Thames Valley
Strategic Clinical Network

POMALIDOMIDE BORTEZOMIB AND DEXAMETHASONE (PVD) 21 day cycle

INDICATIONS

Relapsed/Refractory multiple myeloma

This combination is not funded by NHS England. Individual funding must be agreed prior to treatment initiation

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TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay (Freelite)
   - β_2 microglobulin
   - LDH
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
   - Group and save
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital
Salisbury
Wiltshire
SP2 8BJ

ADDITIONAL INVESTIGATIONS

1. Plasma viscosity if hyperviscosity suspected
2. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology
3. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
6. Document patient's height and weight, dose on actual body weight.
7. Document patient's performance status
8. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE -ASSESMENT

1. Evaluate for presence of neuropathy. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with bortezomib
2. The conditions of the Pomalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of pomalidomide must be in line with the Celgene Pregnancy Prevention Programme
3. Clinical assessment of thrombo-embolic risk
4. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1

DRUG REGIMEN
Schedule is adapted from OPTIMISM Trial

CYCLES 1-8

Pomalidomide	4 mg OD (preferably at night)	Days 1 to 14
Bortezomib	1.3 mg/m^2 given S/C bolus	Days 1, 8 and 15
Dexamethasone	20 mg* PO once daily days of and day after each bortezomib dose	Days 1, 2, 8, 9, 15 and 16

CYCLES 9 onwards

Pomalidomide	4 mg OD (preferably at night)	Days 1 to 14
Bortezomib	1.3 mg/m^2 given S/C bolus	Days 1, 8 only
Dexamethasone	20 mg* PO once daily days of and day after each bortezomib dose	Days 1, 2, 8 and 9

*Consider dose reducing to 10mg in elderly patients >75 years.

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

Triplet therapy can continue until disease progression or unacceptable toxicity

Consider adding clarithromycin 500 mg bd (250mg bd if not tolerating)

Dexamethasone should not be stopped (Unlike lenalidomide-based therapy)

CYCLE FREQUENCY

Repeat every 21 days

DOSE MODIFICATIONS

Haematological toxicity

BORTEZOMIB:
Thrombocytopenia due to Bortezomib is transient and very rarely causes significant bleeding. If baseline platelet count is > 70x10^9/L, then the risk of severe thrombocytopenia is very low

In such patients, FBC should be checked only at the start of the cycle and does not need to be repeated before each dose.

In patients with plts < 70 x 10^9/L at the start of each cycle, the FBC should be checked before each dose, the drug should be withheld until FBC is through and the dose omitted if the platelets are < 25 x 10^9/L unless thrombocytopenia is thought to be mainly due to marrow infiltration by myeloma. In those circumstances, consider proceeding with treatment with platelet transfusion support.

In all other circumstances, if these levels are not reached, then treatment should be withheld and subsequent doses reduced by 25% (i.e. from 1.3 mg/m^2 to 1.0 mg/m^2 or from 1.0 mg/m^2 to 0.7 mg/m^2).

POMALIDOMIDE:
To initiate a new cycle of Pomalidomide, ANC ≥ 1.0 x 10^9/L and Platelets ≥ 50 x 10^9/L

Toxicity	Dose Modification
Neutropenia:	
ANC < 0.5 x 10^9/L or Febrile Neutropenia and ANC < 1.0 x 10^9/L. When ANC return to ≥1 x 10^9/l	Interrupt Pomalidomide, monitor FBC weekly Resume Pomalidomide at 3 mg OD
For each subsequent drop ANC < 0.5 x 10^9/L When ANC ≥ 1.0 x 10^9/L	Interrupt Pomalidomide Resume Pomalidomide at 1 mg less than previous dose
Thrombocytopenia:	
Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide, monitor FBC weekly Resume Pomalidomide at 3 mg OD
For each subsequent drop Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide Resume Pomalidomide at 1 mg less than previous dose

If toxicities occur after dose reductions to 1 mg, then discontinue Pomalidomide.
Weekly injections of G-CSF can be administered to keep maintain dose intensity (aim to keep neutrophil counts >1.0)

Peripheral neuropathy
BORTEZOMIB:
If there are symptoms of peripheral neuropathy, the dose reduction schedule must be invoked (see below). The drug should be stopped if symptoms or signs progress despite this.

Severity of neuropathy	Dose modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m^2 or Change treatment schedule to 1.3 mg/m^2 once per week
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Pomalidomide is structurally similar to thalidomide which is known to induce neuropathy. However, published data suggests that significant neurotoxicity is uncommon

Non-Haematological

BORTEZOMIB:

Toxicity	Dose Modification
Grade ≥ 3 non-haematological toxicities considered to be related to bortezomib	bortezomib should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, it may be reinitiated at a dose reduced by one dose level (from 1.3 mg/m2 to 1 mg/m2, or from 1 mg/m2 to 0.7 mg/m2). For bortezomib-related neuropathic pain and/or peripheral neuropathy, hold and/or modify bortezomib as outlined neuropathy table above.

POMALIDOMIDE

Toxicity	Dose Modification
-Grade 3 or 4 -When resolved to Grade ≤ 2	-Interrupt Pomalidomide -Resume Pomalidomide at 1mg less than previous dose

If toxicities occur after dose reductions to 1 mg, then discontinue Pomalidomide.

Renal & Hepatic impairment:

BORTEZOMIB:

Renal	Hepatic
For dialysis patients, bortezomib should be given after dialysis. No dose reduction necessary	Bili > 1.5 x ULN: reduce to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.

POMALIDOMIDE:

Renal	Hepatic
- No dose adjustment required in renal impairment -On haemodialysis days, patients should take pomalidomide following haemodialysis	Avoid if serum bilirubin > 34 umol/L Careful monitoring is required in hepatic impairment

Venous thromboembolism (VTE): There is an increased risk of thrombosis with pomalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

1. Prophylactic low-molecular weight heparin OR
2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

If VTE occurs, pomalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

INVESTIGATIONS (at the beginning of each cycle)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTs, Ca^{2+}
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle.
- Blood pressure (consider checking for postural drop if symptomatic)
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic fluconazole 50mg OD
- Prophylactic Acyclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and 3 months post therapy.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton Pump Inhibitor or H2 antagonist at clinician's discretion
- Thromboprophylaxis/anticoagulation- as above
- Bone protection as per NSSG Bone Protection protocol MM.3
- Prescribe loperamide if needed for diarrhoea.

Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin, carabamazepine, and phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

If a strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) is co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

EMETIC RISK

Low

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

In the OPTIMISM trials the most commonly reported grade 3 and higher toxicities include neutropenia (42%), and thrombocytopenia (27%), infections (31%).

- **Peripheral neuropathy:** Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia. If these occur see above dose reductions and consider use of Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU. Caution in patients with existing peripheral neuropathy
- **Dizziness and orthostatic hypotension**: Patients should be advised that Bortezomib may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position. Caution in patients with history of syncope, receiving medications associated with hypotension and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells. Patients who experience dizziness or low blood pressure may benefit from 500ml intravenous 0.9% sodium chloride with each dose of bortezomib.
- **Myelosuppression**: Patients may require dose interruption and/or modification due to thrombocytopenia and/or neutropenia as above. Blood counts to be monitored monthly
- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with pomalidomide , and some form of prophylaxis is recommended as above
- **Gastrointestinal**: Nausea, diarrhoea, vomiting and constipation
- **Teratogenic:** The Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of pomalidomide must be in line with the pregnancy prevention programme.
- Fatigue, confusion, peripheral oedema, pneumonia.
- There is a published MHRA drug alert (2015) on pomalidomide and risks of cardiac failure, interstitial lung disease and hepatotoxicity. See weblink: https://www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity

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TREATMENT RELATED MORTALITY

<5%

REFERENCES

1. OPTIMISMM: Phase III Trial of Pomalidomide, Bortezomib, Low-Dose Dexamethasone vs Bortezomib, Low-Dose Dexamethasone in Lenalidomide-Exposed RRMM. ASCO 2018

2. PG Richardson et al. Pomalidomide, bortezomib and low-dose dexamethasone in lenalidomide-refractory and proteasome inhibitor-exposed myeloma. Leukemia (2017) 31, 2695–2701

3. Bortezomib (Velcade®) eMC UK Summary of Product Characteristics for, Janssen, 01 March 2017

4. Pomalidomide (IMNOVID) eMC UK Summary of Product Characteristics for Imnovid 4mg, Celgene, 04 May 2018

REVIEW

Name	Revision	Date	Version	Review date
Faouzi Djebbari (Haematology Pharmacist)	Protocol write up	July 2018	1.0	June 2019
Quality manager	Nursing care plan added	May 2021	1.1	June 2019

Nursing Care Plan: Pomalidomide Bortezomib and Dexamethasone

Indication: Relapsed/refractory Myeloma.

Frequency: 21 day cycles for as long as clinical benefit is maintained.

Alopecia: No

POMALIDOMIDE: Immunomodulator and angiogenesis inhibitor.

Administered orally on **days 1-14**

Emetic risk: Low

Side effects: VTE, fatigue, dizziness and confusion, peripheral neuropathy, diarrhoea/constipation, pneumonia, peripheral oedema. Risks of cardiac failure, interstitial lung disease and hepatotoxicity.

BORTEZOMIB (VELCADE): Proteasome inhibitor.

Administered subcutaneously **on days 1, 8, 15 for cycles 1-8**. Minimum of 72 hours required between doses.

From cycle 9 onwards Bortezomib is given on days 1 and 8 only.

Emetic risk: low

Classification of extravasation: irritant

Side effects: tachycardia, diarrhoea, constipation, anorexia, nausea/vomiting, thrombocytopenia, neutropenia, peripheral neuropathy (sensory and motor), headache, rash, fatigue, postural hypotension, dizziness, shingles, inflammation at injection site, infections, bone marrow depression.

DEXAMETHASONE: corticosteroid tablets

Administered orally on the day of each bortezomib dose and the day after. Taken with or after food preferably at breakfast

Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations

- Lying and standing blood pressure to be recorded pre cycle 1, advise patients that velcade can cause orthostatic hypotension and counsel them to sit upright for a moment before standing from a sitting/lying position.
- Advise patients to maintain a fluid intake of 2-3 litres and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- Assess for presence of peripheral neuropathy before starting treatment and **prior to the start of each cycle.**
- Bloods are required at the start of each cycle. Patients with unstable blood counts (specifically low platelets, see protocol) may require more frequent monitoring.
- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle.