Cyclophosphamide in Autoimmune Disorders - Full Clinical Guideline

1. Introduction

There is an RCT evidence base for the use of pulse IV Cyclophosphamide (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 i.e Scleroderma Lung Disease

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).

2. Indications

2.1 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 clinician's 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.

Lifetime exposure should not exceed 25g. (The long-term toxicity of Cyclophosphamide is determined by cumulative dose)

- Remission should be achieved by 3 months and a further 3 months of pulsed CYC is given after entry into remission (6 months in total)
    - Should remission not be achieved by 3 months, CYC can be continued at 3 weekly until remission is achieved then give further 3 months of pulsed CYC after entry into remission before proceeding to maintenance regimen.
    - Remission should be achieved by 9 months and the total duration of CYC should not exceed 12 months.

Patients intolerant to Cyclophosphamide can be effectively treated with alternative agents such as Rituximab and consider second opinion or discussion in an MDT.

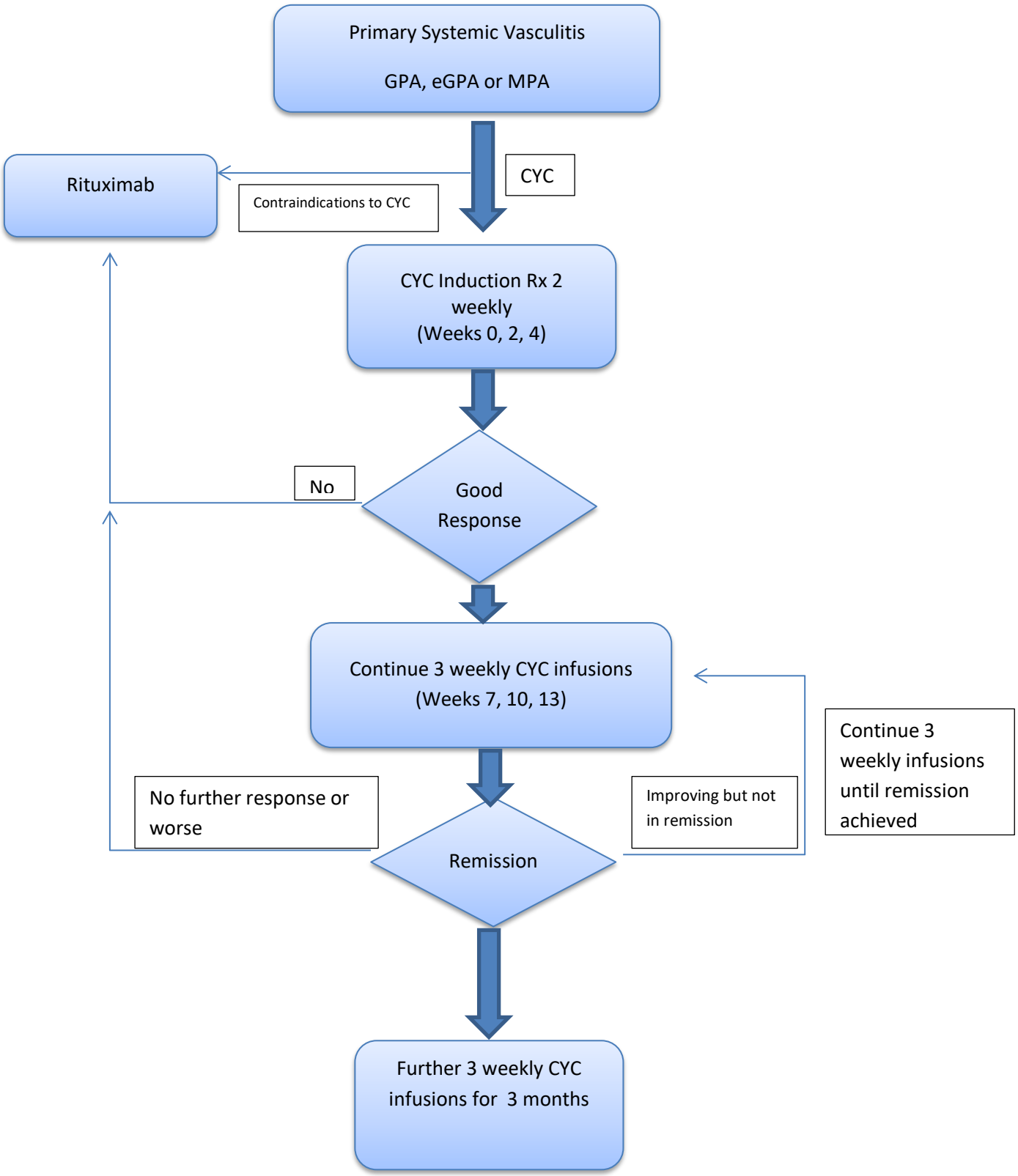
Dose

- 15mg/Kg (reduce dose according to age and renal function as below)
- Maximum CYC infusion dose is 1.5 gm

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

- Diluted in 0.9% Saline and administered as iv drip over 1h or longer if necessary.

Algorithm for treatment of Primary systemic vasculitis



2.2 Scleroderma

Dose: 600mg/m^2.

- Six 4-weekly infusions.
- 600mg/m2.
- Dose adjustments: for eGFR <20 reduce dose by 25%; for eGFR<10 reduce dose by 50%.

Adjunct steroids: Oral Prednisolone: 10 – 20mg alternate days.

2.3 Lupus Nephritis

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

- Intravenous CYC 500mg 2weekly 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

The high dose NIH regimen can also be used at the supervising consultant's discretion: Monthly IV CYC at 500-1000 mg/m2 body surface area for 6 months followed by 3 monthly IV CYC later for 2 years.

Lower doses have been proven to be as effective and safer for lupus nephritis in Europe than high dose regimens.

Maintenance therapy

- Either Azathioprine 1-2.5 mg/kg/day or Mycophenolate 500 mg–2 gm/day on completion of IV therapy

Avacopan

- Avacopan in combination with cyclophosphamide or Rituximab may be considered for induction of remission in GPA or MPA, as part of a strategy to substantially reduce exposure to glucocorticoids. Avacopan can facilitate rapid reduction of Prednisolone after 4 weeks.
- Patients at increased risk of glucocorticoid side effects may benefit the most and those with poor renal function where higher doses of CYC are not suitable.
- See AAV guideline on protocol for Avacopan

3. CYC – induced toxicity

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

- The oral dose of mesna should be 40% of the CYC dosage = 400mg (for 1000mg of CYC) .
- If given intravenously, the dose should be 20% of the CYC dosage = 200mg (for 1000mg of CYC).

Given **2 h prior to the pulse of cyclophosphamide and repeated 2 and 6h after** the pulse of cyclophosphamide.

In patients receiving oral CYC, mesna is given for as long as the patient receives CYC treatment.
Surveillance with regular (3 -6 months) urinalysis should be continued indefinitely after a course of CYC

4. Prophylaxis against Pneumocystis Jiroveci:

Patients receiving CYC and GCs should be considered to receive Trimethoprim/sulphamethoxazole 960 mg thrice weekly as prophylaxis against pneumocystis jiroveci.

- If allergic to co-trimoxazole to consult the Trust guideline regarding an alternative such as Dapsone and continue for 3 months post cyclophosphamide.

5. Fluids

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

6. Antiemetic therapy

Oral Metoclopromide 10mg TDS for 48 hours

OR

Po Ondanstentrone 4-8mg BD at the start of infusion and for 2- 3days post infusion

7. ASSESSMENT PRIOR TO THERAPY

1. FBC, U&E, LFT, Infection Screen for HIV, Hep B & C, Tuberculosis (TB) 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 in every female patient of childbearing age or pregnancy test if required.
4. Baseline pulse and blood pressure should be recorded.
5. All patients should be assessed for risk of 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 < 5years: 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 standard outcome measures: • BVAS • BILAG/ SLEDAI
7. Vaccinations before infusion if appropriate.
8. Ensure patient has stopped non-biological DMARDs.

Clinical Assessments to be undertaken before every infusion of cyclophosphamide

Confirm that consent, ID and cannulation policies have been followed.	
Temperature	To exclude active infection.
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.

Monitoring

After the first infusion of CYC check FBC between days 10 and on day of next infusion.

- If Leucocyte count 1–2.0 or neutrophil count 0.5–1.0
  - - Reduce CYC infusion by 40% of previous dose
- Leucocyte count 2–3.0 or neutrophil nadir 1–1.5
  - - Reduce CYC infusion by 20% of previous dose.

Thereafter check the FBC on the day of the infusion or previous day unless there is an adjustment made to the dose of CYC administered or interval period between infusions, in these cases the FBC should be additionally checked at day 10. Renal function should be measured on the day of infusion or previous day and adjustments be made to CYC dose as per table above.
If the WBC count prior to the pulse is $<4 \times 10^9$/l and the neutrophil count is $<2 \times 10^9$/l and check the FBC weekly until it has recovered. Reduce the CYC dose by 25%.

With any further episodes of leucopenia/neutropenia, make a further 25% reduction in dose from the planned dose.

DISCUSSIONS PRIOR TO TREATMENT

Because of the potential short and long term toxicity of CYC, decisions on initiating treatment should be made and documented by the treating Consultant and include the rationale for choosing CYC (rather than an alternative agent) and get informed consent.

Requirements are:

1. Substantial benefits include
    a. Improved survival
    b. Disease control Informed consent
    c. Prevention / amelioration of permanent organ damage.
2. Serious complications and concerns related to treatment with cyclophosphamide
    a. Infection
    b. Infertility, early menopause (circa 50%)
        i. Dependent on cumulative dose and age
    c. Teratogenicity – contraceptive advise as appropriate
    d. Malignancy
        i. Related to cumulative dose of cyclophosphamide > 30g
        ii. Lymphoma 4-11 fold increase
        iii. Skin cancer 4-10 fold increase
        iv. Bladder cancer 4-33 fold increase, 3% at 10 years
    e. Hair loss
    f. 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.

4. Vaccination / screening advice
    Advice to be up to date with Covid vaccinations/ flue and other vaccines
    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. Covid vaccinations and annual influenza vaccinations
    d. Pneumococcal vaccination
    e. HPV vaccination
    f. Cervical screening following cyclophosphamide every 3 years

5. Bone Health

Prophylaxis against osteoporosis should be considered in patients receiving corticosteroids. The need for treatment and fracture risk should be assessed following national guidance

Key References

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Document Controls

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