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. Wegener’s, Churg-Strauss, Microscopic Polyangiitis)
- Renal SLE (and other severe organ manifestations)
- 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 the combination of the:

- British Society of Rheumatology (BSR) and BHPR guidelines for the management of adults with ANCA-associated vasculitis
- EUROLOUPUS
- NIH

2. Scope

This guideline applies to all Rheumatologists and physicians using Cyclophosphamide to treat the conditions stated in the introduction subsection.

3. Recommendations for use

Indications

1. Primary Systemic Vasculitis:

*Induction/consolidation regimen for pulsed IV CYC:*

3 Infusions at 2 weekly intervals then 7 infusions at 3 weekly intervals.

- Remission should be achieved within 3 months and a further 3 months of pulsed CYC is given after entry into remission (i.e. 6 months in total).
- Should remission not be achieved by 3 months, continue CYC infusions at 3 week intervals until remission is reached, then give another 3 months of CYC pulse therapy before you proceed to the remission maintenance regimen.
- Remission should be reached by 9 months and the total duration of CYC should not exceed 12 months.
  - However, 10% of patients will have refractory disease, and if remission not achieved by 9 months consider alternative agents and consider asking a
colleague for a second opinion.

- Lifetime exposure to CYC should not exceed 25 g.

**Dose:**
15mg/kg (reduce according to age & renal function- see below), Maximum CYC infusion dose is 1.5 gm.
*Given over a minimum of 30 minutes.*

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Creatinine</th>
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<tbody>
<tr>
<td></td>
<td>&lt; 300µmol/l</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>15 mg/kg/pulse</td>
</tr>
<tr>
<td>&gt; 60 and &lt; 70</td>
<td>12.5 &quot; &quot; &quot;</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>10 &quot; &quot; &quot;</td>
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</tbody>
</table>

- Dilute in 500 ml of saline 0.9% or dextrose 5% and administer as IV drip over 1h, or longer if necessary.

**Oral cyclophosphamide (CYC)**
- 2mg/kg/day (Age >60 years; reduce dose by 25%, Age > 75 reduce dose by 50%) to a maximum dose of 200mg.
- Continue between 3 to 6 months until remission induced.
- If remission induced before 3 months reduce dose to 1.5mg.kg/day and convert to maintenance treatment at 3 months.
Algorithm for treatment of primary systemic vasculitis

Primary systemic vasculitis
GPA, EGPA, MPA

Rituximab

Contraindications

Cyclophosphamide

Induction remission with CYC
2 weekly X 3 infusions
(Weeks 0, 2, 4)

Good clinical response?

No

Yes, continue CYC

Further CYC infusions X3
3 weekly X 3
(Weeks 7, 10, 13)

Remission

Yes, continue CYC
No, continue if disease refractory or consider RITUXIMAB

Further CYC infusions X 4
3 weekly X 3
(Weeks 17, 20, 23)
2. **Scleroderma**

**Dose:**
- 600mg/m$^2$ (Maximum dose of 1 gm) for six 4-weekly infusions.
- *Dose adjustments:* As per vasculitis protocol
- *Adjunct steroids:* Oral prednisolone: 10 mg daily / 20 mg alternate days.

Lung function should be re-assessed at this stage, and decisions about whether CYC should be stopped and AZA commenced, or CYC continued, should be based on either symptomatic outcome or PFT results. Ideally, where such facilities exist, these decisions should be made in conjunction with a Respiratory physician, either separately or as part of an MDT discussion framework.

3. **Lupus Nephritis**

**Low dose regime (Euro-Lupus Nephritis Trial/ St. Thomas’ Hospital)**
- Intravenous CYC 500 mg in 100 mL N/saline over 30 mins, administered 2 weekly for 6 infusions.
- *Adjunct steroids:* As per vasculitis protocol.

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 more 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.


**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).

Requirements are:

1. **Informed consent**
   - Substantial benefits include
     - Improved survival
     - Disease control
     - Prevention / amelioration of permanent organ damage.
   - Serious complications and concerns related to treatment with cyclophosphamide
     - Infection
     - Infertility, early menopause (circa 50%)
       - Dependent on cumulative dose and age
     - Teratogenicity – contraceptive advise as appropriate
     - Malignancy
       - Related to cumulative dose of cyclophosphamide > 30g
       - Lymphoma 4-11 fold increase
       - Skin cancer 4-10 fold increase
       - Bladder cancer 4-33 fold increase, 3% at 10 years
     - Hair loss
     - GI upset
   - Steroid side effects
     - Mood disturbance, change in appearance, weight gain
     - Diabetes mellitus, bone disease, infection, GI disease
     - Secondary hypoadrenalism.

2. **Information provided to patient**
   - How and when to seek advise
     - Monitoring booklets, steroid card
       - Symptoms and signs of infection
       - Symptoms and signs of on-going disease activity
     - Rheumatology nurse-led help line
   - Vaccination / screening advice
     - Live vaccinations should be avoided until ≥ 3 months after stopping immunosuppression
     - Vaccinations should be completed before treatment if feasible. Otherwise they should be postponed until after induction therapy completed (≥ 4 months after rituximab)
     - Annual influenza vaccination
     - Pneumococcal vaccination
     - HPV vaccination
     - Cervical screening following cyclophosphamide
       - Annual for 3 years
       - Every 3 years thereafter
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 in every female patient of childbearing age.
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
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 (as above).

### Baseline Investigations

**Before First Infusion of Cyclophosphamide**

| FBC & diff | CRP | Ensure WBC ≥ 3.5 x 10⁹ /L but ≤ 11 x 10⁹ /L (Unless high WBC is due to corticosteroids NOT infection) and:
|------------|-----|--------------------------------------------------|
| Neutrophils | ≥ 1.5 x 10⁹ /L | and:
| Platelet | ≥ 50 x 10⁹ /L | and
| No clinical evidence of infection. Discuss raised CRP with Consultant/ SpR. |
| Urea, Electrolytes and Creatinine | As previously stated. |
| Infection Screen: HIV | Hepatitis B | Hepatitis C | Discuss with HIV team / hepatologist if positive. |

Postpone infusion if:
- WBC prior to infusion <3.5
- neutrophil count <1.5,
- platelets < 50
  Then check the FBC weekly.

If the platelet count is 50 -100 then reduce dose by 50%.

If persistent cytopaenia: reduce dose of infusion by 25%.
- With any further episodes of leukopenia/neutropenia make equivalent dose reduction.
Clinical Assessments to be undertaken before every infusion of cyclophosphamide

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>To exclude active infection.</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>To exclude active infection and haematuria. Remember to check for pregnancy in women of child bearing age.</td>
</tr>
<tr>
<td>Check for any new signs and symptoms</td>
<td>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)</td>
</tr>
<tr>
<td>Check how previous cycles were tolerated</td>
<td>If patient had nausea despite taking domperidone after the last treatment, then arrange for an outpatient prescription to be written for ondansetron.</td>
</tr>
<tr>
<td>Check that patient has stopped any other immunosuppressant drugs.</td>
<td>This should be done prior to the first infusion.</td>
</tr>
<tr>
<td>Confirm that consent, ID and cannulation policies have been followed.</td>
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</tbody>
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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.

**LOGISTICS**

CYC should usually only be infused in either a Cytotoxic designated Day Case area or a designated ward. It should only be prescribed by the consultant or by a 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 staffs 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 CYC is administered. If CYC 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

Prednisolone

Regimen

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Prednisolone (mg/kg/day)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>0.75</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>8</td>
<td>0.28</td>
</tr>
<tr>
<td>10</td>
<td>0.25</td>
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</table>

**Prednisolone dose mg/day**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>At end 3 month</td>
<td>12.5</td>
</tr>
<tr>
<td>At end 5 month</td>
<td>10</td>
</tr>
<tr>
<td>At end 6 months</td>
<td>7.5 mg</td>
</tr>
<tr>
<td>At 9 months</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

(Adapted from the current EUVAS MyCyc trial).

Use of parenteral steroid should be at the discretion of the responsible clinician, and used if either rapid induction is needed or there is intolerance of oral medication. IV Methylprednisolone 0.5-1 gm/kg to a maximum of 1 gm IV can be on 3 occasions at onset of treatment.

Mesna

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.

If given intravenously, the dose should be 20% that of the CYC dosage = 200mg.

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.
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.

Fluids

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

Antiemetic therapy:

PO Ondansetron 4-8 mg BD at the start of infusion, and for 2-3 days post-infusion. Depending on local practice, PO Metoclopramide 10 mg TDS for 48 hours could also be used.

Bone protection:

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

This list is not exhaustive; please refer to the **British National Formulary** or **Summary of Product Characteristics** available from Medicines Information.

*Increased risk of myelosuppression following concurrent administration of other marrow depressant drugs.*

The Consultant must assess the risk/benefit of further myelosuppression and allow an adequate washout period (usually one week) when switching from mycophenolate or azathioprine. Patients must be counselled on how to recognise signs and symptoms of myelosuppression and what action to take if these develop (see under Febrile Neutropenia – above). Patients must be issued with a medicines monitoring booklet.

*Manufacturer advises avoid concomitant use of cyclophosphamide with clozapine (increased risk of agranulocytosis).*

If this situation arises the consultant must assess the risk/benefit in conjunction with the consultant psychiatrist managing clozapine therapy. Clozapine therapy requires strict blood monitoring and if the FBC is abnormal, clozapine therapy may need to be stopped.

*Allopurinol may increase risk of myelosuppression with cyclophosphamide.*

There is some evidence that the incidence of serious bone marrow suppression can be increased but this has not been confirmed in a controlled study and the interaction is not established with clear certainty. No additional action required as increased toxicity would be detected as part of pre-treatment investigations.

*Itraconazole: may enhance adverse effects of cyclophosphamide*

No additional action required as increased toxicity would be detected as part of pre-treatment investigations.

*Sulphonylureas: enhanced hypoglycaemic effect.*

Patients should be advised that hypoglycaemia may occur and to monitor blood glucose if they experience signs and symptoms of hypoglycaemia and treat accordingly.
Appendix

Standard GP Letter for Cyclophosphamide – IV/Oral

After discussing the risks and benefits of Cyclophosphamide using the ARC 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, and 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 Prochlorperazime 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


Gluck T. Vaccinate your immunocompromised patients. Rheumatology 2006;45:9–10


Tashkin DP et al, Cyclophosphamide versus Placebo in Scleroderma Lung Disease. NEJM 2006;354:2656-2666


Stamp L, Hust M. Is there a role for Consensus Guidelines for PCP prophylaxis in immunosuppressed patients with rheumatic diseases?. J Rheumatol 2010;374:686-688