Chemotherapy Protocol

MULTIPLE MYELOMA

VTD (SC-28)-BORTEZOMIB (SC)-DEXAMETHASONE-THALIDOMIDE (28 day)

Regimen

- Multiple Myeloma – VTD (28)-Bortezomib (SC)-Dexamethasone-Thalidomide (28 day)

Indication

- First or subsequent treatment of 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
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 prior to each cycle.
- LFTs and U&Es prior to each cycle.
- Paraprotein and / or light chains prior to each cycle.
- Pregnancy testing in women of childbearing potential. A negative pregnancy test must be obtained within 3 days of starting thalidomide the test must be repeated every 4 weeks (every 2 weeks in women with irregular menstrual cycles) with the final test 4 weeks after the last dose of thalidomide.
- 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 patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Dose modifications based on haematological parameters apply to bortezomib only.

Neutrophils ($x10^9$/L)	**Dose Modifications (bortezomib)**
0.5 or greater	100%
less than 0.5	Consider treatment delay or dose reduction or growth factor support. Seek consultant advice.
Platelets ($x10^9$/L)	**Dose Modifications (bortezomib)**
25 or above	100%
less than 25	Consider treatment delay or dose reduction or platelet transfusion. Seek consultant advice.

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.
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
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.

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.

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 elderly or unable to tolerate the standard dose of dexamethasone the dose given the day after bortezomib may be omitted or consider a dose reduction.

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

28 day cycle for up to 6 cycles

Cycle 1

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1, 8, 15, 22	Subcutaneous injection
Dexamethasone	20mg once a day in the morning	1,2,8,9 15,16, 22,23	Oral
Thalidomide	50mg once a day at night	1-28	Oral

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m^2	1, 8,15, 22	Subcutaneous injection
Dexamethasone	20mg once a day in the morning	1,2,8,9, 15,16, 22, 23	Oral
Thalidomide	100mg once a day at night	1-28	Oral

The thalidomide dose may be increased if the previous dose has been tolerated.

Dose Information

- Bortezomib will be dose banded according to the agreed bands
- Dexamethasone is available as 2mg and 500mcg tablets
- Thalidomide is available as 50mg capsules

Administration Information

- At least 72 hours should elapse between consecutive doses of bortezomib.
- Dexamethasone should be taken in the morning, with or after food.
- 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

- metoclopramide 10mg three times a day oral when required

- 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

- Consider allopurinol 300mg once a day for 7 days for the first cycle only oral

- Anti-infective prophylaxis;

  - aciclovir 400mg twice a day oral
  - consider co-trimoxazole 960mg once a 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.

Other 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 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.

Coding

- Procurement – X70.8

- Delivery – X72.9, X72.4

References

1. Ludwig H, Greil R, Masszi T et al. Bortezomib, thalidomide and dexamethasone with or without cyclophosphamide for patients with previously untreated multiple myeloma: 5 year follow up. Br J Haematol 2015; 171 (3): 344-354.
2. Cavo M, Pantani L, Petrucci MT et al. on behalf of GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) Italian Myeloma Network. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood. 2012; 120(1): 9-19.

REGIMEN SUMMARY

VTD (SC-28)-Bortezomib (SC)-Dexamethasone-Thalidomide (28 day)

Cycle 1

Day 1, 8, 15, 22

1. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines

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

3. Dexamethasone 20mg oral once a day in the morning on days 1, 2, 8, 9, 15, 16, 22 & 23 of the cycle
   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. Thalidomide 50mg once a day for 28 days oral
   Administration Instructions
   Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg.
   Take at night to avoid daytime drowsiness.

5. 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

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

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

8. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only 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.

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.

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 28 days or nearest original pack size.

Cycle 2, 3, 4, 5, 6

Day 1, 8, 15, 22

11. Bortezomib 1.3mg/m^2 subcutaneous injection

Take Home Medicines

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

13. Dexamethasone 20mg oral once a day in the morning on days 1, 2, 8, 9, 15, 16, 22 & 23 of the cycle
    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.

14. Thalidomide 100mg once a day at night for 28 nights oral
    Administration Instructions
    Thalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients. Oral chemotherapy. Only available as 50mg capsules, please ensure dose modifications occur in multiples of 50mg.
    Take at night to avoid daytime drowsiness.

15. 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

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

17. 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.

18. 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.

19. Thromboprophylaxis according to local formulary choice. For example;

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 28 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 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.