NHS

Thames Valley
Strategic Clinical Network

DARATUMUMAB WITH BORTEZOMIB, CYCLOPHOSPHAMIDE AND DEXAMETHASONE (D-VCD)

INDICATION

Newly diagnosed AL amyloidosis

This combination is unlicensed and not funded by NHS England. It is currently available for private patients only.

TREATMENT INTENT

Disease modification

Note: Mayo-stage III patients have an overall mortality risk of 50% in the first year.

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - NTproBNP, Troponin levels
   - CRP
   - Baseline random blood glucose level
   - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
   - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Consider annual flu and pneumococcal vaccination pre therapy
   - urine albumin/ creatinine ratio, urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay (Freelite)
   - β_2 microglobulin
   - LDH
   - 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
Salisbury NHS Foundation Trust
Salisbury Disctrict hospital
Salisbury, Wilts, SP2 8BJ

   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.

- **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.**
- Imaging as per NICE/network guidance and clinical presentation
- Bone marrow aspirate and trephine (and immunophenotype if appropriate)

Additional investigations:

1. Plasma viscosity if hyperviscosity suspected
2. Counselling about risks in pregnancy - There are no human data to inform a risk with use of daratumumab during pregnancy. However, Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta after the first trimester of pregnancy. Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.
3. 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. Obtain written consent for the treatment.
4. Fertility - all relevant patients should be offered fertility advice as appropriate.
5. Hydration - ensure fluid intake of at least 2 litres per day.
6. Document patient's height and weight dose on actual body weight.
7. Document patient's performance status.
8. Treatment must be agreed at the relevant MDT

REGIMEN SPECIFIC PRE-ASSESMENT

1. Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.
2. Advise patients to inform their other HCPs that they have received daratumumab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.
3. Evaluate for presence of neuropathy prior to starting bortezomib. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with bortezomib. Baseline clinical assessment must be documented in the notes before the first dose of bortezomib is prescribed.
4. Echocardiogram/ cardiac MRI as appropriate
5. Patients with suspected/proven cardiac amyloid should be managed as an inpatient on a cardiology ward for at least the first cycle, joint care with cardiologist. Admit patients for chemotherapy if systolic BP 1800pg/mL, or Mayo stage III or IV. Consider referral for a specialist review at the national amyloidosis centre

DRUG REGIMEN

Cycles 1-2:

Daratumumab pre-meds	Paracetamol 1g PO, Montelukast 10mg PO on **(cycle 1 only)**, Chlorphenamine 4mg PO Dexamethasone 20mg PO	Days 1, 8, 15 and 22 To be given 1 hour prior to daratumumab injection
Daratumumab	Subcutaneously at 1800mg fixed dose over 3-5 minutes	Days 1, 8, 15 and 22
Bortezomib	1.3 mg/m^2 given SC bolus	Days 1, 8, 15 and 22
Cyclophosphamide	500 mg PO or IV	Days 1, 8, 15 and 22
Dexamethasone	20 mg PO This component of the regimen is given as part of the daratumumab pre-meds. Dose can be adjusted according to tolerability at the clinician's discretion	Days 1, 8, 15 and 22
Daratumumab post-meds	Dexamethasone 4 mg PO	Days 2, 9, 16 and 23

Cycles 3-6:

Daratumumab pre-meds	Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 20mg PO	Days 1 and 15 To be given 1 hour prior to daratumumab injection
Daratumumab	Subcutaneously at 1800mg fixed dose over 3-5 minutes	Days 1 and 15
Bortezomib	1.3 mg/m^2 given SC bolus	Days 1, 8, 15 and 22
Cyclophosphamide	500 mg PO or IV	Days 1, 8, 15 and 22
Dexamethasone	20mg PO On days 1 and 15, this component of the regimen is given as part of the daratumumab pre-meds On non-daratumumab days (D8,22), 20mg is to be taken by patient Dose can be adjusted according to tolerability at the clinician's discretion	Days 1, 8, 15 and 22
Daratumumab post-meds	Dexamethasone 4 mg PO	Days 2 and 16

Cycle 7- Onwards

Daratumumab	Pre-meds: 1 hour prior to daratumumab Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 20mg PO	Day 1
	Daratumumab subcutaneously at 1800mg fixed dose over 3-5 minutes	Day 1

From cycle 7 onwards, no dexamethasone is required on day after daratumumab.

CYCLE FREQUENCY

D-VCD is given as a quadruplet combination on cycles 1-6, followed by single agent daratumumab from cycle 7 onwards, for up to 2 years. Each cycle is repeated every 28 days until disease progression or unacceptable toxicity

Additional Post-medications:

The use of post-daratumumab medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. Following the first four doses, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

METHOD OF SUBCUTANEOUS DARATUMUMAB ADMINISTRATION:

Inject the subcutaneous dose (15 mL) 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 the dose at other sites of the body as no data are available.

Injection sites should be rotated for successive injections. The subcutaneous dose 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.

DOSE MODIFICATIONS

Prior to initiating a new cycle of therapy:

- Platelets ≥ 50 x 10^9/L and ANC ≥ 1.0 x 10^9/L and Hb ≥ 80
- Non-haem toxicities should resolve to G1 or baseline

Haematological Toxicity:

Cyclophosphamide: If prolonged G4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle, omit cyclophosphamide for 1 week. Restart at same dose when neutrophils and platelets recovered. If recurrent, i.e. if neutrophils < 1.0 x 10^9/L and platelets < 50 x 10^9/L on day 1 of subsequent cycles (when previously > than these levels), omit cyclophosphamide and consider dose reduction of cyclophosphamide for subsequent doses. If the patient was receiving 500 mg weekly, reduce to 400 mg, if 400 mg reduce to 300 mg, if 300 mg reduce to 200 mg. If patients receiving 50mg daily omit for a week and consider reduced frequency.

Daratumumab: no dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of G4 haematological toxicity or G3 or higher thrombocytopenia with bleeding. Patients with neutropenia should be monitored for signs of infection. Daratumumab delay may be required to allow recovery of blood cell counts. In lower body weight patients receiving daratumumab subcutaneous formulation, higher rates of neutropenia were observed; however, this was not associated with higher rates of serious infections.

Bortezomib: withhold at G3 non-haem or G4 haem toxicities. Once resolved, re-initiate at 25% reduced dose (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless the benefit outweighs risk.

Peripheral neuropathy

Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

Grading of neuropathy	Dose modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m^2 or change treatment schedule to 1.3 mg/m^2 once per week if patient currently on twice weekly
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate treatment at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Hepatic/Renal Impairment

Bortezomib

Renal	Hepatic
Clinical decision if GFR < 20ml/min In dialysis patients, give after dialysis	Bilirubin > 1.5 x ULN: reduce to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.

Daratumumab:

Renal	Hepatic
No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population PK analyses no dosage adjustment is necessary for patients with 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

Cyclophosphamide:

Renal	Hepatic
Clinical decision GFR > 20ml/min 100% dose GFR 10 – 20ml/min 75% dose GFR < 10ml/min 50% dose For dialysis patients, give before dialysis and at a minimum interval of 12 hours prior to dialysis	Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision

INVESTIGATIONS – during treatment

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle
- FBC, U&Es, LFTs, Ca^{++}, glucose – every 3 - 4 weeks.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib.
- Blood pressure (consider checking for postural drop if symptomatic)
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay.
- Every 2 cycles, NTproBNP/ Troponin, Urine protein/ creatinine ratio, urine albumin/creatinine ratio
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of therapy and for 3 months after the completion of bortezomib
- Consider prophylactic levofloxacin 500mg od for 12 weeks (cycles 1-3)
- Prophylactic fluconazole 50mg OD.
- In patients with suspected/proven cardiac amyloid, add Doxycycline 100mg BD, and monitor/counsel patients regarding photosensitivity
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Bone protection as per NSSG Bone Protection protocol MM.3: this can be used if patient has myeloma in addition to their amyloid diagnosis
- Consider use of loperamide if required for the management of transient diarrhoea.

Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir), or CYP3A4-inducers (rifampicin, carabamazepine, phenytoin, phenobarbital, and St John's wort).

EMETIC RISK

Low risk.

EXTRAVASATION RISK

Neutral: daratumumab
Irritant: bortezomib

ADVERSE EFFECTS (AEs)/REGIEMN SPECIFIC COMPLICATIONS

- **AEs from the safety run-in of 28 patients in the phase 3 ANDROMEDA study:**
  In the safety run-in phase of ANDROMEDA trial, twenty-six patients (93%) experienced AEs considered related to treatment; AEs in 21 patients (75%) were considered to be related to daratumumab. A total of 14% of patients experienced any-grade peripheral sensory neuropathy with DARA SC plus CyBorD (no grade 3-4 events). Grade 3-4 infections included pneumonia (n =3 [11%]), cellulitis (n= 2 [7%]), and peritonitis, upper respiratory tract infection, and vascular device infection (n= 1 each [4%]). (Palladini et al 2020).
  All-grade cardiac AEs included palpitations (n= 2 [7%]) and arrhythmia, atrial fibrillation, atrial flutter, and congestive cardiac failure (n= 1 each [4%]; atrial fibrillation and cardiac failure were considered treatment-related). Congestive cardiac failure was the only grade 3-4 cardiac AE.
  All-grade renal/urinary disorder TEAEs included pollakiuria (n = 4 [14%]), acute kidney injury (n = 3 [11%]; 1 [4%] treatment-related), hematuria, renal impairment, urinary retention (n = 2 each [7%]; 1 [4%] renal impairment considered treatment-related), and chronic kidney disease, dysuria, nephrolithiasis, nocturia, urinary incontinence, and urinary tract pain (n= 1 each [4%]; incontinence and pain were considered treatment-related). The only grade 3-4 renal/ urinary disorder TEAE was acute kidney injury (n= 2 [7%]). (Palladini et al 2020).
  Serious AEs occurred in 12 patients (43%) and included fall and acute kidney injury (11% each) and pneumonia and cellulitis (7% each; cellulitis). A total of 5 patients (18%) died: 3 (11%) because of complications of high-dose melphalan and ASCT (septic shock and multiorgan system failure, recurrent infections, and septic shock, respectively), and 2 (7%) because of progression of amyloidosis-related organ dysfunction. (Palladini et al 2020).
  Infusion-related reactions occurred in 1 (4%) patient, and included chest discomfort, cough, hypotension, oropharyngeal pain, and sneezing, all of which were grade 1. All occurred on cycle 1 day 1 except hypotension (cycle 1, day 8; considered probably related to DARA SC), and all resolved. A total of 6 injection-site reactions occurred in 3 (11%) patients. All injection-site reactions were grade 1 and included erythema, bruising, and skin discoloration; none led to changes in treatment. (Palladini et al 2020).

- **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 dose. 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 typed and screened prior to starting daratumumab.
  III. Important information on safety and risk minimisation of Daratumumab and interference with Blood Compatability Testing can be found of the summary of product characteristics on the following links:
  http://www.medicines.org.uk/emc/RMM.539.pdf
  http://www.medicines.org.uk/emc/RMM.545.pdf

  IV. Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.

V. Ask patients to tell their other HCPs that they have received daratumumab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.

- **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.

- **Infusion reactions with subcutaneous injection (as per SC daratumumab SPC):**

  Daratumumab solution for subcutaneous injection can cause severe and/or serious infusion-related reactions (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 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. Daratumumab therapy should be discontinued immediately and permanently.

  To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following daratumumab 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.

- **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.

- **Risk of reactivation of hepatitis B virus (MHRA alert 2019):**

  Hepatitis B virus reactivation has been reported in patients treated with daratumumab, including several fatal cases worldwide

  All patients must be screened for hepatitis B virus before initiation of daratumumab; patients with unknown serology who are already on treatment should also be screened

  Monitoring is required for patients with positive serology for clinical and laboratory signs of

hepatitis B reactivation during treatment, and for at least 6 months following the end of daratumumab treatment

Patients with positive serology need to be advised to seek medical help immediately if they experience signs and symptoms suggestive of hepatitis B virus reactivation

Treatment with daratumumab should be stopped in patients with hepatitis B virus reactivation; appropriate treatment needs to be instituted in consultation with experts in the treatment of hepatitis B virus infection; consult with experts before resuming daratumumab in patients with adequately controlled viral reactivation

Suspected adverse drug reactions associated with daratumumab need to be reported to the Yellow Card Scheme

TREATMENT RELATED MORTALITY

Patients with Mayo Stage III amyloid have an approximate 50% mortality in the first year. Patients should be carefully counselled about this very high risk.

REFERENCES

1. Darzalex 1800mg ® (Daratumumab), eMC UK Summary of Product Characteristics for Janssen, Aug 2020
2. Palladini G, Kastritis E, Maurer MS, Zonder J, Minnema MC, Wechalekar AD, Jaccard A, Lee HC, Bumma N, Kaufman JL, Medvedova E, Kovacsovics T, Rosenzweig M, Sanchorawala V, Qin X, Vasey SY, Weiss BM, Vermeulen J, Merlini G, Comenzo RL. Daratumumab plus CyBorD for patients with newly diagnosed AL amyloidosis: safety run-in results of ANDROMEDA. Blood. 2020 Jul 2;136(1):71-80. doi: 10.1182/blood.2019004460. PMID: 32244252; PMCID: PMC7332897.

REVIEW

Name	Revision	Date	Version	Review date
NSSG Myeloma Group	New protocol	December 2020	1.0	June 2021