MONOGRAPH

Rituximab

Scope (Staff):	Medical, Pharmacy, Nursing, Anaesthetic Technicians
Scope (Area):	Perth Childrens Hospital (PCH)

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this DISCLAIMER

⚠ HIGH RISK MEDICINE ⚠

QUICKLINKS

Dosage/Dosage Adjustments	Administration	Compatibility	Monitoring

DRUG CLASS

Non-cytotoxic antineoplastic antibody[1]

Rituximab is a High Risk Medicine.

INDICATIONS AND RESTRICTIONS

At PCH, rituximab is restricted to prescribing by or in consultation with a:

- Haematologist/ Oncologist
- Rheumatologist
- Neurologist
- Respiratory Physician
- Nephrologist

CONTRAINDICATIONS

- Hypersensitivity to rituximab, murine proteins, Chinese hamster ovary cell proteins or any component of the formulation.[2, 3]
- Previous mucocutaneous reactions with rituximab.[2]
- History of or current progressive multifocal leukoencephalopathy (PML).[2]

- Patients with severe, active infections.[2]

PRECAUTIONS

- Vaccination status not up to date – a patients vaccination history must be considered prior to initiation.[2] Review the patient's vaccination status and, if possible, administer any required vaccines prior to therapy.[2]
    - Specific consideration should be taken into vaccination against *streptococcus pneumoniae*, *Neisseria meningitis* and seasonal influenza.
    - Refer to the Vaccination and Immunosuppressive Therapy guideline
- Hepatitis B virus (HBV) reactivation – screen all patients for HBV prior to, during and post rituximab. Discontinue rituximab in patients who develop HBV reactivation.[2]
- Tuberculosis (TB) reactivation – assess the risk of TB reactivation in patients who are receiving concomitant therapy with other immunosuppressive agents and who are[4]:
    - Born overseas in a TB endemic country
    - Live in a TB endemic country
    - Are a known contact of TB
- Severe mucocutaneous reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome) – have been reported with rituximab use. Cease treatment with rituximab if a reaction occurs.[2]
- Infusion-related reactions – may occur with rituximab use. Give premedications (as outlined in the dosage & dosage adjustments section) and monitor the patient throughout the infusion.[2] Refer to the monitoring section for the appropriate management of such reactions.[2]
- Severe infections and hypogammaglobulinemia – serious and fatal bacterial, fungal and viral infections can occur during and following rituximab therapy.[5] In addition, these infections have been observed in patients with prolonged hypogammaglobulinemia following therapy.[2] As outlined in the monitoring section, record baseline immunoglobulin levels and monitor throughout and after therapy.[6] Consider IVIG replacement if indicated and discontinue therapy if severe infections occur.[6]
- Progressive multifocal leukoencephalopathy (PML) – has been reported in patients with haematologic malignancies and autoimmune diseases.[2] Evaluate patients who develop neurological symptoms. Consider consulting a Neurologist, obtaining a brain MRI and preforming a lumbar puncture.[2]
- Cytopenia's (including lymphopenia, leukopenia, neutropenia, thrombocytopenia and anaemia) – may develop. Monitor blood counts during and after treatment.[2]
- Tumour lysis syndrome (TLS) – has been reported in patients with non-Hodgkin lymphoma who received rituximab. Administer aggressive hydration and anti-hyperuricemia therapy as prophylaxis in patients at high risk of developing TLS.[2]

- Severe nephrotoxicity – may occur following treatment.[2] Monitor renal function in all patients and use with caution in patients with pre-existing renal impairment.[2]
- Gastrointestinal obstruction / perforation – has been reported in patients who received rituximab therapy. Evaluate patients who develop symptoms of abdominal pain or repeated vomiting.[2, 5]
- Cardiovascular effects – perform cardiac monitoring (ECG) during and following each infusion in patients who have a history of arrhythmia or angina, as well as patients who develop clinically significant arrhythmias.[2]
- Hypotension – transient hypotension may occur. Consider withholding antihypertensives for 12 hours before and during infusion to reduce risk.[1]

FORMULATIONS

Listed below are products available at PCH, other formulations may be available, check with pharmacy if required:

- 100 mg/10 mL vial
- 500 mg/50 mL vial

Imprest location: Formulary One

DOSAGE & DOSAGE ADJUSTMENTS

Dosing in Overweight and Obese Children: Calculate dose on measured body weight

Renal impairment:

- No adjustment required.[2]

Hepatic impairment:

- No adjustment required.[2]

Haemodialysis:

- Rituximab is not cleared by haemodialysis; rituximab may be administered pre or post dialysis[7]

Plasmapheresis:

- Rituximab is cleared by plasmapheresis. Separate administration by at least 48 hours[8]

PREMEDICATIONS:

Premedications should be given before each infusion to reduce the severity of infusion-related reactions.[9] These medications should be written on the “Once Only Medication” section on the WA paediatric Hospital Medication Chart (pHMC).

1. Loratadine (orally) – give 1 hour prior to infusion[9]
2. Paracetamol (orally) – give 1 hour prior to infusion[9]
3. Hydrocortisone (intravenously) – give immediately prior to infusion[2]

- > 4 weeks of age: 4 mg/kg (maximum 100 mg)
- Oncology/ Haematology patients: The requirements for hydrocortisone should be reviewed on an individual patient basis in view of steroids being part of a patient's chemotherapy treatment regimen.

Adrenaline must be readily available for all patients.

DOSAGE:

Rituximab must be prescribed on the Rituximab Variable Rate Infusion Chart MR353.08 / MR860.17 with incremental rate increases written in mL/hour.

IV Infusion:

- > 4 weeks of age:
  - 375 mg/m^2 (maximum 500 mg) once each week for up to 4 doses[9] OR
  - 750 mg/m^2 (maximum 1000 mg) on Day 0 and Day 14[9]
  - Additional courses may be considered depending on patient condition, response and toxicity[9]
- Oncology / Haematology Patients: Dose as per Childrens Oncology Group guidelines

RECONSTITUTION & ADMINISTRATION

PREPARATION:

- During pharmacy operating hours, infusions must be prepared by the Pharmacy Compounding Service (PCS)
  - When prepared by PCS, the infusion is stable for 7 days when stored between 2ºC and 8ºC.[10]
  - Orders prepared by PCS must be reviewed by a clinical pharmacist prior to compounding
- After hours, rituximab may be prepared on the ward and used immediately.[11]
  - Rituximab should NOT be prepared by staff who are pregnant or immunocompromised.[12]
  - At the ward level, the following Personal Protective Equipment should be worn during preparation and administration[12]:
    - N95 mask
    - Gloves
    - Protective eye wear – to be worn during preparation and when connecting and disconnecting the infusion.
    - Gowns are not required.
- Dilute dose to a final concentration of 1 mg/mL with a compatible fluid[11].
  - For fluid restricted patients a maximum concentration of 4 mg/mL can be used[11]

- Mix gently before administration. DO NOT SHAKE.[11]

ADMINISTRATION:

- Patients < 50kg[2]:
  - Initial rate: 1 mg/kg/hour (maximum 50 mg/hour).
  - If tolerated, increase the rate by 1 mg/kg/hour (maximum 50 mg/hour) every 30 minutes to a maximum of 400 mg/hour
- Patients ≥ 50kg[13]:
  - Initial Infusion[13]:
    - Initial rate: 50 mg/hour
    - If tolerated, increase the rate by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour
  - Subsequent Infusions[13]:
    - Begin at an initial rate of 100 mg/hour
    - If tolerated, increase the rate by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour
- Oncology/ Haematology patients: Administer as per the Children's Oncology Group guidelines.

<u>Infusion-related reactions:</u>

Infusion-related reactions are most common with the first infusion and can cause symptoms such as fever, chills and/or rigors, nausea, vomiting, urticaria, itch, headache, bronchospasm, dyspnoea, angioedema, rhinitis and hypotension.[1]

- The majority of these reactions are mild and transient with the risk decreasing with each subsequent infusion.[14]
- If an infusion-related reaction occurs, stop the infusion and treat symptomatically if appropriate.[1]
- For mild to moderate reactions, the infusion can be restarted at half the previous rate once symptoms have resolved.[9]
- For severe reactions, cease the infusion and do not restart.[9]

COMPATIBILITY *(LIST IS NOT EXHAUSTIVE)*

Compatible fluids: Sodium Chloride 0.9%, Glucose 5%[11]

Do not mix rituximab with other medications including via a Y-site[11]

MONITORING

NOTE: All patients receiving rituximab must have completed the required pre-screening and immunological assessment prior to initiation.

Prior to administration:

- Review vaccination history - review the patient's vaccination status and, if possible, administer any required vaccines prior to therapy.[2]
    - Specific consideration should be taken into vaccination against *streptococcus pneumoniae*, *Neisseria meningitis* and seasonal influenza.
- Screen for Hepatitis B infection[2]
- Assess the risk of Tuberculosis reactivation[4]
- Obtain baseline full blood count with differential, lymphocyte subsets, memory B cells and immunoglobulins (IgG, IgM and IgA)[2]
- Pregnancy testing and advice (where appropriate)[2]
- Obtain baseline creatinine, urea and electrolyte levels and liver function tests[2]
- Measure uric acid levels (oncology patients)[2]
- Measure baseline temperature, pulse, respiratory rate and blood pressure[15]

During infusion:

- Measure temperature, pulse, respiratory rate and blood pressure every 15 minutes for the first 2 hours of the infusion, then every 30 minutes thereafter until completion of the infusion[16]
    - Continue to monitor patients for at least 30 minutes post infusion completion (or as directed by the treating team)[15]
- Monitor for infusion related reactions[1] and manage as outlined in the "Reconstitution and Administration" section
- Consider cardiac monitoring for patients with pre-existing cardiac conditions[2]

IMPORTANT - A "Code Blue" must be called immediately, and appropriate measures commenced, whenever anaphylaxis is suspected (Resuscitation and Responding to Clinical Deterioration).

Ongoing monitoring post infusion:

- Lymphocyte subsets[17]
    - Measure 1 month, 6 months and 12 months post infusion[17]
    - Continue to measure every 6 months until B cell numbers return to normal[3]
- Serum immunoglobulins (IgG, IgM and IgA)[17]
    - Measure every 3 – 6 months[17]

- Continue measuring every 3 – 6 months until IgM and IgG levels are within the normal range on 2 consecutive occasions

ADVERSE EFFECTS

Common: infusion-related reactions, bacterial and viral infections, neutropenia, leukopenia, lymphopenia, angioedema, nausea, pruritus, rash, fever, chills, asthenia, headache, decreased immunoglobulin levels, arrhythmias, musculoskeletal pain.[1, 2]

Infrequent: thrombocytopenia, anaemia, angina, myocardial infarction, heart failure, hyperglycaemia, peripheral oedema, paraesthesia, hypoesthesia, insomnia, dizziness, anxiety, atrial fibrillation, hypotension or hypertension, bronchospasm, dyspnoea, cough, vomiting, diarrhoea, abdominal pain, arthralgia, myalgia, flushing, malaise.[1, 2, 5]

Rare: serum sickness, severe skin conditions days to months after treatment (including Stevens-Johnson syndrome, toxic epidermal necrolysis, vesiculobullous dermatitis), pneumonitis, cranial neuropathy (vision or hearing loss), progressive multifocal leukoencephalopathy, latent infection reactivation (including hepatitis B virus, varicella zoster virus, cytomegalovirus, herpes simplex virus and tuberculosis) [1, 2, 5]

STORAGE

- Vial: Store between 2ºC and 8ºC. Do not freeze. Protect from light.[3]

INTERACTIONS

This medication may interact with other medications; consult PCH approved references (e.g. Clinical Pharmacology), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

Please note: The information contained in this guideline is to assist with the preparation and administration of **rituximab**. Any variations to the doses recommended should be clarified with the prescriber prior to administration

Related CAHS internal policies, procedures and guidelines

High Risk Medicines

Vaccination and Immunosuppressive Therapy

Labelling of Injectable Medications and Fluids

Medication Administration

Medication Safety

Medication Preparation, Checking and Administration

Prescribing – Authorisation, Approval and Governance

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