Thames Valley
Strategic Clinical Network

Guidelines for administration of rapid infusion Rituximab

INTRODUCTION:

Administration of rituximab can be associated with substantial infusion- related reactions (IRRs). Grade 1 and 2 IRRs are relatively common during the first rituximab infusion but infusion related toxicities are uncommon with subsequent infusions. More severe infusion related toxicities include hypersensitivity reactions (fever, rash, cardiovascular and respiratory compromise) and rarely fatal cytokine release syndrome (characterised by severe dyspnoea, bronchospasm or hypoxia in addition to fever, chills, rigors, urticaria, and angioedema). Cytokine release syndrome has been associated with features of tumour lysis syndrome, occurring 1 to 2 hours after infusion of rituximab. Patients with a high tumour burden in addition to those with pulmonary insufficiency or infiltration are at risk and should be monitored very closely and a slower rate of infusion considered. Pre-medication with an analgesic, antihistamine and corticosteroid is recommended

Data suggests that a rapid (90 minute) rituximab infusion schedule is well tolerated and safe, when administered from the 2nd infusion onwards in patients who have tolerated their first infusion of rituximab. Many day-care units have implemented this locally as a safe and time efficient method of reducing the infusion time.

Notes:

- **The rapid (90 minute) rate of infusion is unlicensed, inform patients in line with the unlicensed medicines policy**
- **Refer to Appendix 1 for grading of possible rituximab infusion related adverse events.**

INCLUSION CRITERIA FOR RAPID INFUSION

Patients receiving subsequent rituximab infusion who have received and tolerated the first full dose (375mg/m^2 for NHL and 500mg/m^2 for CLL) rituximab infusion at standard rate without a grade 2 or more infusion-related adverse reactions when rituximab is prescribed in the following settings:

- Rituximab combined with steroid and non-steroid containing chemotherapy (**excluding CLL patients on FCR chemotherapy).**
- In NHL, rituximab monotherapy including as 2 or 3 monthly maintenance in patients who have received previous rituximab infusion as part of the combination induction therapy.
- For CLL patients, they must have previously received the full 500mg/m^2 without ≥ 2 IRR, rapid infusion therefore would usually start from cycle 3 on-ward.

EXCLUSION CRITERIA FOR RAPID INFUSION

Previous ≥ grade 2 infusion related toxicity or hypersensitivity reaction to rituximab
High tumour burden, Bulky disease and/or lymphocyte count > 5 x 10^9/L
Patients with pre-existing cardiac or pulmonary insufficiency
Patients receiving split dose rituximab
Patient on clinical trials- follow trial protocol
CLL patients receiving FCR chemotherapy

ADMINISTRATION

Consider withholding anti-hypertensive medications for 12 hours prior to rituximab.

Premedication (30 minutes prior to rituximab)
Paracetamol 1000mg po
Chlorphenamine 10mg iv
Hydrocortisone 100mg IV bolus* (or steroid component of chemotherapy regimen).

*from cycle 2 onward (cycle 3 onward in case of CLL), steroid-premedication if not part of the chemotherapy regimen can be omitted with subsequent cycles if the patient has not experienced Grade 2 or above Infusion Related Reaction.

First Infusion

The initial infusion is **50mg/h** for the **first 30 minutes**.
Thereafter, if no reaction, the rate can be escalated in **50mg/h** increments **every 30 minutes** to a maximum rate of **400mg/h**

Subsequent infusions:

After the first infusion, subsequent infusions can be given at either the licensed rate or rapid rate (for those eligible to receive rapid infusion).

Subsequent infusions licensed rate

Subsequent doses of rituximab can be infused at an initial rate of **100 mg/h**, and increased by **100 mg/h** increments at **30 minute** intervals, to a **maximum of 400 mg/h**.

Subsequent infusions Rapid rate (for those eligible to receive rapid infusion)

Cycle 2 and subsequent cycles (cycle 3 onward in case of CLL)
Rituximab prepared in 500 ml sodium chloride 0.9%.
Infuse 100 ml of the rituximab 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).**
Monitor patient for adverse effects.

REFERENCES

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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**
Cytokine release syndrome	Mild 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 (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					

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.					