Chemotherapy Protocol

Myeloma

Bortezomib (twice weekly) Daratumumab Dexamethasone Cycles 9 onwards

Regimen

- Myeloma – Bortezomib (twice weekly) with daratumumab and dexamethasone
  Note bortezomib is given during cycles 1 to 8 only

Indication

- Daratumumab in combination with bortezomib and dexamethasone is recommended for use within the Cancer Drugs Fund as an option for treating relapsed multiple myeloma in people who have had 1 previous treatment.
- A weekly bortezomib regimen is available for patients who experience neuropathy or those with pre-existing neuropathy. Note both regimens include 32 doses of bortezomib; therefore bortezomib continues to the end of cycle 10 in the weekly regimen. Ensure the correct daratumumab cycle 9 onwards is selected.

Toxicity

Drug	Adverse Effect
Daratumumab	Infusion related reactions, hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, respiratory tract infections (including pneumonia), neutropenia, thrombocytopenia, anaemia, lymphopenia, peripheral neuropathy, diarrhoea, muscle spasms, fatigue, pyrexia and peripheral oedema, blood transfusion related events. Daratumumab interferes with indirect antiglobulin tests as it binds to CD38 on red blood corpuscles (RBCs) and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered. Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response **Please inform blood transfusion when a patient is prescribed daratumumab – before first administration in cycle 1.**
Dexamethasone	Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, Cushingoid changes, glucose intolerance.

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

Monitoring

Drugs

- FBC, U&Es, Ca^{2+} and LFTs prior to day one of each cycle of treatment.
- Paraprotein and / or light chains prior to each cycle.
- All patients should be tested for hepatitis B virus (HBV) before initiating treatment with daratumumab. Those patients who test positive for HBV infection should be discussed with a consultant specialising in HBV prior to initiating treatment with daratumumab to plan monitoring requirements whilst on treatment. Patients should also be tested for hepatitis C, CMV and HIV at the same time.
- Send a blood 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.
- Regular monitoring of blood glucose is considered good practice due to dexamethasone use.

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

No dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity. Always refer to the responsible consultant, as any dose 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 daratumumab, the neutrophil count must be $1x10^9$/L or greater and the platelet count must be $50x10^9$/L or greater, unless the low counts are due to bone marrow infiltration with myeloma. In this situation the daratumumab may be administered at

the discretion of the treating consultant haematologist with the appropriate blood product and growth factor support.

Neutrophils (x10^9/L)	Dose Modifications Daratumumab
Less than 0.5x10^9/L or febrile neutropenia (fever greater than or equal to 38.5℃ and neutrophils less than 1)	Interrupt daratumumab treatment and monitor FBC weekly. Once neutrophils recover to 1x10^9/L, resume daratumumab at a dose of 16mg/kg.
Platelets (x10^9/L)	**Dose Modifications**
Daratumumab Less than 50x10^9/L	Interrupt daratumumab treatment and monitor FBC weekly. Once platelets recover to 50x10^9/L or greater resume daratumumab at a dose of 16mg/kg.

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin µmol/L		AST/ALT units/L	Dose (% of original dose)
Daratumumab	No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population pharmacokinetic analysis no dosage adjustments are necessary for patients with hepatic impairment			

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Daratumumab	No adjustments necessary	

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes

Infusion related reactions (IRR)

Infusion reactions are reported in approximately half of patients who receive daratumumab and may occur up to 48 hours after the infusion has finished. The majority of infusion related reactions, 46%, occur with the first infusion, 2% with the second infusion and 3% with subsequent infusions. Signs and symptoms include bronchospasm, hypoxia, dyspnoea, hypertension, respiratory symptoms such as cough, wheezing, larynx and throat tightness and irritation, laryngeal oedema, pulmonary oedema, nasal congestion and allergic rhinitis.

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

IRR grade	Dose modification
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.

Regimen

28 day cycle. Continue daratumumab until disease progression. Note that cycle length changes from 21 days to 28 days from cycle 9 onwards.

Cycle 9 onwards
Bortezomib is given cycles 1 to 8 only

Drug	Dose	Days	Administration
Daratumumab	16mg/kg	1	Intravenous infusion in 500ml sodium chloride 0.9%
Dexamethasone	20mg once a day	1	Oral Can be given as dose equivalent as iv bolus Reduce dose to 10mg (or iv dose equivalent) in over 75yrs
Dexamethasone	4mg	2 and 3	To reduce the risk of delayed infusion reactions

Dose Information

- Daratumumab will be prescribed in accordance with the national dose bands (20 NS).
- Dexamethasone is available as 4mg, 2mg and 500microgram tablets and 3.3mg in 2ml injection (equivalent to 4mg orally)

Administration Information

- The rate of daratumumab administration varies and depends on infusion related reactions. In order to determine the rate of the second and ongoing infusions all reactions and the first reaction free infusion must be recorded in the ARIA journal.

- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.

	Final volume	Initial rate (first hour)	Rate increment[a]	Maximum rate
First infusion	500ml	25ml/hour	25ml/hour every hour	100ml/hour
Second infusion[b]	500ml	50ml/hour	50ml/hour every hour	200ml/hour
Subsequent infusions[c]	500ml	100ml/hour	50ml/hour every hour	200ml/hour

[a] Consider the incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion

[b] Escalate only if the patient's first infusion of daratumumab was well tolerated (defined by an absence of NCI-CTC grade 2 or greater infusion-related reactions during the first 3 hours). If the previous infusion was not well tolerated then instructions for the first infusion

[c] Escalate only if the patient's first 2 infusions of daratumumab were well tolerated (defined by an absence of NCI-CTC grade 1 or greater infusion-related reactions during a final infusion rate of greater than or equal to 100 ml/hr). If the previous infusion was not well tolerated, then instructions for the second infusion will be used.

For guidance on infusion rates in the case of infusion related reactions. See the managing infusion reactions section above.

Rapid Infusion Protocol

Data from a prospective, single-center and open label safety study of an accelerated daratumumab infusion suggests that a rapid (90 minute) daratumumab infusion schedule is well tolerated and safe, when administered from the 3rd infusion onwards in patients who have tolerated the 500mL daratumumab infusion at the manufacturer recommended rates.

- The rapid rate of infusion is currently unlicensed.

Inclusion criteria for daratumumab rapid rate infusion

- Patients from third daratumumab infusion onwards who have received and tolerated the previous daratumumab 100mL/hour initial infusion rate with escalation to the standard manufacturer licensed rate without Grade 1 infusion related reactions.
- Patients who have given consent to rapid rate daratumumab infusion if required by the individual Trust

Exclusion criteria for daratumumab rapid rate infusion

- Previous greater than or equal to grade 3 infusion related toxicity with daratumumab

- Infusion related reactions greater than or equal to grade 1 with the most recent daratumumab infusion given at the standard manufacturer licensed rate.
- Cardiac amyloid patients
- Patients receiving daratumumab as part of clinical trials (follow trial protocol)

Rapid infusion rate

Daratumumab prepared in 500mL sodium chloride 0.9%

- Infuse 100mL of the daratumumab infusion (20%) of the dose **over 30 minutes**
- Then infuse the remaining 400mL (80% of the dose) **over 60 minutes** (total infusion time 90 minutes).

Monitoring

- Check vital signs before the start of the infusion, every 15 minutes during the first 60 minutes of the infusion and at the end of the infusion for all daratumumab infusions.
- Monitor patient for adverse effects. For the first rapid rate infusion, observe patients in the Day Unit for 30 minutes after infusion completion to assess for delayed infusion related reactions.
- Closer monitoring is required if the patient has a history of uncontrolled hypertension, pre-existing COPD, asthma or other respiratory comorbidities. These patients should be discussed with the consultant.

Additional therapy

- No anti-emetics are required

- Premedication required 1 to 3 hours before every daratumumab infusion:

  - dexamethasone – see regimen for dose details
  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral

- Consider anti-infective prophylaxis including;

  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
  - fluconazole 100mg once a day oral if recurrent oral candidiasis

- 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 an H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

- As required for the treatment of infusion related reactions for patients at high risk of respiratory complications;

  - sodium chloride 0.9% 500ml intravenous
  - salbutamol 2.5mg nebulised

- hydrocortisone sodium succinate 100mg intravenous
- chlorphenamine 10mg intravenous
- paracetamol 1000mg oral
- oxygen as required

Additional Information

- All instances of infusion related reaction must be recorded on ARIA. Daratumumab will continue to be administered at the cycle one rate until a reaction free infusion is noted.

- Daratumumab interferes with indirect antiglobulin tests as it binds to CD38 on red blood corpuscles (RBCs) and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered.

- Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

Coding

- Procurement –X71.5

- Delivery – X72.1

References

1. Janssen-Cilag Limited (18 Dec 2018). Darzalex 20mg/ml Summary of Product Characteristics. Electronic Medicines Compendium. Online at https://www.medicines.org.uk/emc/product/7250 , accessed 01 July 2019.
2. National Institute for Health and Care Excellence (2019). Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma. [TA573]. London: National Institute for Health and Care Excellence.
3. Thames Valley Strategic Cancer Network Myeloma Group MM47 DaraVelDex Protocol version 2.0 April 2019.
4. 90 minute daratumumab infusion is safe in multiple myeloma. Leukemia. Hallie Barr et al. Accessed 27/11/18 https://doi.org/10.1038/s41375-018-0120-2.

REGIMEN SUMMARY

Bortezomib (twice weekly) Daratumumab Dexamethasone Cycles 9 onwards

Cycle 9 onwards day 1

1. Chlorphenamine 10mg intravenous

2. Dexamethasone 20mg oral
   Administration Instructions
   Administer 20mg orally – Can be administered as intravenous equivalent. Reduce dose to 10mg orally or intravenous equivalent over 75 years old.

3. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

4. Daratumumab 16mg/kg in 500ml sodium chloride 0.9% intravenous infusion
   Administration Instructions
   The rate of daratumumab administration varies and is dependant the occurance and severity of infusion related reactions. Please refer to the protocol for details of the rate of administration and management of such reactions
   Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.

5. Chlorphenamine 10mg intravenous when required for the relief of infusion related reactions

6. Hydrocortisone 100mg intravenous when required for the relief of infusion related reactions

7. Paracetamol 1000mg oral when required for the relief of infusion related reactions

8. Salbutamol 2.5mg nebulised when required for the relief of infusion related reactions

9. Sodium chloride 0.9% 500ml intravenous infusion when required for the relief of infusion related reactions

Cycle 9 onwards Take home medicines

10. Dexamethasone 4mg on days 2 and 3 oral
    Administration Information
    Take in the morning with or after food. Days 2 and 3 i.e. for two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions

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

12. 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.

13. 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.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	July 2019	None	Harriet Launders Pharmacist Dr Deborah Wright Pharmacist	Dr Mathew Jenner 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 should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.