Chemotherapy Protocol

MULTIPLE MYELOMA

MPV (SC)-BORTEZOMIB (SC)-MELPHALAN (PO)-PREDNISOLONE (35 day)

Regimen

- Multiple Myeloma – MPV(SC)-Bortezomib (SC)-Melphalan (PO)-Prednisolone (35 day)

Indication

- The treatment of relapsed or refractory multiple myeloma

Toxicity

Drug	Adverse Effect
Bortezomib	GI disturbances, peripheral neuropathy, hypotension, dizziness, blurred vision, headache, musculoskeletal pain, pyrexia
Melphalan	Gastro-intestinal disturbances, stomatitis, nausea, vomiting, alopecia, myalgia, muscle atrophy and fibrosis
Prednisolone	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. FBC on days 8, 15, and 22 are optional
- Paraprotein or light chains every 5 weeks
- Regular monitoring of blood glucose is considered good practice but 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 melphalan only.

Neutrophils ($x10^9$/L)	**Dose Modifications (bortezomib, melphalan)**
1 or greater	100%
less than 1	Delay treatment for up to 2 weeks until the neutrophils are $1x10^9$/L or above and then continue with full dose and growth factor support and/or dose reduction. If recovery takes longer than 2 weeks consider stopping treatment.
Platelets ($x10^9$/L)	**Dose Modifications (melphalan)**
75 or above	100%
less than 75	Delay treatment for up to 2 weeks until the platelets are $75x10^9$/L or above and then continue with reduced dose. If recovery takes longer than 2 weeks consider stopping treatment.

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)**
Melphalan	N/A		N/A	No dose adjustment 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)**
Melphalan	30 or greater	100%
	less than 30	Initiate treatment at 75% increase at subsequent cycles if tolerated
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

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.

Prednisolone

For patients who are elderly or unable to tolerate the standard dose of prednisolone the dose may be reduced or omitted as appropriate.

Regimen

35 day cycle for 8 cycles

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1, 8, 15, 22	Subcutaneous injection
Melphalan	7mg/m^2	1,2,3,4	Oral
Prednisolone	60mg/m^2	1,2,3,4	Oral

Response to treatment should be assessed each cycle. Continue to a maximum of eight treatment cycles if there is at least a partial response, defined as a 50% reduction in paraprotein after four cycles.

Prednisolone may be omitted or the dose reduced at the clinician's discretion.

Dose Information

- Bortezomib will be dose rounded to the agreed bands
- Melphalan dose will be rounded to the nearest 2mg (up if halfway)
- Melphalan is available as 2mg tablets
- Prednisolone dose will be rounded to the nearest 5mg (up if halfway)
- Prednisolone is available as 5mg, 20mg and 25mg tablets

Administration Information

- Melphalan tablets should be stored in the fridge
- Prednisolone should be taken in the morning, with or after food

Additional Therapy

- Anti-emetics

  As take home medication

  - metoclopramide 10mg three times a day oral when required

- Consider 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

- 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.

Coding

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

References
1. San Miguel JF, Schlag R, Khuageva NK et al. Bortezomib plus melphalan and prednisolone for multiple myeloma. N Engl J Med 2008; 359: 2613-2614.

REGIMEN SUMMARY

MPV (SC)-Bortezomib (SC)-Melphalan (PO)-Prednisolone (35 day)

Cycle 1

Day 1, 8, 15, 22

1. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

2. Melphalan 7mg/m^2 once a day on days 1, 2, 3, 4 days oral
   Administration Instructions
   Tablets should be stored in the refrigerator. Oral chemotherapy,

3. Prednisolone 60mg/m^2 once a day on days 1, 2, 3, 4 days oral
   Administration Instructions
   Take in the morning, with or after food.

4. Metoclopramide 10mg 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 35 days oral
   Administration Instructions
   Please supply 35 tablets or an original pack if appropriate.

6. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 35 days oral
   Administration Instructions
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 35 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 oral

   Please dispense 35 days or nearest original pack.

Cycle 2 onwards

Day 1, 8, 15, 22

9. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines (day 1 only)

10. Melphalan 7mg/m^2 once a day on days 1, 2, 3, 4 days oral
    Administration Instructions
    Tablets should be stored in the refrigerator. Oral chemotherapy.

11. Prednisolone 60mg/m^2 once a day on days 1, 2, 3, 4 days oral
    Administration Instructions
    Take in the morning, with or after food.

12. Metoclopramide 10mg 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

13. Aciclovir 400mg twice a day for 35 days oral
    Administration Instructions
    Please supply 35 tablets or an original pack if appropriate..

14. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 35 days oral
    Administration Instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 35 days.
    This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice

15. 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 35 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 2016	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Mathew Jenner 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.