MONOGRAPH

CYCLOPHOSPHAMIDE

(Rheumatology/Nephrology)

Scope (Staff):	Medical, Pharmacy, Nursing, Anaesthetic Technicians
Scope (Area):	All Clinical Areas

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

Alkylating agent with immunosuppressant properties.[1]

Cyclophosphamide is a High Risk Medicine.

INDICATIONS AND RESTRICTIONS

- Systemic Lupus Erythematosus (SLE)[2]
- Juvenile Dermatomyositis[3]
- Vasculitis[3,4]
- Nephrotic Syndrome[5,6]

Note: This protocol refers to intravenous or oral cyclophosphamide therapy for the management of rheumatological/renal conditions only. In the management of malignancy, treatment protocols at CAHS are strictly as per the Children's Oncology Group (COG) or any other CAHS Ethics approved study protocol.

CONTRAINDICATIONS

- Hypersensitivity to cyclophosphamide or any component of the formulation.
- Pregnancy– Cyclophosphamide is a known teratogen.[7,8] Pre-infusion pregnancy testing should be performed for female patients of child-bearing potential. Refer also to “Precautions” and “Monitoring”.
- Active infection - Due to the risks of neutropenia, therapy should be delayed in patients who have systemic or life-threatening infection.[7]
- Full blood counts (neutropenia/thrombocytopenia) - Absolute neutrophil count (ANC) nadir must be ≥1 x 109 and/or a thrombocyte count of ≥100 x 109 prior to a scheduled infusion. Note, however, that some indications are associated with a disease-related thrombocytopenia/neutropenia. In this clinical scenario, the ultimate decision to proceed with therapy rests with the treating Consultant.

PRECAUTIONS

- **Teratogenicity**- Contraceptive measures may need to be considered in female patients of childbearing potential.[7,8]
- **Gonadal suppression**- Subfertility or infertility may occur in males and females and is related to cumulative dose and duration of treatment. The treating doctor must discuss the reproductive health implications of receiving cyclophosphamide (including measures to preserve fertility, pregnancy and contraception) with the patient (and parent/carer, as appropriate) prior to commencing therapy. [7,8]
- **Opportunistic infection** - *Pneumocystis jirovecii* pneumonia risk becomes increasingly significant with longer exposure to immunosuppressants.[7] Consider prophylaxis with a suitable antimicrobial (see CHAMP Medical Prophylaxis).
- **Hydration status** - Patient must have adequate urine output and a urine specific gravity of ≤1.010 before an intravenous infusion can proceed. Refer also to Monitoring. Patients with fluid overload should receive reduced rates of IV hydration. Mesna is mandatory for these patients.
- Cyclophosphamide is considered possibly porphyrinogenic.[8]

FORMULATIONS

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

- 50 mg tablets
- 10 mg/mL oral suspension – Prepared by the PCH Pharmacy Compounding Service.
- Cyclophosphamide intravenous infusions are compounded extemporaneously by the Pharmacy Compounding Service.

Imprest location: Formulary One

DOSAGE & DOSAGE ADJUSTMENTS

Dosing in Overweight and Obese Children:

The American Society of Transplant and Cellular Therapy recommends using adjusted body weight (ABW) with the adjustment co-factor of 0.25 (ABW25) when 'measured body weight'/'ideal body weight' (MBW/IBW) >1.2 and if ≤1.2 use IBW or MBW.[9]

Doses are often based on Body Surface Area (BSA), which is calculated using the following formula:

$$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times weight\ (kg)}{3600}}$$

Intravenous:[12]

- In order for the correct calculation of dose, patients must have their height and weight taken prior to each scheduled infusion. Intravenous doses must be rounded to the nearest 20 mg and made up to a volume equal to 125 mL/m² with sodium chloride 0.9%.
- Intravenous cyclophosphamide doses are prescribed on a Parenteral Fluid Therapy Order Chart (MR828.00). In addition, pre-hydration, antiemetic, mesna (if required) and post-cyclophosphamide hydration must also be specified (see "Administration" below).
- To allow for its preparation, the Pharmacy Compounding Service requires **at least 24 hours notice prior** to a patient's scheduled infusion.
- An induction cycle of treatment typically involves a total of SIX intravenous 'pulse' doses. Maintenance doses thereafter are less frequent and are guided as per the treating Consultant based on the patient's clinical response.
- Prior to each subsequent dose, adjustments or treatment delays may be necessary based on specific haematological and biochemical parameters.

For patients < 18 months of age:

- Initial dose: 16.6 mg/kg – 25 mg/kg 'pulse' given ONCE monthly.
- Subsequent doses are based upon clinical response. The maximum dose is 33.2 mg/kg/dose ONCE monthly.

For patients ≥ 18 months – 18 years:

- Initial dose: 500 mg/m² (500 mg ***multiplied*** by the BSA)
- Subsequent doses are based on clinical response. The maximum dose is 1000 mg/m² per 'pulse' given ONCE monthly.

Oral:

- Tablets should not be cut or crushed.
- Doses should, where possible, be rounded to the nearest 50 mg. Alternatively, the required dose may be achieved by averaging over a number of days (e.g. 50 mg one day and 100 mg the following day would give an average dose of 75 mg/day over those 2 days).
- Cyclophosphamide oral suspension may be considered if neither of these options is suitable.

Nephrotic Syndrome:

≥ 4 weeks of age:

- 2 mg/kg once daily for 12 weeks OR 3 mg/kg once daily for 8 weeks. The maximum total cumulative dose is 168 mg/kg.[5]
- Generally, patients should receive only one course. A decision to give further courses should only be made by a consultant after discussion with parents/carers regarding adverse effects, including neutropenia, gonadal toxicity, and increased risk of malignancy.[6]

SLE nephritis:

≥ 1 year of age:

- 1-1.5 mg/kg (maximum 150 mg) once daily for 2 to 4 months.[5]

Dosage adjustment in neutropenia:[11]

Intravenous:

Where there is neutropenia (ANC ≤1.5 x 10^9) and/or an overall leucopenia (total White Cell Count ≤3.5 x 10^9) – Decrease subsequent doses by 250 mg/m² OR (8.3 mg/kg for patients < 18 months).

Oral:

The treating doctor must be informed of any patient that develops a suspected drug-related neutropenia and/or thrombocytopenia. Therapy should be withheld until counts recover.

Renal impairment:[10]

GFR (mL/min)	Recommendation
≥ 20	Unchanged
10-20	75-100% of normal dose
< 10	50-100% of normal dose

- eGFR calculator

Hepatic impairment:[5]

Serum bilirubin = 53 – 85 micromol/L OR transaminases > 3 times upper limit of normal	Administer 75% of dose
Serum bilirubin > 85 micromol/L	Avoid use

RECONSTITUTION & ADMINISTRATION

NOTE: CYCLOPHOSPHAMIDE IS A CYTOTOXIC AGENT.

The reconstitution of cyclophosphamide must only be performed by a pharmacist in an area approved for the preparation of cytotoxic agents. Refer to the PCH Pharmacy Compounding Service.

Intravenous cyclophosphamide infusions are to be given only by Registered or Clinical Nursing staff trained and assessed as competent in the safe handling, administration and disposal of cytotoxic preparations.

- All associated Clinical Staff must read and understand the content within the hospital's "Antineoplastic (Cytotoxic) Agents - Safe Handling and Administration" document.
- The use of intravenous mesna is optional for cyclophosphamide doses ≤1000 mg/m² and is at the discretion of the treating Consultant. There may be clinical scenarios where mesna should be considered irrespective of cyclophosphamide dose. Seek advice from the treating Consultant. Where it is to be used, it should be administered as;
    - A pre-cyclophosphamide dose equal to 20% of the cyclophosphamide dose, and
    - A post-cyclophosphamide dose equal to 100% of the cyclophosphamide dose, added to and given as part of the mandatory post-cyclophosphamide hydration.
- Mesna may be dosed orally in those patients being managed with oral cyclophosphamide. Oral mesna is TWICE the calculated intravenous dose.[1] Contact a Clinical Pharmacist for advice if required.

The following sequence should be followed in the prescribing and administration of intravenous cyclophosphamide:

- Pre-hydration at 200 mL/m²/hour, continued until starting criteria are met (see "Monitoring"), then
- Administer ondansetron, then
- Mesna, if ordered (20% of the cyclophosphamide dose given as a 15-minute IV infusion), then
- Cyclophosphamide (as a 1-hour IV infusion), then
- Post-cyclophosphamide hydration (at 125 mL/m²/hour) for a minimum of 4 hours. If the patient is to receive mesna (the post-cyclophosphamide dose is 100% of the cyclophosphamide dose) it should be added to this hydration fluid.

- The patient MAY be discharged after 4 hours of mandatory IV post-hydration. They should be encouraged to drink and void their bladder every 2 hours until bedtime.
- For all other patients, continue IV hydration until discharged.

COMPATIBILITY *(LIST IS NOT EXHAUSTIVE)*

Compatible fluids:[13]

Sodium chloride 0.9%, glucose 5%, glucose 5% in sodium chloride 0.9%, Compound sodium lactate (Hartmann's) solution.

Compatible at Y-site:[14]

Amifostine, amikacin, ampicillin, anidulafungin, aztreonam, benzylpenicillin, bleomycin, calcium folinate, cefazolin, cefotaxime, cefoxitin, cefuroxime, cisplatin, cladribine, clindamycin, doxorubicin, droperidol, erythromycin lactobionate, etoposide phosphate, filgrastim, fludarabine, fluorouracil, furosemide (frusemide), gemcitabine, gentamicin, heparin sodium, idarubicin, linezolid, melphalan, mesna, methotrexate, metoclopramide, metronidazole, mitomycin, ondansetron, oxaliplatin, paclitaxel, palonosetron, piperacillin sodium-tazobactam sodium, propofol, sargramostim, sodium bicarbonate, thiotepa, tobramycin, topotecan, trimethoprim-sulfamethoxazole, vancomycin, vinblastine, vincristine, vinorelbine.

Only commonly used drugs are listed below. This is not a complete list of incompatible drugs. Compatibilities of IV drugs must be checked when two or more drugs are given concurrently.

INCOMPATIBLE drugs: [14]

No information.

MONITORING

- Full blood count, urea and electrolytes, creatinine and liver function tests[7,8] are essential prior to each dose and 10-12 days post dose, as this correlates with white cell count nadir. Refer to *Contraindications* and *Precautions*.
- Blood pressure:
  - Immediately prior to infusion, then post infusions as follows:
    - 1 hourly for first 4 hours then, only if the patient has not yet been discharged;
    - 2 hourly for next 4 hours then,
    - 4 hourly thereafter
- Urinalysis: Specific gravity (SG) should be ≤1.010 before the infusion can proceed. Urine output maintained at 3 mL/kg/hour. Consider measures to maintain this rate (e.g. furosemide (frusemide) bolus).
- Haematuria: New-onset evidence of blood in the urine must be reported to the treating team.
- Pregnancy testing for female patients of childbearing potential should be considered prior to each infusion, and is at the discretion of the treating Consultant. Cyclophosphamide's active metabolites are mutagenic and teratogenic.

ADVERSE EFFECTS[1]

Common: Myelosuppression, alopecia, anorexia, haemorrhagic cystitis, nasal congestion (with rapid injection).

Infrequent: Hyperpigmentation of skin and nails, metallic taste, loss of taste.

Rare: Heart failure, pulmonary fibrosis (with long-term high-dose treatment), hepatic sinusoidal obstruction syndrome (high dose), water retention resembling SIADH resulting in hyponatraemia and seizures (more common with high doses).

Extravasation of cyclophosphamide should be managed as described in the PCH "Extravasation of Antineoplastic (Cytotoxic) Agents" guideline.

STORAGE

Protect from light.[2]

IV solutions: Refrigerate – do not freeze.

Oral tablets: Store below 25°C.[2]

PCH oral suspension: Refrigerate – do not freeze.

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 **cyclophosphamide**. Any variations to the doses recommended should be clarified with the prescriber prior to administration

Related CAHS internal policies, procedures and guidelines

Antineoplastic (Cytotoxic) Agents - Safe Handling and Administration

CHAMP Medical Prophylaxis

Dosing in Overweight and Obese Children

Extravasation of Antineoplastic (Cytotoxic) Agents

Furosemide (frusemide)

High Risk Medicine

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