Cyclophosphamide IV in Autoimmune Disorders - Full Clinical Guideline

Ref No. CG-RHEUM/2018/011

Introduction

There is an RCT evidence base for the use of pulse IV CYC in the following situations

- Remission Induction therapy in Systemic Vasculitis (e.g Granulomatosis with polyangitis; Eosinophilic granulomatosis with polyangitis; Microscopic polyangiitis and other forms of vasculitis)
- Lupus Nephritis (and other severe organ manifestations of Systemic Lupus Erythythematosus)
- CTD-ILD

Use in other situations e.g. Rheumatoid Vasculitis, Inflammatory Myopathy, is supported by an evidence base but no there are no RCT data.

The protocols for each condition are different, and should be adjusted by the treating Consultant according to disease and response to treatment.

These guidelines are based upon a combination of the:

- British Society of Rheumatology (BSR) and BHPR guidelines for the management of adults with ANCA-associated vasculitis
- BSR guidelines for the management and treatment of SLE.
- American college of rheumatology (ACR) guidelines for the management and treatment of lupus nephritis
- EUROLUPUS
- National Institution of Health (NIH).

Indications

1. Primary Systemic Vasculitis:

Pulsed IV Cyclophosphamide is preferred due to lower toxicity non-inferiority and reduced risk of infection. The following regime is in accordance with BSR ANCA positive vasculitis guidance https://doi.org/10.1093/rheumatology/ket445 :.

Adjunct steroids: IV Methylprednisolone 500-750mg 3 pulses followed by oral prednisolone 0.5mg/kg/day, reducing per clinicians discretion.

- 3 infusions at 2 weekly intervals then up to 7 infusions at 3 weekly intervals.
- 15mg/kg (reduce according to age & renal function- see below).
- Maximum single Cyclophosphamide infusion dose is 1.5 gm.

- Each individual course of Cyclophosphamide should be ≥3 months and ≤6

months.

- Lifetime exposure to Cyclophosphamide should be ≤25 g since the long-term toxicity of Cyclophosphamide is determined by cumulative dose.
- Patients on Cyclophosphamide should be monitored regularly and the dose should be reduced if there is Cyclophosphamide -induced leucopenia/neutropenia.
- Patients intolerant to Cyclophosphamide can be effectively treated with Rituximab.
- To be administered as per local practice.
- Give over a minimum of 30 minutes.

Dose adjustment according to age and renal function

Age (years)	**eGFR (ml/min/1.73m^2)**	
	>30	**<30**
< 60	15 mg/kg/pulse	12.5 mg/kg/pulse
> 60 and < 70	12.5 mg/kg/pulse	10 mg/kg/pulse
> 70	10 mg/kg/pulse	7.5 mg/kg/pulse

2. **CTD-ILD**

- Six 4-weekly infusions.
- 600mg/m$^{2.}$
- Dose adjustments: for eGFR<20 reduce dose by 25%; for eGFR<10 reduce dose by 50%.
- For systemic sclerosis patients use oral prednisolone: 10-20 mg alternate days.

3. **Lupus Nephritis**

Low dose regime (Euro-Lupus Nephritis Trial / St. Thomas' Hospital)

- Intravenous Cyclophosphamide; 500mg 2 weekly for 6 infusions.
- *Adjunct steroids:* IV Methylprednisolone 500-750mg 3 pulses followed by oral prednisolone 0.5mg/kg/day for 4 weeks, reducing to <10mg/day by 4-6 months http://doi.org/10.1093/rheumatology/kex286.

The high dose NIH regimen can also be used at the supervising consultant's discretion*:* Monthly IV Cyclophosphamide at 500-1000mg/m^2 BSA for 6 months followed by MMF/AZA as per ACR guidance: https://www.rheumatology.org/portals/0/files/ACR%20Guidelines%20for%20Screening,%20Treatment,%20and%20management%20of%20lupus%20nephritis.pdf.

The lower dose regimen has been proven to be as effective and safe yet less toxic for lupus nephritis in Europe in comparison to the high dose regimens.

Discussions prior to treatment

Due to the potential short and long term toxicity of *Cyclophosphamide*, decisions on initiating treatment should be made and documented by the treating consultant and include the rationale for choosing *Cyclophosphamide* (rather than an alternative agent).

Requirements are:

Informed consent

1. Substantial benefits include
    a. Improved survival
    b. Disease control
    c. Prevention / amelioration of permanent organ damage.
2. Serious complications and concerns related to treatment with cyclophosphamide
    a. Infection
    b. Infertility (consider sperm banking)
    c. Early menopause (circa 50%)
        i. Dependent on cumulative dose and age
    d. Teratogenicity – contraceptive advise as appropriate
    e. Malignancy
        i. Related to cumulative dose of cyclophosphamide > 25g
        ii. Lymphoma 4-11 fold increase
        iii. Skin cancer 4-10 fold increase
        iv. Bladder cancer 4-33 fold increase, 3% at 10 years
    f. Hair loss
    g. GI upset
3. Steroid side effects
    a. Mood disturbance, change in appearance, weight gain
    b. Diabetes mellitus, bone disease, infection, GI disease
    c. Secondary hypoadrenalism

Information provided to patient

1. How and when to seek advise
    a. Monitoring booklets, steroid card
        i. Symptoms and signs of infection
        ii. Symptoms and signs of on-going disease activity
    b. Rheumatology nurse-led help line
2. Vaccination / screening advice
    a. Live vaccinations should be avoided until ≥ 3 months after stopping immunosuppression
    b. Vaccinations should be completed before treatment if feasible. Otherwise they should be postponed until after induction therapy completed (≥ 4 months after rituximab)
    c. Annual influenza vaccination
    d. Pneumococcal vaccination
    e. Consider HPV vaccination (for HPV negative patients < 25years old)
    f. Encourage 3 yearly cervical screening in compliance with national screening.

Assessment prior to therapy

1. FBC, U&E, LFT and urinalysis for blood & protein with results checked prior to ordering the first treatment.
2. History and examination to elicit any **contra-indications** to treatment, which include recurrent significant infection (chest, throat or urine) and adverse reaction to past CYC treatments. Any reaction to the previous infusions should be discussed with Consultant.
3. Pregnancy should be ruled out by careful history and pregnancy testing in every female patient of childbearing age. (prior to first cyclophosphamide infusion).
4. Baseline pulse and blood pressure should be recorded.
5. All patients should be assessed for risk of active tuberculosis by taking a full history, physical examination and performing a chest X-ray. Further testing with Interferon Gamma Release Assays (IGRA) may be appropriate in those at highest risk of latent infection – those born in areas of high endemic prevalence living in the UK for < 5 years; those of African, Asian, S.American or European descent; those with a history of contact with smear positive TB. Such cases should be discussed with a specialist with interest in TB.
6. Disease activity should be assessed before the treatment is commenced and assessed at regular intervals, using appropriate standard outcome measures:
7. Vaccinations (as above).
8. Ensure patient has stopped non-biological DMARDs.

Baseline Investigations

Before First Infusion of Cyclophosphamide

FBC & diff CRP	Ensure WBC ≥ 3.5x 10^9/L but ≤ 11x 10^9/L (Unless high WBC is due to corticosteroids **NOT** infection) **and :** Neutrophils ≥ 1.5 x 10^9/l **and** Platelet ≥ 50 x 10^9/L **and** No clinical evidence of infection. Discuss raised CRP with Consultant/ SpR.
Electrolytes Creatinine LFTs	As previously stated.
Infection Screen: HIV Hepatitis B Hepatitis C	Discuss with HIV team / hepatologist if positive.

Clinical Assessments to be undertaken before every infusion of cyclophosphamide

Temperature	To exclude active infection.
Urinalysis	To exclude active infection, haematuria.
Check for any new signs and symptoms	Check for sore throat or cough to help exclude active infection. There should be no clinical evidence of infection before proceeding with scheduled dose. Assess disease symptoms. Assess hydration (check sodium and urea)
Check how previous cycles were tolerated.	If patient had nausea despite taking anti-emetics after the last treatment, then arrange for an outpatient prescription to be written for an alternative.
Check that patient has stopped any other immunosuppressant drugs.	This should be done prior to the first infusion.
Confirm that consent, ID and cannulation policies have been followed.	

After the first infusion of Cyclophosphamide check FBC at day 10. If

- leucocyte count 1–2.0 or neutrophil count 0.5–1.0
  - reduce Cyclophosphamide infusion by 40% of previous dose
- leucocyte count 2–3.0 or neutrophil count 1–1.5
  - reduce Cyclophosphamide infusion by 20% of previous dose.

Thereafter check the FBC within 48 hours prior to the infusion unless there is an adjustment made to the dose of Cyclophosphamide administered or interval period between infusions, in these cases the FBC should be additionally checked at day 10.

Renal function should be measured within 48 hours of infusion and adjustments made to Cyclophosphamide dose as per table above.

If any of the above blood tests are out of the specified ranges, please contact the supervising consultant.

Logistics
Cyclophosphamide should usually only be infused in either a cytotoxic designated day case area or a designated ward. It should usually be prescribed by the consultant or by an SpR who has been signed off as competent to prescribe chemotherapy. The infusion can only be administered by a nurse who has completed the chemotherapy module. Medical staff are not allowed to infuse.

FBC, U&E, LFT & urine dipstick should be done as per protocol and infection should be excluded. The results should be reviewed before Cyclophosphamide is administered. If Cyclophosphamide is prescribed before the bloods are taken then the responsible clinician should authorise in writing its administration after reviewing the results.

Response to treatment should be assessed at regular intervals.

Adjunctive therapies

Mesna

Mesna (2-mercaptoethane sulphonate sodium) should be considered for protection against urothelial toxicity in all patients receiving Cyclophosphamide and especially in those receiving oral Cyclophosphamide. It is given with each pulse of Cyclophosphamide.

Oral Mesna should be given 0-2 hours prior to the pulse of cyclophosphamide and repeated 2 and 6 hours after the pulse of cyclophosphamide 400mg/dose.

Certain centres give oral Mesna instead of IV Mesna due to the aseptic lab technique which does not allow mixing of IV cyclophosphamide and Mesna.

Prophylaxis against Pneumocystis jiroveci:

Patients receiving Cyclophosphamide and GCs should be considered to receive trimethoprim/sulphamethoxazole 960 mg thrice weekly or 480mg daily as prophylaxis against pneumocystis jiroveci.

Dapsone is an alternative if septrin-allergic

Fluids

Patients should be encouraged to drink at least 2 L of water on the day of infusion.

Antiemetic therapy:

PO Metoclopramide 10 mg TDS for 48 hours

Or

PO Ondansetron 4-8 mg BD at the start of infusion, and for 2-3 days post-infusion.

Bone protection:

Should be considered in accordance with Royal College of Physicians SIOP guidelines. (C).

Appendix

Standard GP Letter for Cyclophosphamide – IV/Oral

After discussing the risks and benefits of Cyclophosphamide using the ARUK information sheet, *(name of patient)* has consented to treatment.

He/She is aware that this is an immunosuppressive drug that has a potential to increase the risk of infections and knows to seek urgent medical advice if any symptoms of infection occur (e.g. sore throat, fever, cough, diarrhoea, discomfort on passing urine). If she/he does consult you, please consider that *he/she* may be neutropenic and require intravenous antibiotics and therefore, admission to (name of hospital) via the medical take.

Immunisation with pneumovax and an annual flu vaccine is recommended and we have advised contacting your surgery to organise this.

He/She has been screened for varicella zoster antibodies and *has/does not have* chicken pox immunity *(remove this statement depending on local policy for checking)*.

(Women)
She is aware that Cyclophosphamide can adversely affect a developing foetus and it is essential to avoid pregnancy during, and for 6 months after, treatment. She is aware of the need for adequate contraception and she may seek your further advice. Cyclophosphamide can potentially cause an earlier menopause with associated loss of fertility.

(Men)
He knows to avoid fathering a child during, and for 6 months after treatment, and is aware of the need for adequate contraception. Cyclophosphamide is cytotoxic and could reduce future fertility; we have discussed sperm banking which has been *arranged/ declined.*

Ondansetron has been used to prevent nausea, but if this does occur and oral or sublingual drugs cannot be tolerated then I.M. Metoclopramide or Prochlorperazine may be helpful. Mesna has been given to reduce the risk of bladder irritation/cystitis. Cotrimoxazole has been started to reduce the risk of pneumocystis jirovecii (PCP) infection having ascertained no history of sulphonamide allergy.

Key References

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Documentation Controls

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Consultation with:	
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