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 (NICE TA763).

Requires Blueteq approval.

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 District Hospital, Salisbury NHS Foundation Trust
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 Pregnancy Prevention Programme (PPP) 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

Induction: 4 cycles. Followed by autologous stem cell transplant (ASCT)

Consolidation: 2 cycles of D-VTD as consolidation therapy post-ASCT.

This regimen was based on CASSIOPEIA trial and has been slightly modified to simplify the schedule (e.g., SC instead of IV daratumumab, weekly bortezomib instead of twice weekly, and dexamethasone days 22-23 on cycles 3-6).

Cycles 1-2:

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Cycle 1 only - Montelukast 10mg Chlorphenamine 4mg Dexamethasone 20mg	1, 8, 15 and 22	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1, 8, 15 and 22	Subcutaneous
Bortezomib	1.3 mg/m2	1, 8, 15 and 22	Subcutaneous
Thalidomide	50 mg	Once daily (nocte)	Oral
Dexamethasone	40 mg* *This is the total dexamethasone dose for the day, so includes any pre-medication dose that was due.	1,2 8,9 15,16 22,23	Oral

Cycles 3-6:

NICE approval stipulates cycle 5-6 will be given post autologous stem cell transplant.

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 20mg	1 and 15	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1 and 15	Subcutaneous
Bortezomib	1.3 mg/m^2	1, 8, 15 and 22	Subcutaneous
Thalidomide	50 mg	Once daily (nocte)	Oral
Dexamethasone	20mg* *This is the total dexamethasone dose for the day, so includes any pre-medication dose that was due.	1,2 8,9 15,16 22,23	Oral

Additional post-dose medications:

Consider additional medications (e.g., inhaled corticosteroids, short and long acting bronchodilators) for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications.

Following the first four doses, if the patient experiences no major IRRs, these inhaled post-daratumumab medications may be discontinued.

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 reduction. • Consider dose delay in G3 thrombocytopenia with bleeding, or G4 haematological toxicity to allow count recovery.
Bortezomib	• Any G3 haematological toxicity – Discuss with consultant, in some cases bone marrow infiltration may affect interpretation, consider withholding treatment. • G4 haematological toxicity – withhold treatment. • Once resolved, re-initiate at 25% reduced dose (e.g., 1.3 mg/m^2 → 1.0 mg/m^2; 1.0 mg/m^2 → 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:

	Severity	Recommendation
Bortezomb	G1, no pain or loss of function	None
	G1 with pain or G2	Reduce to 1.0 mg/m2
	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.
	G4 and/or severe autonomic neuropathy	Discontinue
Thalidomide	• G2 or above - Stop or dose reduced if there are symptoms of progressive peripheral neuropathy causing functional disability. • Where resolution to G1 or less after a two-week gap, consider cautious re-introduction of thalidomide at a dose of 50mg daily.	

Renal and 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**
No dose reduction necessary. For dialysis patients, bortezomib should be given after dialysis. It is unclear whether baseline kidney dysfunction influences the risk of bortezomib-related renal adverse events.	Bilirubin 1.0 - 1.5 x ULN: No dose reduction required. 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 reduction to 0.5 mg/m^2 in subsequent cycles based on tolerability.

*Renal adverse events (i.e., AKI, thrombotic microangiopathy), although infrequent, have been reported with bortezomib treatment.

Thalidomide	
Renal	**Hepatic**
No dose reduction necessary	No dose reduction necessary

INVESTIGATIONS

Repeat at the start of each treatment 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

- ***Cycle 1 only*** - Allopurinol 300 mg daily for 7 days (TLS prophylaxis)
- Aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl <10ml/min) for the duration of treatment and 3 months post therapy.
- Fluconazole 50mg OD
- Apixaban 2.5mg BD (unless other risk factors or drug interactions present, always clinically assess - see thromboprophylaxis information in adverse effects section below)
- Consider levofloxacin 500mg OD for 12 weeks (cycles 1-3). Adjust for renal function. Beware tendonitis risk.
- Co-trimoxazole 960mg OD on M/W/F
- H2 antagonist - famotidine 40mg OD (unless established on PPI)
- Bone protection as per NSSG Bone Protection protocol MM.3
    - Note patients will need dental review prior to any bisphosphonate treatment.

INTERACTIONS

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

EXTRAVASATION RISK

Bortezomib - Irritant
Daratumumab - Neutral

EMETIC RISK

Low

ADVERSE EFFECTS/REGIMEN SPECIFIC COMPLICATIONS

Common/known side-effects:

Neutropenia (all grade: 29%, ≥ G3-4: 28%), thrombocytopenia (all grade: 20%, G3-4: 11%), and

lymphopenia (all grade: 18%, G3-4: 17%). Peripheral neuropathy, constipation, asthenia, peripheral oedema, nausea, pyrexia, paresthesia and stomatitis. Infusion reactions were also reported (all grade: 35%, G3-: 4%) – see further information below.

Suspected adverse reactions associated with daratumumab should be reported to the MHRA Yellow Card Scheme.

- **Peripheral neuropathy:** Patients should be advised to report pain, hypersensitivity, prickling, numbness, and paraesthesia. If these occur, consider dose reduction. Consider use of amitriptyline, gabapentin/pregabalin and pain team referral. Local neuropathy assessment tools should be utilised. *Use caution in patients with existing peripheral neuropathy.*
- **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. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells *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 fludrocortisone and/or sympathomimetics. Patients who experience dizziness or low blood pressure may benefit from 500ml intravenous 0.9% sodium chloride with each dose of bortezomib.
- **Drowsiness, somnolence and sedation:** 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 (rare) Stevens-Johnson syndrome, thalidomide should be discontinued permanently.
- **Gastrointestinal:** Nausea, diarrhoea, vomiting and constipation are very common and ileus has been reported.
- **Other warnings:** Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

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 DOAC 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.

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.

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 Compatibility Testing can be found of the summary of product characteristics (www.medicines.org.uk)
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.

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.

Teratogenicity

Thalidomide is **a powerful human teratogen**, inducing a high frequency of severe and life-threatening birth defects. **The** Pregnancy Prevention Program (PPP) associated with the brand of thalidomide being dispensed must be observed for all male and female patients. All prescribing and dispensing of thalidomide must be in line with the pregnancy prevention program requirements.

Patients should be informed not to donate blood or semen during or within 4 weeks of stopping thalidomide treatment. Women of childbearing potential should be maintained on effective contraception during treatment and for at least 4 weeks after stopping 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, BMS® eMC UK Summary of Product Characteristics, BMS, March 2022.
4. Mateos, MV, Nahi, H, Legiec W, Grosicki S, Vorobyev V, Spicka I, Hungria V, Korenkova S, Bahlis N, Flogegard M, Bladé J, Moreau P, Kaiser M, Iida S, Laubach J, Magen H, Cavo M, Hulin C, White D, De Stefano V, Usmani SZ. (2020). Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *The Lancet. Haematology*, *7*(5), e370–e380.
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
NSSG Myeloma Group	Updated with CDF approval	February 2022	2.0	June 2022
NSSG Myeloma Group	Removed CDF funding, now under NHSE with NICE TA. Minor formatting and rewording of content. TVCN logo updated to TVCA. Addition of	June 2023	3.0	June 2024

	Apixaban 2.5mg BD as preferred VTE prophylaxis.			