times a day when required for the relief of nausea
    Administration Instructions
    When required for the relief of nausea. Please supply 28 tablets or nearest original pack size

18. Ondansetron 8mg twice a day starting on the evening of day 1 for 5 days

19. Aciclovir 400mg twice times a day for 21 days
    Administration Instructions
    Please supply 21 days or an original pack if appropriate.

20. 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.

21. 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 size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 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.