

Chemotherapy Protocol

Myeloma

Clarithromycin-Dexamethasone (20)-Pomalidomide

Regimen

- Myeloma – Clarithromycin-Dexamethasone (20)-Pomalidomide

Indication

- Pomalidomide, in combination with low-dose dexamethasone, is recommended as an option for treating multiple myeloma in adults at third or subsequent relapse; that is, after 3 previous treatments including both lenalidomide and bortezomib.
- This protocol with a dose of dexamethasone of 20mg is recommended for those aged over 75 years.

Toxicity

| Drug | Adverse Effect |
|----------------|---|
| Clarithromycin | Rash, hyperhidrosis, gastrointestinal disturbances, insomnia, headaches |
| Dexamethasone | Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance. |
| Pomalidomide | Teratogenicity, cardiac failure, atrial fibrillation, thromboembolic events, interstitial lung disease, pneumonia, neutropenia, thrombocytopenia, leucopenia, anaemia, decreased appetite, dyspnoea, cough, gastrointestinal disturbance, bone pain, muscle spasm, fatigue, pyrexia, peripheral oedema, renal failure, peripheral neuropathy, skin reactions. |

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

Monitoring

Drugs

- FBC at baseline, then every two weeks for the first 8 weeks of treatment (the full cycle may be dispensed on day 1). Thereafter monitor prior to each cycle.
- U&Es, Ca²⁺ and LFTs prior to day one of each cycle of treatment.
- Paraprotein and/or light chains prior to each cycle.
- For all women of childbearing potential a negative pregnancy test must be obtained within the 3 days prior to starting pomalidomide. 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 pomalidomide.

- All patients should be tested for hepatitis B virus (HBV) before initiating treatment with pomalidomide. Those patients who test positive for HBV infection should be discussed with a consultation specialist in HBV prior to initiating treatment with pomalidomide. Pomalidomide in combination with dexamethasone should be used cautiously in patients previously infected with HBV, including patients who are anti-HBc positive but HBsAg negative. These patients should be closely monitored for signs and symptoms of active HBV infection throughout therapy.
- Perform a venous thromboembolism (VTE) risk assessment prior to starting treatment. Prescribe thromboprophylaxis.
- Regular monitoring of blood glucose is considered good practice.

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 the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or where the haemoglobin is less than 8g/dL (80g/L).

Consider growth factor support as an alternative to the options below, particularly where there is evidence of bone marrow suppression.

To initiate a new cycle of pomalidomide, the neutrophil count must be $1 \times 10^9/L$ or greater and the platelet count must be $50 \times 10^9/L$ or greater. No dose reductions are necessary for either clarithromycin or dexamethasone for haematological toxicity.

| Neutrophils ($\times 10^9/L$) | Dose Modifications |
|---|--|
| Less than $0.5 \times 10^9/L$ or febrile neutropenia (fever greater than or equal to $38.5^\circ C$ and neutrophils less than $1 \times 10^9/L$) | Interrupt pomalidomide treatment and monitor FBC weekly. Once neutrophils recover to $1 \times 10^9/L$, resume pomalidomide at a dose of 3mg once a day. |
| For each subsequent drop to less than $0.5 \times 10^9/L$ | Interrupt pomalidomide treatment and monitor FBC weekly, once neutrophils recover to $1 \times 10^9/L$ or greater then resume pomalidomide at 1mg less than previous dose. |
| Platelets ($\times 10^9/L$) | Dose Modifications |
| Less than $25 \times 10^9/L$ | Interrupt pomalidomide treatment and monitor FBC weekly. Once platelets recover to $50 \times 10^9/L$ or greater resume pomalidomide at a dose of 3mg once a day. |
| For each subsequent drop to less than $25 \times 10^9/L$ | Interrupt pomalidomide and monitor FBC weekly and once platelets recover to $50 \times 10^9/L$, resume pomalidomide at 1mg less than previous dose. |

Hepatic Impairment

Patients with serum total bilirubin greater than 2mg/dL were excluded from clinical studies. Hepatic impairment has a modest effect on the pharmacokinetics of pomalidomide. No adjustment of the starting dose of pomalidomide is required for patients with hepatic impairment as defined by the Child-Pugh criteria. However, patients with hepatic impairment should be carefully monitored for adverse reactions and dose reduction or interruption of pomalidomide should be used as needed. However, as markedly elevated levels of alanine aminotransferase and bilirubin have been observed in patients treated with pomalidomide together with cases of hepatitis that resulted in treatment discontinuation, regular monitoring of liver function is recommended for the first 6 months of treatment with pomalidomide and as clinically indicated thereafter.

Renal Impairment

No dose adjustment of pomalidomide is required for patients with renal impairment. Where patients are receiving haemodialysis, the pomalidomide dose should be taken following haemodialysis.

Pomalidomide

Cardiac Failure

Cardiac failure is a known common adverse reaction associated with pomalidomide treatment (ie occurs in between 1/10 and 1/100 patients who take pomalidomide). In most cases, this side effect occurs in patients with cardiac disease or cardiac risk factors and within six months of starting pomalidomide. Pomalidomide can cause atrial fibrillation, which may precipitate cardiac failure. Monitor for signs and symptoms of cardiac impairment.

Interstitial Lung Disease

Interstitial lung disease (ILD), including cases of pneumonitis, have been observed with pomalidomide. Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. Pomalidomide

should be interrupted during investigation of these symptoms and if ILD is confirmed, appropriate treatment should be initiated. Pomalidomide should only be resumed after a thorough evaluation of the benefits and the risks.

Pregnancy

As pomalidomide is structurally related to thalidomide a teratogenic effect is expected, therefore, it must not be taken during pregnancy. All women of child bearing potential (even if they have amenorrhoea) must use one effective method of pregnancy prevention at least 4 weeks before therapy, during therapy and even in the case of dose interruptions, and for at least a further 4 weeks after stopping therapy. Additionally a negative pregnancy test is required prior to commencing each cycle of therapy. Men are required to undertake to use a barrier method of contraception. The conditions of the Celgene Pregnancy Prevention Programme must be fulfilled for all patients unless there is reliable evidence that the patient does not have childbearing potential.

Skin

Pomalidomide interruption or discontinuation should be considered for WHO grade 2-3 skin rash. Pomalidomide must be discontinued for angioedema, WHO grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected, and should not be resumed following discontinuation from these reactions.

Venous Thromboembolism (VTE)

Patients receiving pomalidomide in combination with dexamethasone have developed venous thromboembolic events (predominantly deep vein thrombosis and pulmonary embolism) and arterial thrombotic events (myocardial infarction and cerebrovascular accident). Appropriate VTE prophylaxis is recommended. All patients should receive aspirin unless contra-indicated. Patients deemed to be at high risk of VTE should receive a low molecular weight heparin.

The duration of thromboprophylaxis remains unclear but guided by risk factors such as active disease (e.g. for the first 4 to 6 months of treatment until disease control achieved) and de-escalated or discontinued unless there are ongoing significant risk factors. If patients are treated with a low molecular weight heparin consider switching patients to aspirin after six cycles of therapy or after maximum response is achieved.

A high index of suspicion for venous thromboembolism should always be maintained. If a venous thrombosis or embolism NCI-CTC grade 3 or above occurs then stop treatment and start full anticoagulation. Pomalidomide may be restarted at the clinician's discretion, once the patient is fully anti-coagulated.

Modifiable risk factors for thromboembolic events should be managed wherever possible to reduce the risk of VTE (e.g. smoking cessation; control of hypertension and hyperlipidaemia). Medicines that may increase the risk of thromboembolism, such as oestrogens and erythropoietic agents, should be used with caution during pomalidomide treatment.

For all other NCI-CTCAE grade 3 or 4 adverse reactions, judged to be related to pomalidomide, stop treatment. Restart treatment when the adverse reaction has resolved to NCI-CTC grade 2 or below at 1 mg less than the previous dose, or at the consultants discretion.

[Dexamethasone](#)

| Dose Level | Dose |
|--------------|------|
| 3 (starting) | 20mg |
| 2 | 12mg |
| 1 | 8mg |

If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by one dose level.

| Toxicity | Grade (NCI-CTC) | Dose modification |
|------------------------------|-----------------|--|
| Dyspepsia | 1 - 2 | Maintain dose and treat with histamine (H ₂) antagonist or proton pump inhibitor. Decrease by one dose level if symptoms persist. |
| | 3 or above | Interrupt dose until symptoms are controlled. Add H ₂ blocker or proton pump inhibitor and decrease one dose level when dose restarted. |
| Oedema | 3 or above | Use diuretics as needed and decrease dose by one dose level. |
| Confusion or mood alteration | 2 or above | Interrupt dose until symptoms resolve. When dose restarted decrease dose by one dose level. |
| Muscle weakness | 2 or above | Interrupt dose until the muscle weakness is grade 1 or below. Restart with dose decreased by one level. |
| Hyperglycaemia | 3 or above | Decrease dose by one dose level. Treat with insulin or oral hypoglycaemic agents as needed |
| Acute pancreatitis | | Discontinue patient from dexamethasone treatment regimen. |
| Other | 3 or above | Stop dexamethasone dosing until adverse event resolves to grade 2 or below. Resume with dose reduced by one level. |

[Regimen](#)

28 day cycle until disease progression or intolerance (12 cycles will be set in Aria)

| Drug | Dose | Days | Administration |
|------|------|------|----------------|
|------|------|------|----------------|

| | | | |
|----------------|-------------------|----------------|------|
| Clarithromycin | 500mg twice a day | 1-28 inclusive | Oral |
| Dexamethasone | 20mg | 1, 8 15 and 22 | Oral |
| Pomalidomide | 4mg once a day | 1-21 inclusive | Oral |

[Dose Information](#)

- Pomalidomide is available as 1mg, 2mg, 3mg and 4mg hard capsules.
- Clarithromycin is available as 250mg and 500mg tablets
- Dexamethasone is available as 500microgram, 2mg and 4mg tablets

[Administration Information](#)

- Pomalidomide should be taken at the same time each day. The capsules should be swallowed whole, preferably with water, with or without food and not be opened, broken or chewed.
- Pomalidomide can cause drowsiness it may be advisable to take it at night.
- If a dose of pomalidomide is forgotten on one day, the normal prescribed dose should be taken the next day. Patients should not adjust the dose to make up for missing a dose on previous days.
- It is recommended to press only on one end of the pomalidomide capsule to remove it from the blister thereby reducing the risk of capsule deformation or breakage.
- Dexamethasone should be taken in the morning with or immediately after food.
- All prescriptions for pomalidomide must be accompanied by an electronic prescription authorisation form (ePAF).

[Additional therapy](#)

- Thromboprophylaxis, the choice depending on risk factors and duration of therapy.
- Consider allopurinol 300mg once a day for seven days for the first cycle only oral
- Consider anti-infective prophylaxis including (included in ARIA);
 - aciclovir 400mg twice a day oral
 - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
 - fluconazole 50mg once a day 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 H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to pomalidomide.
- It must be made clear to all staff, including those in the community, that pomalidomide should only be prescribed under the supervision of a consultant haematologist.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.
- For all patients taking pomalidomide; the patient, prescriber and supplying pharmacy must comply with the Celgene pregnancy prevention programme (PPP).
- Clarithromycin and pomalidomide interact with many other medications. Always check for drug interactions.

Coding

- Procurement – X71.5
- Delivery – X73.1

References

1. Celgene Limited (2016). Imnovid 4mg Summary of Product Characteristics. Electronic Medicines Compendium. Online at <http://www.medicines.org.uk/emc/medicine/29475>, accessed 25 January 2017.
2. National Institute for Health and Care Excellence (2017). Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib. [TA427]. London: National Institute for Health and Care Excellence.
3. Celgene Limited (2013). Imnovid (Pomalidomide) Healthcare Professionals Information Pack UK Version 1.0.
4. Dimopoulos MA, Palumbo A, Corrodini P et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. *Blood* (2016); 128 (4): 497-503.

REGIMEN SUMMARY

Clarithromycin-Dexamethasone (20)-Pomalidomide

Cycle 1

Take home medicines

1. Clarithromycin 500mg twice a day for 28 days oral
2. Dexamethasone 20mg on days 1, 8, 15 and 22, oral
Administration Information
Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.
3. Warning – Pregnancy Prevention Programme
Administration Instructions
Pomalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.
4. Pomalidomide 4mg once a day on days 1-21 oral
Administration Information
Oral chemotherapy
Pregnancy prevention programme
Take at the same time each day. Swallow the capsules whole, preferably with water, with or without food.
5. Allopurinol 300mg once a day for 7 days, oral
Administration information
Take in the morning with food and plenty of water. This should be supplied for the first cycle.
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 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.
8. Fluconazole 50mg once a day for 28 days oral
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 supply 28 days or the nearest original pack size.

10. Thromboprophylaxis according to risk factors

Administration Instructions

The choice of thromboprophylaxis is dependent on risk factors. Aspirin 75mg once a day in the morning may be prescribed for low risk individuals. For those deemed high risk consider a low molecular weight heparin such as;

- 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 onwards

Take home medicines

1. Clarithromycin 500mg twice a day for 28 days oral

2. Dexamethasone 20mg on days 1, 8, 15 and 22, oral

Administration Information

Take in the morning with or after food. Please dispense all days on day 1 of the cycle. This may be dispensed in one bottle, or individual bottles according to local practice.

3. Warning – Pregnancy Prevention Programme

Administration Instructions

Pomalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

4. Pomalidomide 4mg once a day on days 1-21 oral

Administration Information

Oral chemotherapy

Pregnancy prevention programme

Take at the same time each day. Swallow the capsules whole, preferably with water, with or without food.

5. Aciclovir 400mg twice a day for 28 days oral

Administration Instructions

Please supply 28 days or an original pack if appropriate.

6. 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.

7. Fluconazole 50mg once a day for 28 days oral

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 supply 28 days or the nearest original pack size.

9. Thromboprophylaxis according to risk factors

Administration Instructions

The choice of thromboprophylaxis is dependent on risk factors. Aspirin 75mg once a day in the morning may be prescribed for low risk individuals. For those deemed high risk consider a low molecular weight heparin such as;

- 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 2018 | None | Mrs Eleanor Taylor Pharmacist Dr Deborah Wright Pharmacist | Dr N Ryman 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 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.