Thames Valley
Strategic Clinical Network

DARATUMUMAB WITH LENALIDOMIDE AND DEXAMETHASONE

INDICATION

Relapsed 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
   - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
   - 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)
   - Transfusion assays add
   - β_2 microglobulin
   - 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.
   - Imaging as per NICE/network guidance and clinical presentation

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

Additional investigations:

- o Plasma viscosity if hyperviscosity suspected.

2. 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.
3. Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
4. Counselling - all patients should receive verbal and written information on oral chemotherapy.
5. Ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures
6. Fertility - all patients should be offered fertility advice, as appropriate.
7. Hydration - fluid intake of at least 3 litres /day should be attempted.
8. Document patient's height and weight, dose on actual body weight.
9. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE-ASSESMENT

- The conditions of the Lenalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients.
- Clinical Assessment of thrombo-embolic risk.
- **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that patient is due to commence daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of daratumumab to red cells.**

DRUG REGIMEN

Cycles 1 &2

Daratumumab	Pre-meds: 1 hour prior to infusion Montelukast 10mg PO on **(cycle 1 only)**, Paracetamol 1g PO, Chlorphenamine 10 mg IV, **Dexamethasone** 20mg* IV bolus or PO (can be reduced to 12mg following the second infusion)	Days 1, 8, 15 and 22
	Daratumumab 16mg/kg Intravenous infusion.	Days 1, 8, 15 and 22
	Post-infusion: **Dexamethasone** 20mg PO*	Days 2, 9, 16 and 23 i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*
	***Note: Pre- and post- infusion dexamethasone is also being used as the weekly steroid component of the triple combination regime.	
Lenalidomide	The starting dose of lenalidomide is 25 mg orally once daily. Dose reductions may apply see below.	Days 1 to 21

Cycles 3 to 6

Daratumumab	Pre-meds: 1 hour prior to infusion Paracetamol 1g PO, Chlorphenamine 10 mg IV, **Dexamethasone** 12mg* IV bolus or PO **Daratumumab** 16mg/kg Intravenous infusion. Post-infusion: **Dexamethasone** 12mg PO*	Days 1 and 15 Days 1 and 15 Days 2 and 16 i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*
	***Note: On daratumumab weeks, pre- and post- infusion dexamethasone also being used as the weekly steroid component of the triple combination regime.	
Dexamethasone	40mg PO once weekly* (The dose may be reduced in the elderly or if steroid-related side effects develop)	Days 8 and 22*
	*Note: On days 1 and 15, the weekly dexamethasone dose as part of the triple combination is administered as the pre- and post-infusion steroids.	
Lenalidomide	The starting dose of lenalidomide is 25 mg PO once daily. Dose reductions may apply see below.	Days 1 to 21

Cycle 7- Onwards

Daratumumab	Pre-meds: 1 hour prior to infusion Paracetamol 1g PO, Chlorphenamine 10 mg IV, **Dexamethasone** 12mg* IV bolus or PO **Daratumumab** 16mg/kg Intravenous infusion. Post-infusion: **Dexamethasone** 8mg PO*	Day 1 Day 1 Day 2 i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*
	***Note: On daratumumab weeks, dexamethasone is also being used as the weekly steroid component of the triplet combination regime.	
Dexamethasone	40mg PO once weekly* (The dose may be reduced in the elderly or if steroid-related side effects develop)	Days 8, 15 and 22*
	*Note: On day 1, the weekly dexamethasone dose as part of the triple combination is administered as per the pre- and post-infusion steroids.	
Lenalidomide	The starting dose of lenalidomide is 25 mg PO once daily. Dose reductions may apply see below.	Days 1 to 21

INFUSION RATES

The first dose of daratumumab must be given as an inpatient

Administer via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate. Consider incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion.

	Dilution volume (Sodium chloride 0.9%)	**Initial rate (first hour)**	**Rate increment**	**Maximum rate**
First infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.
[b] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥ 100mL/hr in the first two infusions.
Note: For guidance on infusion rates **in the case of infusion related reactions**. See the managing infusion reactions section below.

CYCLE FREQUENCY

The cycle is repeated every 28 days until disease progression.

DOSE MODIFICATIONS

Myelosuppression:
Lenalidomide treatment should not normally be given if the Absolute Neutrophil Counts (ANC) < 1.0 x 10^9/L, and/or platelet count < 30 x 10^9/L. If the low counts are thought to be due to myeloma per se, the use of G-CSF and platelet support should be considered.
No dose adjustments are made for daratumumab.

Recommended dose adjustments during treatment and to restart treatment:
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 alone. For other grade 3 or 4 toxicities, lenalidomide should be interrupted and restarted at the next lower dose level once toxicity has resolved to grade 2 or less.
Note: Consider re-escalating lenalidomide dose provide toxicities have completely resolved.
Starting dose = 25 mg/day.

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/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 < 1.0 x 10^9/L	Interrupt lenalidomide treatment. Administer G-CSF for 3 days and recheck FBC.
Return to ≥ 1.0 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at 25 mg once daily
Return to ≥ 1x 10^9/L when dose-dependent haemato-logical toxicities other than neutropenia are observed	Resume lenalidomide at 15 mg once daily
For each subsequent drop below < 1.0x 10^9/L	Interrupt lenalidomide treatment. Administer G-CSF for 3 days.
Return to ≥ 1.0 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.

Renal/Hepatic Impairment:
DARATUMUMAB:

Renal	Hepatic
No dosage adjustment is necessary for patients with pre-existing renal impairment	No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment

LENALIDOMIDE:

Renal		Hepatic
CrCl 30- <50 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 to15mg 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 – during treatment

- FBC, U&Es, LFTs, Ca^{++}, glucose – every 3 - 4 weeks.
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Random blood glucose/ blood sugar

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Prophylactic fluconazole.
- Thromboprophylaxis/anticoagulation as above.
- Prophylactic aciclovir 200 mg bd to tds (depending on renal function).
- Consider prophylactic co-trimoxazole if heavily pre-treated or previous autograft. Pentamidine can be considered for patients who are intolerant or allergic to co-trimoxazole.
- Consider prophylactic laxatives to be taken if needed.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Consider cholestyramine if suspicion of bile salt malabsorption

EMETIC RISK

Low risk.

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

The most common adverse events are neutropenia, anaemia, thrombocytopenia, upper respiratory tract infections, pneumonia, diarrhoea/constipation, fatigue and infusion reactions.

1- DARATUMUMAB-RELATED:

Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

I. **Blood Transfusion must be notified of this interference with serological testing and Blood Bank must be notified that a patient has received daratumumab.**

II. **Patients must be screened prior to starting daratumumab.**

III. **Transfusion alert card**

Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody detectable on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in all patients with IgG kappa myeloma.

Contraception

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment.

Infusion reactions

- Daratumumab can cause severe infusion reactions. Approximately half of all patients treated have experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing daratumumab. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.
- Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, and hypertension. Signs and symptoms may include respiratory symptoms, such as cough, wheezing, larynx and throat tightness and irritation, laryngeal oedema, pulmonary oedema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.
- Pre-meds must be given 1 hour before the infusion. Patients must be monitored during the entire infusion.
- To reduce the risk of delayed infusion reactions, corticosteroids are given to all patients on the first and second day after all infusions
- Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short-and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders**.**

Managing Infusion related reactions

For infusion reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation as outlined below.

IRR grade	Recommendation
Grade 1-2 (mild to moderate)	Once symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate.
Grade 3 (severe)	If the intensity of the reaction decreases to ≤Grade 2, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate. Permanently discontinue treatment upon the third occurrence of a Grade 3 or greater reaction.
Grade 4 (life threatening)	Permanently discontinue treatment.

Other common adverse effects:

Fatigue, allergic rhinitis, pyrexia, nasopharyngitis, URTI, cough, GI disorders (nausea, constipation, diarrhoea), headache, neutropenia and hypertension have also been reported. The most common serious adverse reactions were pneumonia, and pyrexia.

2- LENALIDOMIDE-RELATED

- **Teratogenicity**: The risk management programme should be observed - see link to manufacturers data sheet on website. The concomitant use of an effective method of contraception is mandatory in all female patients of childbearing potential. Male patients should also use a condom when having sexual intercourse with women of childbearing potential. **Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme**.
- **Diarrhoea:** Diarrhea was reported in 42% of patients requiring use of antidiarrheal medication and supportive care. Bile salt malabsorption occurs in a small % of patients of lenalidomide, and consider addition of cholestyramine
- **Venous thromboembolism (VTE):**
  There is an increased risk of thrombosis, and some form of prophylaxis is recommended as follows:
  1. Aspirin can be appropriate for patients with no additional risk factors for thrombosis
  2. If additional risk factors consider:
     - Prophylactic low-molecular weight heparin, OR
     - Vitamin K antagonists at a therapeutic dose, to maintain an international normalised ratio (INR) of 2–3, OR
     - Direct oral anticoagulant e.g. apixaban for thromboprophylaxis or treatment dose as indicated.

Aspirin is generally not preferred for higher risk patients with additional risk factors such as immobility. If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- **Drowsiness, somnolence and sedation**: 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.

- **Peripheral neuropathy**: Patients should be advised to report prickling, numbness and paraesthesia. Lenalidomide is structurally related to thalidomide, which is known to induce neuropathy. However, published data suggests that significant toxicity is uncommon.
- **Dizziness and orthostatic hypotension**: Patients should be advised that lenalidomide may cause orthostatic hypotension and that, if affected, they should sit upright for a few minutes prior to standing up from a recumbent position.
- **Other warnings**: Patients should be informed not to donate blood or semen during or within 8 weeks of stopping lenalidomide treatment.
- **There is an MHRA alert on an increased rick 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

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REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung (Specialist Cancer Pharmacist)	New document	Feb 2017	1.0	Feb 2019
Faouzi Djebbari (Haematology Pharmacist)	Updated renal and hepatic impairment, concurrent medication and references	July 2017	1.1	June 2018