Thames Valley
Strategic Clinical Network

DARATUMUMAB WITH BORTEZOMIB, THALIDOMIDE AND DEXAMETHASONE (D-VTD)

INDICATIONS

Treatment of adult newly diagnosed multiple myeloma patients, who are eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

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

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
   - CRP
   - Baseline random blood glucose level
   - 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)
   - 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 (address below)
   - 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 (with immunophenotyping for kappa/lambda if appropriate)

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

Additional Investigations

1. Plasma viscosity if hyperviscosity suspected
2. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology
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.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
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. Evaluate for presence of neuropathy. 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
2. The conditions of the Thalidomide Celgene Pregnancy Prevention Programme must be fulfilled for all male and female patients.
3. Clinical assessment of thrombo-embolic risk.
4. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1

DRUG REGIMEN

This regimen consists of 4 cycles of D-VTD (daratumumab in combination with bortezomib, thalidomide and dexamethasone), then autologous stem cell transplant (ASCT), followed by 2 cycles of D-VTD as consolidation therapy.

Clinicians may opt for the alternative schedule of all 6 D-VTD cycles to be administered prior to ASCT.

This regimen was based on CASSIOPEIA trial and has been slightly modified to simplify the schedule (e.g. SC instead of IV daratumumab and, weekly bortezomib instead of twice-weekly).

METHOD OF SUBCUTANEOUS DARATUMUMAB ADMINISTRATION:

Subcutaneous administration is the preferable route for daratumumab in current clinical practice.

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.

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
Thalidomide	50 -100 mg PO (preferably nocte) Start at 50mg and increase as tolerated	Daily
Dexamethasone	40 mg PO (this includes dexamethasone pre-meds) i.e. on daratumumab days, 20mg is to be administered in addition to the 20mg pre-med dose. On non-daratumumab days, 40mg is to be administered.	Days 1,2, 8,9,15,16,22,23

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
Thalidomide	50 -100 mg PO (preferably nocte) Start at 50mg and increase as tolerated	Daily
Dexamethasone	20mg PO (this includes dexamethasone pre-meds) i.e. on daratumumab days, the pre-med dose of dexamethasone is sufficient. On non-daratumumab days, 20mg is to be administered.	Days 1,2, 8,9,15,16, 22 and 23

Additional Post-dose 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-daratumumab medications may be discontinued at the discretion of the physician.

CYCLE FREQUENCY

Repeat every 28 days.

DOSE MODIFICATIONS

Prior to initiating a new cycle of therapy:

- Platelets ≥ 70 x 10^9/L and ANC ≥ 1.0 x 10^9/L
- Non-haem toxicities should resolve to G1 or baseline

Haematological toxicity:

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.

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 benefit outweighs risk.

Peripheral neuropathy:
BORTEZOMIB:
If there are symptoms of peripheral neuropathy, the dose reduction schedule must be invoked (see below).The drug should be stopped if symptoms or signs progress despite this.

Severity of neuropathy	Posology modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m^2
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

THALIDOMIDE:
Thalidomide should be stopped or dose reduced if there are symptoms of progressive peripheral neuropathy causing functional disability (grade 2 or above). Consider cautious re-introduction of thalidomide at a dose of 50mg daily if symptoms resolve to grade 1 or better after a two-week gap Subsequent cautious dose escalation should be considered if symptoms permit.

Renal & Hepatic impairment:

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

Bortezomib:

Renal	Hepatic
For dialysis patients, bortezomib should be given after dialysis No dose reduction necessary	Bil 1.0-1.5 x ULN: no dose reduction required Bili > 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.

Thalidomide:

Renal	Hepatic
No dose reduction necessary	No dose reduction necessary

INVESTIGATIONS (at the beginning of each cycle)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTs, Ca^{2+}
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle.
- Blood pressure (consider checking for postural drop if symptomatic)
- Consider bone marrow assessment / PET scan after four cycles for non-secretory Myeloma.
- 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.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and 3 months post therapy.
- Prophylactic fluconazole 50mg OD
- Consider levofloxacin 500mg od for 12 weeks (cycles 1-3)
- Prophylactic co-trimoxazole 960mg OD on M/W/F
- Proton Pump Inhibitor or H2 antagonist at clinician's discretion
- Thromboprophylaxis/anticoagulation- see VTE section below
- Bone protection as per NSSG Bone Protection protocol MM.3

Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin, carabamazepine, phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

Extravasation risk:

Bortezomib-irritant

Daratumumab-neutral

EMETIC RISK
Low

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

- **Most common side effects reported in CASSIOPEIA trial:**

  The most common haematological toxicities reported were: neutropenia (all grade: 29%, ≥G3-4: 28%), thrombocytopenia (all grade: 20%, G3-4: 11%), and lymphopenia (all grade: 18%, G3-4: 17%). The most common non-haematological toxicities were: peripheral neuropathy, constipation, asthenia, peripheral oedema, nausea, pyrexia, paraesthesia and stomatitis. Infusion reactions were also reported (all grade: 35%, G3-: 4%).

- **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 lab 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:**

  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.

- **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

  Teratogenicity: The Celgene Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme.

  Peripheral neuropathy: Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia. If these occur see above dose reductions and consider use of Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU. Caution in patients with existing peripheral neuropathy

  Venous thromboembolism (VTE): There is an increased risk of thrombosis with thalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

  1. Prophylactic low-molecular weight heparin OR
  2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- **Dizziness and orthostatic hypotension**: Patients should be advised that Bortezomib may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position. Caution in patients with history of syncope, receiving

medications associated with hypotension and patients who are dehydrated. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells. Patients who experience dizziness or low blood pressure may benefit from 500ml intravenous 0.9% sodium chloride with each dose of bortezomib.

- **Gastrointestinal:** Nausea, diarrhoea, vomiting and constipation are very common and ileus has been reported.
- **Drowsiness, somnolence and sedation**: Take the thalidomide dose at night time. Thalidomide 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 thalidomide.
- **Skin toxicity**: in the event of toxic skin reactions such as Stevens-Johnson syndrome, thalidomide should be discontinued permanently.
- **Other warnings**: Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

1. Bortezomib (Velcade®) eMC UK Summary of Product Characteristics, Janssen, February 2019
2. Darzalex ® (Daratumumab), eMC UK Summary of Product Characteristics for Janssen, Jan 2019
3. Thalidomide, Celgene® eMC UK Summary of Product Characteristics, Celgene, April 2019
4. Maria-Victoria Mateos , Hareth Nahi , Wojciech Legiec , Sebastian Grosicki , Vladimir Vorobyev , Ivan Spicka , Vania Hungria , Sibirina Korenkova , Nizar Bahlis , Max Flogegard , Joan Bladé , Philippe Moreau , Martin Kaiser , Shinsuke Iida , Jacob Laubach, Hila Magen, Michele Cavo, Cyrille Hulin, Darrell White, Valerio De Stefano, Pamela L Clemens, Tara Masterson, Kristen Lantz, Lisa O'Rourke , Christoph Heuck , Xiang Qi , Dolly A Parasrampuria , Zhilong Yuan , Steven Xu, Ming Qi , Saad Z Usmani. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematology. Volume 7, ISSUE 5, e370-e380, May 01, 2020
5. Philippe Moreau et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019 Jul 6;394(10192):29-38.

REVIEW

Name	Revision	Date	Version	Review date
NSSG myeloma group	New protocol	September 2020	1.0	June 2021
NSSG Myeloma Group	Updated schedule as per trial	December 2020	1.1	June 2021