Daratumumab, bortezomib & dexamethasone (DVd)

Indication

Treatment of relapsed multiple myeloma in patients who have had 1 previous treatment.

(NICE TA573)

ICD-10

Codes with a prefix C90

Regimen details

Cycles 1 to 3 (21 day)

Day	Drug	Dose	Route
1*, 8 and 15	Daratumumab	16mg/kg	IV infusion
1, 2, 4, 5, 8, 9, 11, 12, 15 and 16	Dexamethasone	§20mg (see pre med section)	IV bolus first dose then PO
1, 4, 8 and 11	Bortezomib	1.3 mg/m^2	SC bolus

*To facilitate administration, the dose on cycle 1 day 1 may be split over two consecutive days i.e. 8 mg/kg on day 1 and day 2 (see administration section below).

Cycles 4 to 8 (21 day)

Day	Drug	Dose	Route
1	Daratumumab	16mg/kg	IV infusion
1, 2, 4, 5, 8, 9, 11 and 12	Dexamethasone	§20mg (see pre med section)	PO
1, 4, 8 and 11	Bortezomib	1.3 mg/m2	SC bolus

Cycle 9 onwards (28 day)

Day 1	Drug	Dose	Route
1	Daratumumab	16mg/kg	IV infusion
1	Dexamethasone	§20mg (see pre med section)	PO
2	Dexamethasone	8mg	PO

§ From the CASTOR trial protocol, dexamethasone dose may be reduced to 20 mg once weekly for patients older than 75 years, BMI < 18.5, with poorly controlled diabetes mellitus or who had previous unacceptable side effects associated with glucocorticoid therapy. For those treated with the standard regimen that experience dexamethasone toxicity the dose may be initially reduced to 40 mg/week (20mg day of and day after daratumumab), and if toxicity persists then reduced further to 20 mg weekly (day of daratumumab).

Cycle frequency

Cycles 1-8 21 days, cycles 9 onwards 28 days

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

Bortezomib is administered by SC injection. **At least 72 hours must elapse between doses of bortezomib**. If a planned dose of bortezomib is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

The first and subsequent doses of daratumumab should be given in an environment with resuscitation facilities. Consider giving the first dose of daratumumab as an inpatient.
Daratumumab should be administered in sodium chloride 0.9% and via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate (table below). Consider incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion.

	Volume of sodium chloride 0.9%	Initial infusion rate (first hour)	Rate increment	Maximum rate
First infusion (week 1)				
Single dose (16mg/kg) infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Split dose (8mg/kg) infusion	500mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion 16mg/kg (week 2)*	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions 16mg/kg (week 3 onwards) #	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

* Escalate only if the patient's first infusion of daratumumab was well tolerated (absence of >Grade 1 infusion-related reactions during the first 3 hours). If the previous infusion was not well tolerated, then instructions for the first infusion will be used.
# Escalate only if the patient's first 2 infusions of daratumumab were well tolerated (absence of >Grade 1 infusion-related reactions during a final infusion rate of ≥100 mL/hr). If the previous infusion was not well tolerated, then instructions for the second infusion will be used.
Note: For guidance on infusion rates in the case of infusion related reactions see adverse effects section below.

Accelerated infusion

From the third dose onwards daratumumab may be given at an accelerated infusion rate administering 20% of the dose over 30 minutes and 80% over 60 minutes, according to local practice. **(Note: this is an unlicensed infusion rate and should be agreed via the local governance process before implementation).**

Pre-medication

1-3 hours prior to daratumumab infusion:
Paracetamol 500mg-1g PO,
Chlorphenamine 10mg IV,
Dexamethasone 20mg IV bolus pre first dose daratumumab then PO,
Hydration fluids may be required, ensure a fluid intake of at least 3 litres/day on treatment days in cycle 1,
Consider montelukast 10mg PO administered >30 mins prior to first infusion and subsequent infusions in cycle 1.

Post-infusion medication

For the prevention of delayed infusion reactions to daratumumab, oral corticosteroid (at least 20mg methylprednisolone or equivalent such as 4mg dexamethasone) should be administered on the day after infusions.

For patients with a history of obstructive pulmonary disorder, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four infusions, if the patient experiences no major infusion related reactions, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

Emetogenicity

This regimen has low emetic potential.

Additional supportive medication

Allopurinol 300 mg OD (100mg OD if CrCl < 20mL/min) for days 1-7 in cycle 1.
Prophylactic aciclovir for the duration of treatment and for 3 months afterwards.
Consider prophylactic co-trimoxazole.
Prophylactic antifungals as per local policy.
Proton pump inhibitor or H_2 antagonist.
Loperamide if required.
Bisphosphonates as per local protocol.

Extravasation

Daratumumab is not vesicant.
Bortezomib is neutral (group 1).

Pre-treatment evaluation

Investigation	Validity period
FBC and film	14 days
Group and Save	Inform transfusion laboratory that patient is due to commence daratumumab.
U+Es including creatinine	14 days
LFTs	14 days
Pregnancy test (if female of child bearing potential)	72 hours

There are no human data to inform a risk with use of daratumumab during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta and based on mechanism of action, daratumumab may cause foetal myeloid or lymphoid-cell depletion and decreased bone density.

Other investigations:
It is advisable to assess the following before starting treatment and during treatment as clinically indicated:
Plasma viscosity
Uric acid
Calcium
Glucose
β2 microglobulin
Serum protein electrophoresis and immunofixation for quantification of serum monoclonal (M) protein and immunoglobulins
Serum free light chain assay
Urine collection for light chain excretion
HIV, hepatitis B and hepatitis C screen **Note**: Patients with known acute or chronic infective diseases were excluded from clinical studies

Consider bone marrow aspirate and trephine (with immunophenotype) and myeloma FISH
WB CT, MRI, PET-CT or skeletal survey as clinically indicated
MRI whole spine if suspicion of spinal cord compression
Pulmonary function

Consider baseline echocardiogram (risk of bortezomib-induced cardiomyopathy)

Investigations pre subsequent cycles

Investigation	Validity period
FBC	72 hours
U+Es including creatinine	72 hours
LFTs	72 hours

Glucose, calcium, Ig's, M protein quantification; serum free light chain assay as clinically indicated.
Consider bone marrow assessment after four cycles for oligosecretory myeloma.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance	≥ 20mL/min
Bilirubin	< 1.5 x ULN
AST/ALT	< ULN

Dose modifications

- **Haematological toxicity**

Daratumumab: no specific modifications or dose reductions are advised. Dose delays are advised to allow recovery of blood counts.

Bortezomib: withhold for grade 3 non-haematological or grade 4 haematological toxicities. Once toxicity has resolved, re-initiate at 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.

- **Renal impairment**

Daratumumab: no dose modifications required.

Bortezomib: if CrCl < 20mL/min use with caution. If patient is on dialysis, administer after dialysis.

- **Hepatic impairment**

Daratumumab: no dose modifications are required in mild hepatic impairment (bilirubin ≤1.5 x ULN or AST/ALT ≤ULN). Daratumumab has not been studied in moderate to severe hepatic impairment (bilirubin > 1.5 × ULN and any elevation of AST/ALT) – use with caution.

Bortezomib: If bilirubin > 1.5 x ULN consider starting dose of 0.7mg/m^2 for cycle 1. For subsequent cycles consider increasing dose to 1mg/m^2 or reducing dose to 0.5mg/m^2 according to tolerability.

- **Neurotoxicity**

Neuropathy grade	Bortezomib dose
Grade 1 with no pain	100%
Grade 1 with pain or grade 2 but not interfering with daily living	*1.0mg/m^2
Grade 2 with pain or grade 3	Withhold until symptoms resolved Restart at dose of 0.7mg/m^2
Grade 4	Discontinue

*Alternatively switch to weekly dosing schedule for bortezomib (DVd contains 32 doses of bortezomib) with dexamethasone the day of and day after bortezomib.

- **Other toxicities**

Bortezomib: Any other ≥ grade 3 non-haematological toxicity withhold bortezomib until recovered to ≤ grade 1. Recommence with dose reduction of one level.

Adverse effects - for full details consult product literature/ reference texts

Infusion reactions

• Daratumumab can cause severe infusion reactions. Approximately half of all patients treated experienced a reaction, mostly during the first infusion however infusion reactions can also occur with subsequent infusions. The median time to onset of reactions was within the first two hours of infusion and nearly all reactions occurred during infusion or within 4 hours of completing daratumumab. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.

• Severe adverse reactions have occurred, including bronchospasm, hypoxia, dyspnoea, and hypertension. Signs and symptoms may include cough, wheezing, larynx and throat tightness and irritation, laryngeal oedema, pulmonary oedema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.

• Pre-medications must be given at least 1 hour before the infusion. Patients should be monitored during the entire infusion and for 30 minutes to an hour post infusion first and subsequent infusions, according to local monoclonal antibody infusion protocols.

• Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short-and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders.

Managing Infusion related reactions (IRR)

For infusion reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation as outlined below.

IRR grade	Recommended action
Grade 1-2 (mild to moderate)	Once symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate.
Grade 3 (severe)	If the intensity of the reaction decreases to ≤Grade 2, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate. Permanently discontinue treatment upon the third occurrence of a Grade 3 or greater reaction.
Grade 4 (life threatening)	Permanently discontinue treatment.

Other adverse effects:
Myelosuppression
Atrial fibrillation
Peripheral neuropathy
Fatigue
Peripheral oedema
Allergic rhinitis, nasopharyngitis,
Pyrexia
Dyspnoea
Cardiotoxicity
Orthostatic hypotension
URTI, pneumonia, cough
GI disorders (nausea, constipation, diarrhoea),
Headache
Hypertension
Hyperglycaemia
Cutaneous reactions
Mortality (5.5% from AE in CASTOR study)

Significant drug interactions – for full details consult product literature/ reference texts

Daratumumab: no interaction studies have been performed.

Bortezomib:
Antihypertensives: Risk of additive hypotensive effect. Close monitoring of BP is required.
Oral antidiabetic agents: Hyper- and hypoglycaemia has been reported. Close monitoring of blood glucose is required.
Ciclosporin: increased risk of severe neuropathy: avoid concomitant use.
High dose vitamin C: reduced efficacy of bortezomib: avoid concomitant use.
Cytochrome P34A inhibitors (ketoconazole and other azole antifungals, clarithromycin, erythromycin) may increase bortezomib levels: avoid concomitant use.
Cytochrome P34A inducers (rifampicin, carbamazepine, phenytoin, St Johns Wort) may reduce bortezomib levels: avoid concomitant use.

Additional comments

Interference with Blood Transfusion Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and may result 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 infusion. 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 upon.

- The blood transfusion laboratory must be notified of this interference with serological testing and notified that a patient has received daratumumab.
- Patients must have a Blood Group and Antibody screen prior to starting daratumumab.
- Patient will require red cell phenotyping/genotyping.
- Ensure patients are given a Patient Alert Card for daratumumab and are instructed to carry this for 6 months after stopping treatment and show the card to healthcare professionals that treat them.
- Counsel patients to tell their other health care professionals that they received daratumumab, particularly before a transfusion.

Interference with determination of monoclonal protein concentration

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 on the determination of complete response and of disease progression in all patients with IgG kappa myeloma.

Contraception

To avoid exposure to the foetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment. There are no human data to inform a risk with use of daratumumab during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta and based on mechanism of action, daratumumab may cause foetal myeloid or lymphoid-cell depletion and decreased bone density.

References

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