BORTEZOMIB LENALIDOMIDE AND DEXAMETHASONE (VRD)

INDICATION

Induction therapy for Multiple Myeloma

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

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)
   - Hevylite analysis (if paraprotein level difficult to quantify)
   -
   - 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

- Plasma viscosity if hyperviscosity suspected
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology

2. Fertility - all patients should be offered fertility advice, as appropriate.
3. Hydration - fluid intake of at least 3 litres /day should be attempted.
4. Document patient's height and weight, dose on actual body weight.
5. Treatment must be agreed at the relevant MDT.
6. Document patient's performance status
7. 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. Obtain written consent for the treatment including signing Celgene risk Pregnancy Prevention Programme forms

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. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1 bortezomib.
3. The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the Celgene Pregnancy Prevention Programme.
4. Clinical Assessment of thrombo-embolic risk.

DRUG REGIMEN

Bortezomib	1.3 mg/m^2 given SC bolus	Days 1, 4, 8 and 11.
Lenalidomide	25 mg PO (preferably nocte)	Days 1-14.
Dexamethasone	20 mg PO once daily	On the day of and day after each Bortezomib dose. This will be on days 1, 2, 4, 5, 8, 9, 11 & 12

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

Bortezomib can also be administered weekly on days 1, 8 and 15 of a 21 days cycle.

CYCLE FREQUENCY

Repeat every 21 days, continue until maximal response plus two cycles or unacceptable toxicity up to a maximum of 6 - 8 treatment cycles. For patients eligible for transplant, interrupt treatment after 4 cycles to collect PBSC. Suitable patients can later continue on maintenance lenalidomide until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

Haematological toxicity:

BORTEZOMIB: Thrombocytopenia due to Bortezomib is transient and very rarely causes significant bleeding. If baseline platelet count is > 70 x 10^9/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).

LENALIDOMIDE: Treatment should not normally be given if ANC < 0.5 x 10^9/L, and/or platelet count < 30 x 10^9/L. If low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered.

Dose adjustments, as summarised below, are recommended to manage grade 3 or 4 neutropenia or thrombocytopenia, or other grade 3 or 4 toxicity judged to be related to lenalidomide.
Dose reductions below are based on a starting dose of 25 mg/day. Please be aware that some patients can start a reduced dose from cycle 1

Thrombocytopenia:

When platelets	Recommended Course
First fall to < 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at 15 mg once day
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mg once daily). Do not dose below 5 mg once daily.

Neutropenia:

When neutrophils	Recommended Course
First fall to < 0.5 x 10^9/L	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at 25 mg once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at 15 mg once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment. Administer G-CSF for 3 days.
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level (i.e. if was on 15 mg, reduce to 10 mg - or if was on 10 mg, reduce to 5 mgonce daily). Do not dose below 5 mg once daily.

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.

Grading of neuropathy	Bortezomib 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 (if the current dose is twice 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

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

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.

Lenalidomide

Renal		**Hepatic**
CrCl 30 – 49 mL/min CrCl < 30 mL/min, no dialysis CrCl < 30 mL/min, requiring dialysis	10mg once daily* 15 mg every other day** 5 mg once daily***	No formal studies. No specific dose recommendations
***Can increase to 15mg OD if no response and patient tolerating ** Can increase to 10mg OD if no response and patient tolerating *** On dialysis day, administer dose after dialysis		

INVESTIGATIONS (at the beginning of each cycle)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC U&E, Ca^{++}
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib
- Ig's, paraprotein, urinary BJP where present. Freelite assay may provide an early indication of response
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- 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. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl)<10ml/min) for the duration of treatment and for 3 months after stopping bortezomib
- Prophylactic fluconazole 50mg OD
- 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- see VTE section below.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Prescribe loperamide if needed for diarrhoea.
- Consider cholestyramine if suspicion of bile salt malabsorption with lenalidomide

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,

carbamazepine, phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

Extravasation risk: bortezomib-irritant

EMETIC RISK

Low

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

- **Teratogenic:** The Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme

- **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.

- **Diarrhoea:** was reported in 42% of patients requiring use of antidiarrheal medication (loperamide), supportive care and adequate hydration. Bile salt malabsorption occurs in a small proportion of patients on lenalidomide, consider dietary adjustments with low fat meal intake and prescribing bile acid sequestrants (colestyramine).

- **Rash**: can occur with lenalidomide. Antihistamines and topical corticosteroids can often be used to treat limited, localized, treatment-related rash, but lenalidomide interruption or discontinuation should be considered for grade 2/3 rash. Re-challenge with lenalidomide is reasonable in patients who do not have a severe rash and will often allow continued treatment. Lenalidomide must be discontinued for angioedema, grade 4 rash, and exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected, and should not be resumed after discontinuation for these reactions.

- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with lenalidomide. 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, lenalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines

- **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 500 mL intravenous 0.9% sodium chloride with each bortezomib dose.

- **Drowsiness, somnolence and sedation:** can occur with lenalidomide. Take the dose at night time. Lenalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking lenalidomide.
- **There is an MHRA alert on an increased risk of secondary malignancies** in three large trials of Lenalidomide treatment. The MHRA recommend vigilance in reporting such events promptly. Quoted incidence is 3 to 4% per annum.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

1. Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood. 2010 Aug 5;116(5):679-86.
2. Velcade ® Borrezomib eMC UK Summary of Product Characteristics, Janssen, February 2019
3. Lonial S, Waller EK, Richardson PG, Jagannath S, Orlowski RZ, Giver CR, Jaye DL, Francis D, Giusti S, Torre C, Barlogie B, Berenson JR, Singhal S, Schenkein DP, Esseltine DL, Anderson J, Xiao H, Heffner LT, Anderson KC; SUMMIT/CREST Investigators. Risk factors and kinetics of thrombocytopenia associated with bortezomib for relapsed, refractory multiple myeloma. Blood. 2005 Dec 1;106(12):3777-84.
4. Jimenez-Zepeda VH, Reece DE, Trudel S, Chen C, Tiedemann R, Kukreti V. Lenalidomide (Revlimid), bortezomib (Velcade) and dexamethasone for heavily pretreated relapsed or refractory multiple myeloma. Leuk Lymphoma. 2013 Mar;54(3):555-60.
5. Richardson PG, Jagannath S, Jakubowiak AJ, Lonial S, Raje N, Alsina M*, et al.* Phase II Trial of Lenalidomide, Bortezomib, and Dexamethasone In Patients (pts) with Relapsed and Relapsed/Refractory Multiple Myeloma (MM): Updated Efficacy and Safety Data After >2 Years of Follow-up. ASH Annual Meeting Abstracts 2010 November 19, 2010; 116(21): 3049.
6. Richardson PG, Weller E, Jagannath S, Avigan DE, Alsina M, Schlossman RL, et al. Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma. J Clin Oncol. 2009 Dec 1;27(34):5713-9.
7. Revlimid® (lenalidomide) 25mg capules. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, December 2018

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Pharmacist	Formatting, adverse effects and pre assessment section	May 2016	1.3	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated haematological toxicity, renal and hepatic impairment, concurrent medications and references	July 2017	1.4	June 2018
Nadjoua Maouche (Haematology pharmacist)	Standardisation of assessment, VTE information, investigations supports, adverse events.	June 2018	1.5	June 2019
Myeloma Protocol Review 2019	Update to: general pre-assessment, cycle frequency, extravasation risk, and references	June 2019	1.6	June 2020
Quality manager	Nursing care plan added	April 2021	1.7	June 2020

Nursing Care Plan: Bortezomib Lenalidomide Dexamethasone (VRD)

Indication: Relapsed or refractory myeloma.

Frequency: 6-8 cycles of 21 days.

Alopecia: No

BORTEZOMIB (VELCADE): Proteasome inhibitor

Administered subcutaneously on **days 1, 4, 8, 11 (can also be given on days 1, 8 and 15 of a 21 day cycle)**. Minimum of 72 hours required between doses.

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.

LENALIDOMIDE (REVLIMID): Immunomodulator and angiogenesis inhibitor.

Administered orally on **days 1-14.**

Emetic risk: minimal.

Side effects: neutropenia, peripheral neuropathy, diarrhoea, constipation, flu like syndrome, infections, fatigue, muscle cramps, rash/itching, venous thromboembolism, bone marrow depression, drowsiness/ sedation (recommended taking at night time).

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.
- 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 (due to the teratogenic effect of lenalidomide).
- Lenalidomide can cause a rash (may be paused if rash is grade 2-3).
- 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.**