Chemotherapy Protocol

MULTIPLE MYELOMA

VCD (SC-28) - BORTEZOMIB (SC)-CYCLOPHOSPHAMIDE-DEXAMETHASONE (28 day)

Regimen

- Multiple Myeloma – VCD (SC-28)-Bortezomib (SC)-Cyclophosphamide (PO)-Dexamethasone (28 day)

Indication

- First or subsequent line treatment of multiple myeloma. This schedule is recommended for elderly patients or if there is any suggestion of neuropathy or postural hypotension.

Toxicity

Drug	Adverse Effect
Bortezomib	GI disturbances, peripheral neuropathy, hypotension, dizziness, blurred vision, headache, musculoskeletal pain, pyrexia
Cyclophosphamide	Dysuria, haemorrragic cystitis (rare), taste disturbances
Dexamethasone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance

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

Monitoring

- FBC, LFTs and U&Es prior to day 1 of each cycle. Days 8, 15 and 22 are optional.
- Paraprotein and / or light chains prior to each cycle.
- Blood glucose on day 1 is considered good practice but is optional.

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.

Dose modifications based on haematological parameters apply to bortezomib and cyclophosphamide only.

Neutrophils ($x10^9$/L)	**Dose Modifications (bortezomib and cyclophosphamide)**
1 or greater	100%
0.9 - 0.5	1st occurrence Omit cyclophosphamide, continue with bortezomib and dexamethasone. If neutrophils have recovered to $1x10^9$/L within 7 days continue with full dose cyclophosphamide. 2nd occurrence or neutrophils remain below $1x10^9$/L for greater than 7 days. Omit cyclophosphamide, continue with bortezomib and dexamethasone. Once neutrophils have recovered to $1x10^9$/L or greater continue cyclophosphamide at a reduced dose or discontinue as appropriate. For those with heavy marrow infiltration it may be more appropriate to continue at full dose bortezomib and use growth factors.
less than 0.5	1st occurrence Withhold cyclophosphamide until neutrophils have recovered to $1x10^9$/L or greater. Continue with a reduced dose of cyclophosphamide and full dose bortezomib. 2nd occurrence Withhold cyclophosphamide until neutrophils have recovered to $1x10^9$/L or greater. Stop cyclophosphamide and continue with bortezomib, consider a dose reduction to $1mg/m^2$ or $0.7mg/m^2$. For those with heavy marrow infiltration it may be more appropriate to continue at full dose bortezomib and use growth factors.
Platelets ($x10^9$/L)	**Dose Modifications (bortezomib and cyclophosphamide)**
50 or above	100%
30 - 49	1st occurrence Omit cyclophosphamide, continue with bortezomib and dexamethasone. If platelets have recovered to $50x10^9$/L within 7 days continue with full dose cyclophosphamide. 2nd occurrence or platelets remain below $50x10^9$/L for greater than 7 days. Omit cyclophosphamide, continue with bortezomib and dexamethasone.

	Once platelets have recovered to $50x10^9$/L or greater continue cyclophosphamide at a reduced dose or discontinue as appropriate
less than 30	1st occurrence Consider withholding bortezomib or administering platelets. Omit the cyclophosphamide until platelets have recovered to $50x10^9$/L or greater. Continue with a reduced dose of cyclophosphamide and full dose bortezomib. 2nd occurrence Consider withholding bortezomib or administering platelets Withhold the cyclophosphamide until platelets have recovered to $50x10^9$/L or greater. Once platelets have recovered to $50x10^9$/L or greater continue cyclophosphamide at a reduced dose or discontinue as appropriate

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)**
Cyclophosphamide	more than 30	or	2-3xULN	Clinical decision. Evidence that exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary.
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.

Renal Impairment

Drug	**Creatinine Clearance (ml/min)**	**Dose (% of original dose)**
Cyclophosphamide	More than 20	100%
	10-20	75%
	Less than 10	omit
Bortezomib	greater than 20	100%
	20 and below	Clinical decision

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

For patients experiencing NCI-CTC grade 1 neuropathy without loss of function or pain continue with full dose bortezomib.

For NCI-CTC grade 1 with pain or grade 2 neuropathy reduce the dose of bortezomib to 1mg/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.

Dexamethasone

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

Regimen

28 day cycle for up to 8 cycles

Response to bortezomib should be assessed after a maximum of four cycles of treatment, treatment should only be continued to eight cycles in people who have a complete or partial response.

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1, 8, 15, 22	Subcutaneous injection
Cyclophosphamide	350mg/m^2 (maximum dose 500mg)	1, 8, 15, 22	Oral
Dexamethasone	20mg once a day	1, 2, 8, 9, 15, 16, 22, 23	Oral

At least 72 hours should elapse between consecutive doses of bortezomib.

Dose Information

- Bortezomib dose will be dose banded according to agreed bands
- Cyclophosphamide is available as 50mg tablets
- Dexamethasone is available as 2mg and 500microgram tablets

Administration Information

- Cyclophosphamide tablets should be swallowed whole with a full glass of water
- Dexamethasone should be taken in the morning, with or after food

Additional Therapy

- Anti-emetics

  As take home medication

  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg once a day on days 1, 8, 15, 22 oral

- Anti-infective prophylaxis;

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

- Consider allopurinol 300mg once a day for seven days for the first cycle only
- 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.

Coding

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

References
1. Leiba M, Kedml M, Duek A et al. Bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, thalidomide and dexamethasone (VTD) based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis. Br J Haematol 2014; 166 (5): 702-710.

REGIMEN SUMMARY

VCD (SC-28)-Bortezomib (SC)-Cyclophosphamide-Dexamethasone (28 day)

Cycle 1

Day 1, 8, 15, 22

1. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

2. Cyclophosphamide 350mg/m^2 (max 500mg) once a day on day 1, 8, 15, 22 of the cycle oral
   Administration Instructions
   Please supply four doses of cyclophosphamide; ONE dose to be taken on days 1, 8, 15 and 22 of the cycle.
   This may be dispensed as a single supply in one container or as separate supplies according to local practice.
   Oral chemotherapy. Only available as 50mg tablets, please ensure dose modifications occur in multiples of 50mg.
   Swallow whole, not chewed with plenty of water.

3. Dexamethasone 20mg once a day on days 1, 2, 8, 9, 15,16, 22 & 23 of the cycle oral
   Administration Instructions
   Please supply eight doses of dexamethasone; ONE dose to be taken on days 1, 2, 8, 9, 15, 16, 22 & 23 of the cycle
   This may be dispensed as a single supply in one container or as separate supplies according to local practice.
   Take in the morning with or after food.

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

5. Ondansetron 8mg once a day on day 1, 8, 15 and 22 of the cycle oral
   Administration Instructions
   Please supply four doses of ondansetron; ONE dose to be taken on days 1, 8, 15 and 22 of the cycle.
   This may be dispensed as a single supply in one container or as separate supplies according to local practice.
   Take 15-30 minutes prior to cyclophosphamide administration.

6. Aciclovir 400mg twice a day for 28 days oral
   Administration Instructions
   Please supply 28 days or an original pack if appropriate.

7. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral
   Administration Instructions
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
   This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

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

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 28 days or nearest original pack size.

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

Day 1, 8, 15, 22

10. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

11. Cyclophosphamide 350mg/m^2 (max 500mg) once a day on day 1, 8, 15, 22 of the cycle oral
    Administration Instructions
    Please supply four doses of cyclophosphamide; ONE dose to be taken on days 1, 8, 15 and 22 of the cycle.
    This may be dispensed as a single supply in one container or as separate supplies according to local practice.
    Oral chemotherapy. Only available as 50mg tablets, please ensure dose modifications occur in multiples of 50mg.
    Swallow whole, not chewed with plenty of water.

12. Dexamethasone 20mg once a day on days 1, 2, 8, 9, 15,16, 22 & 23 of the cycle oral
    Administration Instructions
    Please supply eight doses of dexamethasone; ONE dose to be taken on days 1, 2, 8, 9, 15, 16, 22 & 23 of the cycle
    This may be dispensed as a single supply in one container or as separate supplies according to local practice.
    Take in the morning with or after food.

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

14. Ondansetron 8mg once a day on day 1, 8, 15 and 22 of the cycle oral
    Administration Instructions
    Please supply four doses of ondansetron; ONE dose to be taken on days 1, 8, 15 and 22 of the cycle.
    This may be dispensed as a single supply in one container or as separate supplies according to local practice.
    Take 15-30 minutes prior to cyclophosphamide administration.

15. Aciclovir 400mg twice a day for 28 days oral
    Administration Instructions
    Please supply 28 days or an original pack if appropriate.

16. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice.

17. 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 28 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2016	None	Rebecca Wills Pharmacist 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.