Chemotherapy Protocol

Myeloma

IRD (20) - Dexamethasone (20)-Ixazomib-Lenalidomide

Regimen

- Myeloma – IRD (20) - Dexamethasone (20)-Ixazomib-Lenalidomide

Indication

- Ixazomib and lenalidomide, in combination with dexamethasone, is recommended as an option for treating multiple myeloma provided the following criteria are met:

  - the patient has received two or three prior lines* of treatment and that the numbering of these lines of treatment is in accordance with the International Myeloma Workshop Consensus recommendations. Patients previously treated with only one or more than three lines of treatment are not eligible for ixazomib.

    *A line of therapy is defined as one or more cycles of a planned treatment program. This may consist of one or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner (eg induction chemotherapy and stem cell transplantation is considered to be one line of therapy). A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

  - the patient is neither refractory to previous proteasome inhibitor-based nor lenalidomide-based treatment at any line of therapy (in this context, refractory disease is defined as disease progression on treatment or disease progression within 60 days of the last dose of a proteasome inhibitor or lenalidomide). As lenalidomide is only commissioned by NHS England after two prior therapies, the only eligible patients who have had prior lenalidomide must have received it in the context of a clinical trial in an earlier line of therapy. Such patients must not be refractory to lenalidomide according to the above definition.

  - the patient has either been refractory to one or more lines of therapy or has responded and relapsed after each line of therapy

  - the patient must be treatment naïve to any therapy with ixazomib

  - ixazomib must only be used in combination with lenalidomide and dexamethasone. All three drugs must be commenced at the same time. Ixazomib cannot be added as an additional agent in the treatment of patients who have previously been treated with lenalidomide and dexamethasone.

  - no treatment break beyond six weeks of the expected cycle length

  - WHO performance status of 0, 1 or 2

Toxicity

Drug	Adverse Effect
Dexamethasone	Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, Cushingoid changes, glucose intolerance.
Ixazomib	Peripheral neuropathy, posterior reversible encephalopathy syndrome, rash, GI symptoms, peripheral oedema, thrombocytopenia, hepatotoxicity, Herpes zoster re-activation
Lenalidomide	Peripheral neuropathy, pneumonia, infections, venous thrombotic events, respiratory dysfunction, rashes, hypokalaemia, hypomagnesaemia, hypocalcaemia, teratogenic risk, GI disturbances, flu-like symptoms.

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

Monitoring

Drugs

- FBC at baseline. Thereafter monitor prior to each cycle.
- U&Es, Ca^{2+} 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 lenalidomide. 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 lenalidomide.
- Perform a venous thromboembolism (VTE) risk assessment prior to starting treatment with lenalidomide. Prescribe thromboprophylaxis for patients with additional risk factors.
- 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.

The following table describes dose adjustments for ixazomib and lenalidomide based on toxicity. The starting dose may vary depending on factors such as renal and hepatic function or performance status. The lenalidomide dose should not drop below 5mg.

Dose Level	Ixazomib Dose	Lenalidomide Dose
Starting Dose	4mg	25mg
-1	3mg	15mg
-2	2.3mg	10mg
-3	discontinue	5mg

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.

Prior to starting a cycle of treatment the platelet count must be equal to or higher than $75x10^9$/L and the neutrophil count must be equal to or higher than higher than $1x10^9$/L.

The dose of dexamethasone does not require adjustment for haematological toxicity.

Toxicity	Action	Ixazomib dose when restarting	Lenalidomide dose when restarting
First Occurrence Platelet count less than $30x10^9$/L or neutrophils less than $0.5x10^9$/L	Hold until platelets are greater than or equal to $30x10^9$/L AND the neutrophil count is greater than or equal to $0.5x10^9$/L and consider adding G-CSF	No change	Decrease by 1 dose level
Second Occurrence Platelet count less than $30x10^9$/L or neutrophils less than $0.5x10^9$/L	Hold until platelets are greater than or equal to $30x10^9$/L AND the neutrophil count is greater than or equal to $0.5x10^9$/L and consider adding G-CSF	Decrease by 1 dose level	No change

Hepatic Impairment

Hepatic impairment	Ixazomib dose	Lenalidomide dose
Mild (total bilirubin less than or equal to ULN and AST greater than ULN OR the total bilirubin 1-1.5xULN and any AST)	No doseage adjustment required	No dose adjustment required
Moderate or severe (total bilirubin greater than 1.5xULN)	3 mg	No data

Renal Impairment

Creatinine Clearance (ml/min)	Ixazomib dose	Lenalidomide dose
Greater than or equal to 60	No dose adjustment	No dose adjustment
30 – 59	No dose adjustment	10 mg once a day (may be escalated to 15 mg once a day after 2 cycles if patient is not responding to treatment and is tolerating the drug)
Less than 30 (not requiring dialysis)	3 mg	15 mg every other day
Less than 30 (requiring dialysis)	3 mg	5 mg once a day. On dialysis days, the dose should be administered following dialysis

Other

Toxicity		Action	Ixazomib dose when restarting	Lenalidomide dose when restarting
Rash	NCI-CTC grade 2 or 3	Hold both until less than or equal to NCI-CTC grade 1	Continue at same dose. If it recurs, hold until recovery and then resume with 1 dose level reduction	Resume with 1 dose level reduction Discontinue if greater than or equal to NCI-CTC grade 2 exfoliative skin toxicity
	NCI-CTC grade 4	Discontinue	Discontinue	Discontinue

Toxicity		Action	Ixazomib dose when restarting	Lenalidomide dose when restarting
Peripheral Neuropathy	NCI-CTC grade 1 with pain or grade 2	Hold ixazomib until less than or equal to NCI-CTC grade 1 without pain or patient's baseline	Resume at same dose	Continue at same dose
	Grade 2 with pain or grade 3	Hold both until less than or equal to NCI-CTC grade 1 without pain or patient's baseline	1 dose level reduction	Consider 1 dose level reduction if NCI-CTC grade 3
	Grade 4	Discontinue	Discontinue	Discontinue
Other NCI-CTC grade 3 or 4 non-haematological toxicities		Hold both until recovery to baseline or less than or equal to NCI-CTC grade 1	If toxicity due to ixazomib, resume at 1 dose level reduction once recovered or discontinue	If toxicity due to lenalidomide, resume at 1 dose level reduction once recovered or discontinue. If pneumonitis investigate and discontinue if confirmed

Lenalidomide

Pregnancy

As lenalidomide 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.

Patients should not donate blood or semen while taking lenalidomide and for eight weeks after stopping therapy to prevent foetal exposure via blood transfusion of pregnant women.

Venous Thromboembolism (VTE)

Patients receiving lenalidomide 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 be initially prescribed a low molecular weight heparin at the appropriate prophylactic dose. Aspirin 75mg each morning is an alternative in very low risk patients once a response has been obtained.

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. Lenalidomide 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 lenalidomide treatment.

For all other NCI-CTCAE grade 3 or 4 adverse reactions, judged to be related to lenalidomide, stop treatment. Restart treatment when the adverse reaction has resolved to NCI-CTC grade 2 or below at one dose level below the previous dose, or at the consultant's discretion.

Dexamethasone

Dose Level	Dose
3 (starting)	20mg
2	10mg
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 or the patient chooses to stop treatment (12 cycles will be set in Aria)

Drug	Dose	Days	Administration
Dexamethasone	20mg once a day	1, 8, 15 and 22	Oral
Ixazomib	4mg once a day	1, 8, 15	Oral
Lenalidomide	25mg once a day	1-21 inclusive	Oral

Dose Information

- Dexamethasone is available as 500microgram, 2mg and 4mg tablets and as a 2mg/5ml oral liquid.
- Ixazomib is available as 2.3mg, 3mg and 4mg capsules
- Lenalidomide is available as 5mg, 10mg, 15mg and 25mg capsules

Administration Information

- Dexamethasone should be taken in the morning with or immediately after food.
- Ixazomib should be taken once a week on the same day and at approximately the same time for the first 21 days of a 28 day cycle.
- The ixazomib capsule should be swallowed whole with water, on an empty stomach (at least one hour before or at least two hours after food).
- The ixazomib capsule should not be crushed, chewed, or opened. Direct contact with capsule contents should be avoided as inhalation, ingestion, or skin absorption may be harmful.
- If a dose of ixazomib is missed, it should be taken only if the next scheduled dose is greater than or equal to 72 hours away. A double dose should not be taken to make up for a missed dose.
- If a patient vomits after taking a dose of ixazomib, the patient should not repeat the dose; resume dosing at the time of the next scheduled dose.
- If a dose of lenalidomide is missed, it may be taken up to 12 hours after the time it is normally taken. Otherwise, skip this and take the next dose on the following day at its usual scheduled time.
- All prescriptions for lenalidomide must be accompanied by a prescription authorisation form (PAF).

Additional therapy

- No antiemetics are required.
- Thromboprophylaxis, the choice depending on risk factors and duration of therapy.
- Consider allopurinol 300mg oral once a day for seven days for the first cycle only
- Consider anti-infective prophylaxis including;
  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
- 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 Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to ixazomib and lenalidomide.
- It must be made clear to all staff, including those in the community, that ixazomib and lenalidomide 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 lenalidomide; the patient, prescriber and supplying pharmacy must comply with the Celgene pregnancy prevention programme (PPP).

Coding

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

References

1.Moreau P, Masszi T, Grzasko N, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016; 374:1621-1634.

2.National Institute for Health and Clinical Excellence. Technology Appraisal 505. Ixazomib with lenalidomide and dexamethsone for treating relapsed or refractory multiple myeloma. February 2018. NICE:DOH

REGIMEN SUMMARY

IRD (20)-Dexamethasone (20)-Ixazomib-Lenalidomide

Cycle 1

Take home medicines

1. Dexamethasone 20mg on days 1, 8, 15 and 22 oral
   Administration Information
   Please supply four doses of dexamethasone on day 1 of the cycle, ONE dose to be taken on days 1, 8, 15 and 22
   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.

2. Ixazomib 4mg once a day on days 1, 8, 15
   Administration Instructions
   Please supply all three doses on day 1 of the cycle, ONE dose to be taken on days 1, 8 and 15.
   Oral chemotherapy

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

4. Lenalidomide 25mg 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. 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 local formulary 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

   Aspirin 75mg each morning may be considered once a maximum response has been achieved or afer six cycles

   Please supply 28 days or nearest original pack size.

Cycle 2 onwards

Take home medicines

10. Dexamethasone 20mg on days 1, 8, 15 and 22, oral
    Administration Information
    Please supply four doses of dexamethasone on day 1 of the cycle, ONE dose to be taken on days 1, 8, 15 and 22
    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.

11. Ixazomib 4mg once a day on days 1, 8, 15
    Administration Instructions
    Please supply all three doses on day 1 of the cycle, ONE dose to be taken on days 1, 8 and 15
    Oral chemotherapy

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

13. Lenalidomide 25mg 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.

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

15. 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.

16. 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.

17. Thromboprophylaxis according to risk factors

Administration Instructions

The choice of thromboprophylaxis is dependent on local formulary 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

Aspirin 75mg each morning may be considered once a maximum response has been achieved or afer six cycles

Please supply 28 days or nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2018	None	Dr Deborah Wright Pharmacist	Dr Srinivasan Narayanan 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. These protocols are only one source of information. They should be read in conjunction with the latest Summary of Product Characteristics and published information.