Daratumumab-Bortezomib-Thalidomide-Dexamethasone (Dara-VTD) for patients with newly diagnosed transplant-eligible myeloma.

INDICATION : Newly diagnosed myeloma eligible for PBSCT as per NICE technology appraisal TA 763 02/02/22

Prior to a course of treatment

- Assess cardiac function by history and exam with ECG, CXR. Consider MUGA scan if abnormal. Note bortezomib is contraindicated if severe cardiac impairment.
- Assess for peripheral neuropathy – may worsen on therapy; contraindicated if ≥ Grade 3 sensory
- Check FBC – neutrophils must be >0.5 and platelets must be >25 unless due to myeloma for cycle 1. For subsequent cycles neutrophils should be > 1.0 and platelets >70 prior to each cycle.
- Check renal function and LFTs – *see dose modification.*
- Hepatitis and HIV screen. Hep B reactivation has been reported with daratumumab so monitor viral load if positive serology
- Patients must be counselled about the risk of birth defects with foetal exposure to thalidomide. Prescription must be accompanied by a completed thalidomide prescription authorization form.
- Check PFTs if the patient has a history of airways disease within the last 2 years. If they have COPD, their FEV1 must be 50% of predicted normal or greater, and if they have persistent asthma it must be mild.
- Because CD38 is weakly expressed on human erythrocytes, daratumumab can interfere with antibody screening and cross-matching, though ABO/RhD typing is not usually affected. Once the patient has consented to therapy, **the blood transfusion laboratory must be informed.** Prior to commencing daratumuab take 2 separate transfusion samples at least 15 minutes apart for grouping and local testing if the patient has not been previously grouped and also a further 2 transfusion sample tubes for analysis at NHSBT. Patient plasma can remain pan-reactive for 2 - 6 months after the last daratumumab infusion.
- Consider use of erythropoietin, particularly in anaemic patients with renal impairment
- HMDS must be informed that the patient is on daratumumab on any sample request forms sent to them, as the presence of the antibody can interfere with identification of plasma cells for flow cytometry
- As daratumumab is an IgG k monoclonal can co-migrate with IgG k paraproteins on serum electrophoresis making identification of serological CR more difficult in IgG k myeloma
- Written consent for course

Prior to each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function.
- Urine pregnancy testing for pre-menopausal women younger then 55
- Check FBC, U&Es, creat, LFTs – *see dose modification*. From cycle 2 onwards neutrophils should be 1.0 or above and platelets 70 or above at start of each cycle. Discuss with consultant if cytopenias remain or if renal or hepatic function have changed significantly.
- Encourage patient to drink 3 L fluid daily

Prior to each dose of velcade

- Reassess for peripheral neuropathy – *see dose modifications*
- Bloods do <u>not</u> need repeating if acceptable at start of cycle

Daratumumab The s/c vial volume is 15 ml and the dose is given as a manual push over 3 – 5 minutes in the abdominal s/c tissue alternating sides between individual doses.	1800mg Recombinant human hyaluronidase creates a pocket.	s/c	Weekly on days 1,8,15 & 22 for cycles 1 and 2 then Fortnightly for cycles 3 and 4 pre SCT and cycles 5 and 6 post SCT i.e. days 1 and 15 only.
Bortezomib (Velcade®) (s/c/ bolus)	1.3mg/m^2	s/c	On days 1, 8, 15, 22
Thalidomide	Cycle 1 = 50mg nocte day 1 - 14, 100mg nocte day 15 - 28 Cycle 2 onwards keep thalidomide dose 100mg if tolerating (don't increase to 200 mg)	po	
Dexamethasone	*40mg od	po	On days 1,2, 8,9, 15,16, 22,23

*On Daratumumab days, Dexamethasone is given 1-3 hours before Daratumumab.

(Bortezomib may be administered intravenously if severe localized reactions occur)

Repeat cycle every 28 days

- Give 4 cycles prior and 2 cycles three months post melphalan autograft, then proceed to lenalidomide maintenance
- Patients should be monitored after their first daratumumab injection for reactions with vital signs every 15 minutes for 1 hour then hourly for 3 hours. Patients can be subsequently discharged from day unit. Subsequent doses only require observations for 1 hour before discharge.
- If patient fails to reach at least a minimal response after 4 cycles - *discuss with consultant*

Daratumumab pre-meds	Paracetamol 1g oral, chlorphenamine 4mg oral, dexamethasone 40mg oral as per regimen
Anti-emetic prophylaxis	Metoclopramide
Other medications	Allopurinol 300mg od (100mg if Cr.Cl <20ml/min) for cycle 1 Prophylactic acyclovir 400mg bd recommended VTE prophylaxis – aspirin if low risk, heparin or DOAC (e.g. apixaban 2.5 mg BD) for higher risk Levofloxacin 500mg daily for 12 weeks (i.e. cycle 1 – 3) Consider PPI, fluconazole 50mg daily, bone protection

DaratumumabToxicities

Daratumumab is a monoclonal antibody directed against CD38, an antigen found on the surface of plasma cells. Many of its side effects are therefore similar to other monoclonal antibody therapies such as rituximab, with 50% of patients suffering post injection reactions including flushing, pyrexia, sweats, and dyspnoea. Unlike rituximab, however, daratumumab can also be associated with upper respiratory tract symptoms such as cough, allergic rhinitis nasal congestion and throat irritation, which patients should be warned about in advance to help prepare them for what can be an alarming side effect. Similar to other monoclonal antibodies however, all side effects tend to completely settle after the first injection, such that subsequent doses are usually well tolerated.

Pyrexia	Cough , choking sensation,	Throat irritation
Sweats	Nasal congestion	
Fatigue	Allergic rhinitis,	
Dyspnoea, wheeze	Diarrhoea	
Cytopenias	Hypertension	

Bortezomib dose modifications:

Dose modification for neutropenia (unless due to disease)

- Neutrophils <0.5 on day 1 of cycle — Stop until > 1.0 then restart at 1.0 mg/m^2 if initially 1.3mg/m^2 or 0.7 mg/m^2 if initially 1.0mg/m^2 **OR** GCSF prophylaxis
- No resolution of neutropenia or recurs at 0.7mg/m^2 — Consider stopping treatment – *discuss with consultant*

Dose modification for thrombocytopenia (unless due to disease)

- Platelets <25 on day 1 of cycle — Stop until >25 then restart at 1.0 mg/m^2 if initially 1.3mg/m^2 or 0.7 mg/m^2 if initially 1.0mg/m^2 **OR** Support with platelet transfusion
- No resolution of thrombocytopenia or recurs at 0.7mg/m^2 — Consider stopping treatment – *discuss with consultant*

Dose modifications for peripheral neuropathy

- Grade 1 (but no pain) i.e loss of tendon reflexes or paraesthesiae but not interfering with function — Reduce to 1.3mg/m^2 weekly
- Grade 1 with pain or Grade 2, i.e objective sensory loss or paraesthesia interfering with function but not activities of daily living — Reduce to 1.0mg/m^2 weekly
- Grade 2 with pain or Grade 3, i.e sensory loss or paraesthesia interfering with activities of daily living — Withhold until symptoms resolve, then restart at 0.7mg/m^2 weekly. If symptoms fail to resolve within 2 weeks – stop treatment
- Grade 4, i.e permanent sensory loss that interferes with function — Discontinue bortezomib

Modification for renal dysfunction

- If < 30ml/min *discuss with consultant*. Note that the incidence of serious adverse effects increases with mild-moderate renal impairment. Patients have been treated safely when the creatinine clearance is<30ml/min and on dialysis but monitor carefully for toxicities if renal function is impaired.

Modification for liver dysfunction

- The major route of bortezomib excretion is hepatic and there is limited on the use of bortezomib in patients with hepatic impairment. If bilirubin >30μmol/L use with caution, monitor closely for toxicity and consider dose reduction – *discuss with consultant*

Dose modification for diarrhoea

• If ≥ grade 3 diarrhoea, i.e increase of ≥ 7 stools/day over baseline, incontinence, hospitalization with >24 hrs IV fluids	Reduce dose to 1.0mg/m^2, then 0.7mg/m^2 if symptoms persist

Bortezomib Toxicities

Thrombocytopenia	Nausea
Neutropenic sepsis	Fatigue
Fluid retention & cardiac failure	Diarrhoea, constipation & ileus
Peripheral neuropathy (may be painful)	Hypotension
Fatigue, malaise, weakness	

Management of neuropathy secondary to thalidomide

Sensory	Motor
Loss of deep tendon reflexes, mild paraesthesias but not interfering with function	Asymptomatic weakness on exam only
Sensory alteration or paraesthesias interfering with function but not ADLs	Symptomatic weakness interfering with function but not ADLs
Severe sensory loss or paraesthesias interfering with ADLs	Weakness interfering with ADLs; bracing or assisitance to walk required
Disability	Severe weakness/disability e.g paralysis

Grade 3 or 4 toxicity	Stop thalidomide until symptoms resolve; consider reintroducing at 50mg od and escalation up to 200mg if tolerated
Grade 2 toxicity	Stop thalidomide until toxicity resolves to less than grade 1then restart at 50% dose
Grade 1 toxicity	Reduce dose by 50%

Thalidomide Toxicities

Nausea (none-mild)	Sedation, somnolence
Constipation	Peripheral neuropathy
Tremor	Venous thromboembolism
Foetal abnormalities in pregnancy (phocomelia)	

Dexamethasone dose modification

If dexamethasone poorly tolerated reduce dose to 20mg. If still poorly tolerated consider weekly dosing.

No dose modification needed in renal failure

Dexamethasone Toxicities

Agitation, confusion, depression	Insomnia
Oedema, fluid retention	Peptic ulceration
Proximal myopathy	

References:

NICE Technology Appraisal 763 published 2nd February 2022

Bortezomib, thalidomide and dexamethasone with or without daratumumab before and after autologous stem cell transplantation for newly diagnosed multiple myeloma (Cassiopeia): a randomized open-label, phase 3 study. Moreau et al, Lancet 2019 Jul 6;394 (10192): 29-38.

Written by	Dr Mark Grey, Consultant Haematologist
Date	February 2022
Review date	February 2024