Chemotherapy Protocol

Myeloma

DVd SC (weekly) Bortezomib Daratumumab Dexamethasone Cycles 9 onwards

Regimen

- Myeloma – Bortezomib with daratumumab and dexamethasone

Indication

- Daratumumab in combination with bortezomib and dexamethasone is recommended for use as an option for treating relapsed multiple myeloma in people who have had 1 previous treatment.
- This weekly bortezomib regimen is for patients who experience neuropathy or those with pre-existing neuropathy. Note both the twice weekly and weekly bortezomib 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.
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 may also be tested for hepatitis C, CMV and HIV at the same time if clinically appropriate.
- 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 should be $1x10^9$/L or greater and the platelet count should 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. Bortezomib - Consider treatment delay or dose reduction or growth factor support. Seek consultant advice.
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
Bortezomib Less than $25x10^9$/L	Consider treatment delay or dose reduction or platelet transfusion. Seek consultant advice.

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)
Bortezomib	1.5xULN or below		N/A	100%
	greater than 1.5xULN		N/A	Initiate treatment at 0.7mg/m^2. The dose may be escalated to 1mg/m^2 or reduced to 0.5mg/m^2 in subsequent cycles based on patient tolerability.
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)
Bortezomib	greater than 20	100%
	20 and below	Clinical decision
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)

DARZALEX solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients.

The median time to onset of IRRs following DARZALEX injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia.

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections. If an anaphylactic reaction or life-threatening (Grade 4) reactions

occur, appropriate emergency care should be initiated immediately. DARZALEX therapy should be discontinued immediately and permanently.

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX injection. Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

Interference with Serlogical Testing

Daratumumab binds to CD38 in red blood cells and results in a positive indirect antiglobulin test (Coombs test). Daratumumab mediated positive indirect antiglobulin test may persist for up to six months after the last daratumumab infusion. Daratumumab bound red blood cells masks detection of antibodies to minor antigens in the patients serum. The determination of a patients ABO and Rh blood type are not impacted.

Blood transfusion must be informed that a patient is receiving daratumumab. Patients must be typed and screened prior to daratumumab. All patient must be given an identification card that should be carried for six months after stopping therapy and agree to inform all healthcare professionals who treat them that they have received daratumumab.

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

Reactivation of Hepatitis B Virus

Hepatitis B virus reactivation has been reported in patients treated with daratumumab. All patients must be screened for hepatitis B before initiation of treatment. This includes all patients with unknown serology who are on treatment already.

Monitoring is required for patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during treatment and for at least six months after completion of datatumumab. Those with positive serology must seek medical help immediately if they experience symptoms of hepatitis B. Daratumumab must be stopped if hepatitis B reactivation occurs during 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 and 10

Drug	Dose	Days	Administration
Bortezomib	1.3mg/m2	1,8,15, 22	Subcutaneous
Daratumumab	1800mg	1	Subcutaneous
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	20mg once a day	2, 8, 9, 15, 16, 22, 23	Oral Reduce dose to 10mg in over 75yrs

Cycle 11 onwards

Drug	Dose	Days	Administration
Daratumumab	1800mg	1	Subcutaneous
Dexamethasone	20mg	1	Oral Can be given as dose equivalent as IV bolus
Dexamethasone	4mg	2 and 3	To reduce the risk of delayed infusion reactions

Dose Information

- Dexamethasone is available as 4mg, 2mg and 500microgram tablets and 3.3mg in 1ml injection (equivalent to 4mg orally)

Administration Information

- Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long-acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medicinal products may be discontinued at the discretion of the physician.

- Inject 15 mL Daratumumab solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject Daratumumab solution for subcutaneous injection at other sites of the body as no data are available.

- Injection sites should be rotated for successive injections

- Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

- During treatment with Daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as Daratumumab.

Additional therapy

- No anti-emetics are required

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

  - dexamethasone – see regimen for dose details
  - chlorphenamine 4mg oral
  - 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;

  - 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

Myeloma DVd (weekly) Bortezomib Daratumumab SC Dexamethasone Cycles 9 onwards

Cycle 9 and 10 Day 1

1. Warning – Check if Antihistamine Taken
   Administration Instructions
   Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice;
   Chlorphenamine 4mg Oral
   Loratadine 10mg Oral
   Cetirizine 10mg Oral
   Fexofenadine 120mg Oral
   Acrivastine 8mg Oral

2. Warning – Check if the Dexamethasone Taken
   Administration Instructions
   Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose..

3. Warning – Check if the Paracetamol Taken
   Administration Instructions
   Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

4. Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
   Administration Instructions
   Inject daratumumab 1800mg solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.Injection sites should be rotated for successive injectionsDaratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.

5. Bortezomib 1.3mg/m2 subcutaneous injection

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

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

8. Paracetamol 1000mg oral when required for the relief of infusion related reactions
   Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

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

Cycle 9 and 10 Day 8, 15 and 22

10. Bortezomib 1.3mg/m2 subcutaneous injection

Cycle 9 and 10 Take home medicines

11. Dexamethasone 20mg on days 2, 8, 9, 15, 16, 22 and 23 oral
    Administration Information
    Reduce dose to 10mg in patients over 75 years old
    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.

12. Dexamethasone 20mg on day 1 of the next cycle
    Take in the morning of daratumumab injection
    Note to pharmacy – please dispense 1 dose of dexamethasone 20mg to be taken on day 1 of the following cycle prior to daratumumab

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

14. Anthistamine on the days of daratumumab administration
    Administration Instructions
    Take on the day of daratumumab administration. To be taken 1 -3 hours prior to daratumumab infusion Please supply 1 x OP. This is to cover all cycles. To be supplied as per local formulary choice
    Chlorphenamine 4mg Oral
    Loratadine 10mg Oral
    Cetirizine 10mg Oral
    Fexofenadine 120mg Oral
    Acrivastine 8mg Oral

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.

Cycle 11 onwards day 1

17. Warning – Check if Antihistamine Taken
    Administration Instructions
    Ensure the patient has taken the antihistamine premedication. If not please administer one of the following according to local formulary choice;
    Chlorphenamine 4mg Oral
    Loratadine 10mg Oral
    Cetirizine 10mg Oral
    Fexofenadine 120mg Oral
    Acrivastine 8mg Oral

18. Warning – Check if the Dexamethasone Taken
    Administration Instructions
    Ensure the patient has taken the dexamethasone premedication. If not please administer dexamethasone 20mg oral or intravenous if the patient is unable to tolerate the oral dose

19. Warning – Check if the Paracetamol Taken
    Administration Instructions
    Please check if the patient has taken paracetamol. If not please administer paracetamol 1000mg. The maximum dose is 4000mg/24 hours

20. Daratumumab 1800mg subcutaneous injection over 3 – 5 minutes
    Administration Instructions
    Inject daratumumab 1800mg solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject daratumumab solution for subcutaneous injection at other sites of the body as no data are available.Injection sites should be rotated for successive injectionsDaratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.

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

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

23. Paracetamol 1000mg oral when required for the relief of infusion related reactions
    Please check if the patient has taken paracetamol. The maximum dose is 4000mg/24 hours

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

Take home medicines

25. 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 administration to reduce the risk of delayed infusion reactions

26. Dexamethasone 20mg on day 1 of the next cycle
    Administration Information
    Take in the morning of daratumumab injection
    Note to pharmacy – please dispense 1 dose of dexamethasone 20mg to be taken on day 1 of the following cycle prior to daratumumab

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

28. 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.

29. 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	Oct 2020	None	Nanda Basker 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.