Daratumumab Rapid Rate Infusion

INTRODUCTION

Administration of daratumumab is associated with a high incidence of infusion-related reactions (IRRs), which occurred in approximately half of all patients treated with daratumumab, the majority of IRRs occur during the first infusion. In clinical trials (monotherapy and combination treatments) the incidence of any grade infusion-related reactions was 46% with the first infusion of daratumumab, 2% with the second infusion, and 3% with subsequent infusions. Less than 1% of patients had a Grade 3 infusion-related reaction with second or subsequent infusions. Most severe (≥Grade 3) infusion-related reactions included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse infusion-related reactions of any grade include nasal congestion, cough, chills, throat irritation, vomiting and nausea. Pre-existing history of chronic obstructive pulmonary disease (COPD) constitutes a specific risk factor for developing bronchospasm. Pre- and post-infusion medications should be administered to all patients as per protocol to reduce the risk of infusion-related reactions (IRRs). Patients must be monitored throughout the infusion for signs and symptoms of reaction and managed in line with guidelines in case of developing IRRs.

Data from a prospective, single-center, and open-label safety study of an accelerated daratumumab infusion suggests that a rapid (90 minute) daratumumab infusion schedule is well tolerated and safe, when administered from the 3rd infusion onwards in patients who have tolerated the 500 mL daratumumab infusion at the manufacturer recommended rates.

Notes:

- **The rapid (90 minute) rate of infusion is unlicensed; patients need to consent to receive rapid rate daratumumab in line with the unlicensed medicines policy.**
- **Refer to Appendix 1 for grading of possible infusion-related adverse events.**

INCLUSION CRITERIA FOR DARATUMUMAB RAPID RATE INFUSION

- **Patients on CYCLE 2- Onwards AND must have received and tolerated the previous 500mL daratumumab infusion at the standard manufacturer licensed rate without ≥ Grade 1 IRRs.**
- Patients must demonstrate tolerability of a 500 mL daratumumab infusion at the manufacturer recommended rates prior to receiving the accelerated infusion.
- Patients receiving daratumumab as monotherapy or in combination with bortezomib and dexamethasone (DVd)Patients who have given consent to rapid rate daratumumab infusion.

CAUTION: Pre-existing chronic obstructive pulmonary disease (COPD) constitutes a risk factor for developing bronchospasm with daratumumab infusion. Discuss with the clinician patients with COPD, asthma or other respiratory comorbidities and those with uncontrolled hypertension. For patients with a history of COPD, or asthma administer post-infusion inhaled short and long acting bronchodilators, and inhaled corticosteroids

EXCLUSION CRITERIA FOR DARATUMUMAB RAPID RATE INFUSION

- Previous ≥grade 3 infusion related toxicity with daratumumab.
- IRR ≥grade 1 with the most recent daratumumab infusion given at the standard manufacturer licensed rate i.e. patients must have received and tolerated the previous 500mL daratumumab infusion at the standard manufacturer licensed rate without ≥ Grade 1 IRRs.
- Patients whose most recent dose was prepared in the 1000 mL dilution due to moderate or severe IRR. Patients must demonstrate tolerability of a 500 mL daratumumab infusion at the manufacturer recommended rates prior to receiving the accelerated infusion.
- Cardiac amyloid patients.
- Patients receiving daratumumab as part of clinical trials (follow trial protocol).

ADMINISTRATION OF DARATUMUMAB RAPID RATE INFUSION

Pre- and Post- medication administration with rapid rate infusion

General principle with DarVelDex: the pre- and post-medication dexamethasone is also used as the steroid component of this triplet combination, therefore;

- If daratumumab infusion is given on same day as bortezomib, the pre- and post-medication follows the triplet steroid dosing (i.e. dexamethasone 20mg, unless dose reduced, given on the day of and day after bortezomib).
- If no bortezomib dose is due on the day of daratumumab infusion, the post-medication is dexamethasone 4mg PO for TWO DAYS starting the day after daratumumab infusion
- CARE if bortezomib scheduling is being modified.

Regimen	**Daratumumab Monotherapy** (cycles 2-onwards) & **DaraVelDex (DVd)** (cycles 9-onwards)	**DaraVelDex (DVd) protocol** Cycles 2 to 8
Pre-medication	**30 minutes prior to daratumumab infusion:** • Paracetamol 1000mg PO • Chlorphenamine 10mg IV • Montelukast 10mg PO **(first rapid rate infusion only)** • Dexamethasone 20mg IV (first rapid rate infusion), can be reduced to Dexamethasone 12mg IV/PO following the second rapid rate infusion.	**30 minutes prior to daratumumab infusion:** • Paracetamol 1000mg PO • Chlorphenamine 10mg IV • Montelukast 10mg PO **(first rapid rate infusion only)** • Dexamethasone 20mg IV bolus or PO (give IV prior to the first rapid rate infusion) Note: on bortezomib days, this is also used as the background steroid component of the triple combination regime
Post-medication	Dexamethasone 4mg PO the for TWO DAYS starting the day after daratumumab infusion	• **If daratumumab infusion is given on same day as a bortezomib dose***: dexamethasone 20mg PO the day after daratumumab infusion (i.e. days 2 and 9 of cycles 2 and 3, and day 2 of cycles 4-8)**. • **If no bortezomib dose is due on the daratumumab infusion day**: dexamethasone 4mg PO for TWO DAYS starting the day after daratumumab infusion (i.e. days 16 and 17 of cycles 2-3)
	For patients with a history of chronic obstructive pulmonary disease, or asthma administer post-infusion inhaled short and long acting bronchodilators, and inhaled corticosteroids *Daratumumab is given on the same day as bortezomib on the following days: days 1 and 8 of (cycles 2 and 3), and day 1 (cycles 4-8) **In addition to its role as post-medication, this dexamethasone dose is also used as the background steroid component of the triplet combination (DVd)	

Rapid infusion Rate

CYCLE 2 and subsequent cycle doses for those **patients eligible to receive rapid rate**:
Daratumumab prepared in 500 ml sodium chloride 0.9%.
Infuse **100 ml** of the daratumumab infusion (20% of the dose) **over 30 minutes.**
Then infuse the remaining **400 ml** (80% of the dose) **over 60 minutes** (total infusion time 90 minutes).

Monitoring

- Check vital signs before the start of the infusion, every 15 minutes during the first 60 minutes of the infusion, and at the end of the infusion.
- Monitor patient for adverse effects. For the first rapid rate infusion, observe patients in the DTU for 30 min after infusion completion to assess for delayed infusion related reactions.
- Closer monitoring is required if a patient has a history of uncontrolled hypertension, pre-existing COPD, asthma or other respiratory comorbidities. Discuss these patients with a clinician.

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Dr Karthik Ramasamy Nadjoua Maouche Network Approval	New document	June 2018	1.0	June 2020
Nadjoua Maouche Faouzi Djebbari	Update to include DVd protocol	May	2.0	June 2020

APPENDIX 1: The severity of allergic or infusion related reactions can be graded according to **CTCAE version 4.03 - June 14, 2010**

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances					

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anaphylaxis			Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					