Daratumumab

Indication

Relapsed/refractory multiple myeloma for patients whose prior therapy has included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
Use within the Cancer Drugs Fund:

- after 3 previous therapies and the conditions in the managed access agreement are followed.

(NICE TA510)

ICD-10

Codes with a pre fix C90

Regimen details

Cycles 1 and 2 (weeks 1 to 8)

Day	Drug	Dose	Route
1*, 8, 15 and 22	Daratumumab	16mg/kg	IV infusion
1, 8, 15 and 22	Dexamethasone	20mg (see pre med section)	IV bolus or PO
2, 9, 16 and 23	Dexamethasone	20mg	PO
3,10,17 and 24	Dexamethasone	4mg	PO

*To facilitate administration, the first dose on week 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 3 to 6 (weeks 9 to 24)

Day	Drug	Dose	Route
1 and 15	Daratumumab	16mg/kg	IV infusion
1 and 15	Dexamethasone	20mg (see pre med section)	IV bolus or PO
2 and 16	Dexamethasone	12mg	PO
3 and 17	Dexamethasone	4mg	PO

Cycles 7 (week 25) onwards

Day 1	Drug	Dose	Route
1	Daratumumab	16mg/kg	IV infusion
1	Dexamethasone	20mg (see pre med section)	IV bolus or PO
2	Dexamethasone	8mg	PO
3	Dexamethasone	4mg	PO

The daratumumab may be substituted for 1800mg dose administered via sub-cutaneous injection over 5 minutes. Patients should be observed for at least 6 hours after the end of the SC injection following the first dose (or as per local policy) and, if deemed necessary, after subsequent injections.

Cycle frequency

28 days
If a planned dose is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

Number of cycles

Until disease progression or unacceptable toxicity.

Administration

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% (volume as per table below). It should be administered via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate (as per 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.

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).**

Subcutaneous daratumumab

Administer via sub-cutaneous injection over 5 minutes. Patients should be observed for at least 6 hours after the end of the SC injection following the first dose (or as per local policy) and, if deemed necessary, after subsequent injections.

Pre-medication

1-3 hours prior to daratumumab infusion (or SC injection):
Paracetamol 500mg-1g PO,
Chlorphenamine 10 mg IV or 4mg PO,
Dexamethasone 20mg IV bolus or PO (for subsequent cycles this dose may be reduced)
Hydration may be required, ensure a fluid intake of at least 3 litres/day.
Consider montelukast 10mg PO >30 mins prior to first infusion.

Post-infusion medication

For the prevention of delayed infusion reactions, oral corticosteroid (20 mg methylprednisolone or equivalent such as 4mg dexamethasone) should be administered on day 2 and 3 following all infusions (see dosing table above).

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 7 days for 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.
Bisphosphonates as per local protocol.

Extravasation

Daratumumab is not vesicant.

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 indicated:
Plasma viscosity
Uric acid
Calcium
Glucose
β2 microglobulin
Serum protein electrophoresis and immunofixation for quantitation of serum monoclonal protein and immunoglobulins
Serum free light chain assay
Urine collection for light chain excretion (Bence Jones protein).
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 consider myeloma FISH.
WB CT, MRI, PET-CT or skeletal survey as clinically indicated.
MRI whole spine if suspicion of spinal cord compression.
Pulmonary function

Investigations pre subsequent cycles

Investigation	Validity period
FBC	7 days
U+Es including creatinine	7 days
LFTs	7 days
Glucose	As clinically indicated
Calcium	As clinically indicated
Ig's, M protein quantification ; serum free light chain assay	Monthly after first 2 months

Consider bone marrow assessment after four cycles for non-secretory 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
Haemoglobin	≥ 80g/L
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L
Bilirubin	< 1.5 x ULN
AST/ALT	< ULN

Dose modifications

- **Haematological toxicity**

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

Investigation	Limit
Haemoglobin	≥ 80g/L
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 50 x 10^9/L

No specific modifications advised. No dose reductions are recommended. Dose delays are advised to allow recovery of blood counts.

- **Renal impairment**

No dose modifications required.

- **Hepatic impairment**

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.

- **Other toxicities**

See management of adverse effects below.

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

Treatment reactions

• Daratumumab can cause severe infusion reactions. Approximately half of all patients receiving IV treatment 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. For SC dosing the incidence was much lower, around 2% with a median onset of 3.5 hours.

• 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. For IV treatment 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 receiving SC treatment should be monitored for 6 hours following the first dose. Monitoring following subsequent SC doses is at the clinician discretion.
• To reduce the risk of delayed infusion reactions, corticosteroids should be given to all patients as a pre-med and for the 2 days following each treatment.
• 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
URTI, pneumonia, cough
GI disorders (nausea, constipation, diarrhoea),
Headache
Hypertension

Significant drug interactions – for full details consult product literature/ reference texts
No interaction studies have been performed.

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.

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.

Patients with known acute or chronic infective diseases were excluded from clinical studies.

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