

# SLE

## **Acute severe disease**

Patients with impaired and usually deteriorating renal function with diffuse proliferative nephritis + crescents, or serious disease affecting other organs have been treated with cyclophosphamide-based regimes for many years, and these remain the standard therapy today. Daily cyclophosphamide may still be used in very severe disease, but pulsed regimens have largely substituted in other circumstances. Alternatives to cyclophosphamide are being increasingly explored. Increasingly, pulsed regimens are being preferred to daily administration of cyclophosphamide.

**Oral cyclophosphamide regimen.** Prednisolone at 1mg/kg/day and cyclophosphamide at 2mg/kg/day, rounded down to the nearest 50mg. This is usually 100 or 150mg/day. (2.5mg/kg/day almost invariably results in leucopenia after 2-3 weeks treatment followed by stop-start treatment). Use less in over-55s. Cyclophosphamide is arbitrarily given for 12 weeks followed by a change to azathioprine at 2mg/kg/day (usual start dose = cyclophosphamide dose) or to MMF. Prednisolone is tapered but generally more slowly than in vasculitis once below 20-25mg/day.

**Pulsed cyclophosphamide regimens** are described in detail below. These reduce toxicity and cumulative dose. They also prolong the patient's exposure to cyclophosphamide, possibly an advantage in chronic/relapsing disease. Note that doses should be adjusted to achieve lowering of wbc in severe disease. Dose interval may also be reduced.

**Mycophenolate Mofetil (MMF)** is being increasingly used and early trials have not shown that it is inferior to cyclophosphamide. However SLE is a disease with long evolution. MMF has the advantage of avoiding gonadal toxicity and probably has fewer severe side effects overall. The dose used in trials has been 3g/day, which may not be well tolerated. In subacute setting usually start at 500mg BD and increase at intervals of a few days.

**Plasma exchange** may be used in patients with very severe disease, especially if apparently not responding to drug treatment. Possible indications might be

dialysis-dependent disease, encephalopathy.

**Pulse methylprednisolone** - we hardly ever use this, as there is no evidence that it adds anything to the above regimens, which all include prednisolone 60mg/kg/d, and there are added risks of infection, effects on bone, and sometimes severely exacerbated hypertension.

### **Maintenance after acute severe disease**

In general if patient goes into remission and extrarenal manifestations are controlled, prednisolone is gradually tapered to 10mg/day by 6-9 months, and 5-7.5mg by 1 year. Azathioprine is generally substituted for cyclophosphamide (as for systemic vasculitis) at 3 months; MMF is now an alternative, but the minimum dose should be 1g BD.

We generally taper and stop steroids and then aza/MMF at 18-24 months except in patients with continuing active disease, or who have had several or particularly severe flares of disease. Any deterioration in renal function, especially if baseline function is good, is usually managed after repeat biopsy. Minor or extra-renal flares are often treated with increased steroids followed by slower reduction.

### **Pulsed Cyclophosphamide Therapy**

(Note that this regimen is different from our [current pulsed cyclophosphamide regimen for small vessel vasculitis](#)) 750mg/m<sup>2</sup> is given with Mesna at monthly intervals for 6 months; 500mg/m<sup>2</sup> if elderly or at increased risk of leucopaenia. If WBC nadir (10-14 days post dose) is much >5,000, next dose is increased by 250mg/m<sup>2</sup> to max 1g/m<sup>2</sup>). Consider reducing by 10-15% if WBC <3,500 or neutrophils <1,500. Delay subsequent doses if neutropenia persists (neutrophils <2,000). Reductions for low GFR: see below. Shorten dose interval in severe disease.

Prednisolone is usually increased at the start of this treatment and tapered as above. Three 2-monthly (or two 3-monthly) doses are given after the first 6 pulses. At one year most patients are converted to azathioprine/ MMF and then managed as above. Conversion can be delayed until later, and cyclophosphamide pulses continued for longer in patients believed to be at high risk from recurrent disease.

Haemorrhagic cystitis is very uncommon when cyclophosphamide is used in this

way. Mesna may cause fixed drug eruptions.

## Protocol for pulsed cyclophosphamide

### First pulse

Time	Protocol for IV pulsed cyclophosphamide
<b>0</b>	500ml N saline over 2h plus 500ml oral fluid.
<b>1.5 h</b>	Ondansetron 8mg oral or granisetron 1mg oral, and dexamethasone 10mg orally if patient not taking prednisolone (unlikely)
<b>2.0h</b>	Cyclophosphamide in 250mls N saline over 1h, 750 mg/m <sup>2</sup> or 12 mg/kg (see above). Mesna (20% of the cyclophosphamide dose) added to the same bag
<b>3.0h</b>	Mesna (40%) orally at 4 and 8h after end of infusion. Ondansetron 8mg orally two more doses (not required if using granisetron) <i>AND</i> Domperidone 20mg orally 6h prn for 3 days. Advise oral intake of 2.5-3 litres over next 24h.
<b>10-14d</b>	Check wbc (outpatients or GP).

For IV cyclophosphamide/MESNA, contact Pharmacy at least one day in advance so that it will be ready when the patient arrives. A detailed protocol will come from the Pharmacy with the drug.

Patients should be cautioned to seek help if they become febrile or otherwise unwell during cytotoxic therapy of this type.

### Subsequent pulses

- Ensure WBC recovering before administering next dose (check 1-7d before)
- Adjust dose as described above

- Review antiemetics. If acute vomiting, (1) change oral premed to IV, (2) add second dose of ondansetron/granisetron on day 1, and (3) add haloperidol 1.5mg BD orally on day 1.

## Oral Pulse Therapy

Is possible and effective, and usually taken at home. The cyclophosphamide dose is the same as for IV therapy but is spread over 2-3 days. The need for monitoring of blood tests, and adjustment of doses according to results, applies regardless of the route of administration (see discussion of IV therapy above).

Protocol for oral cyclophosphamide pulses (pdf file) - for patients but also gives information relevant to prescribers.

### Oral pulse cyclophosphamide treatment

#### Each day

- Drink 2-3 litres (preferably 3) every day during this treatment
- Start treatment in the morning, so that you can drink plenty during the day.
- Take an **ondansetron** tablet (8mg) just before or 1-2h before your cyclophosphamide tablets
- Then take the **cyclophosphamide** tablets with plenty of fluid. *[The total dose is as for IV pulses, but divided into 2-3 daily doses]*
- Take **Mesna** tablets, one 400mg tablet three times each day on every day when you are taking cyclophosphamide. One should be taken last thing at night.

Cyclophosphamide and Mesna are usually continued for **2 or 3 days**

Ondansetron should be continued (8mg 12 hourly) for one or two days after that (the first time, for two or three days), to a total of **3 to 6 days**.

Some people need a higher dose than this, or alternatives to ondansetron (e.g. see above)

A blood count is needed 10-14 days after starting each pulse to catch the nadir wbc. Blood tests should be repeated a few days before the next pulse to confirm recovery, at least in the first treatment cycles. Antiemetic therapy may need to be reviewed, though symptoms are rarely severe with this protocol.

## Cyclophosphamide dose reductions in renal impairment

Note that these are conservative recommendations (see [Vasculitis](#)) and they should be individualised in severe disease, paying close attention to 10 day wbc, or there may be a significant risk of undertreatment.

- GFR 15-50mls/min, or on CVVH 75% of dose
- GFR <15mls/min, on IHD/CAPD 50% of dose

### **Gonadal toxicity of cyclophosphamide**

**MALES** - Risks of oligospermia increase above a cumulative dose of 100mg/kg in mature males. This amount is approximately equal to a single three month course of daily cyclophosphamide, or about 8 intravenous pulses.

Cryopreservation of sperm should be offered to all males embarking on non-emergency treatment with cyclophosphamide. Where pulse therapy is being undertaken, cryopreservation should be undertaken before the first pulse. Where a 3-month period of daily treatment is being used, and prior cryopreservation is not feasible, it is reasonable to undertake it well after the end of the course if it is likely that further cyclophosphamide may be required in the future.

**Edinburgh: For cryopreservation of sperm** contact Reproductive Medicine Laboratory to arrange sample storage. Samples should be stored before ANY exposure to cyclophosphamide (either as pulse IV or oral protocol).

**FEMALES** - Thresholds for gonadal toxicity are believed to be higher in mature women (200-300mg/kg) and in prepubertal girls (400mg/kg). The consequences - premature menopause - may only become apparent years or decades later.

**Edinburgh:** experimentally, a programme of ovarian cryopreservation has been set up for children jointly between Oncology at the RHSC and the Dept Gynaecology at the RIE. The programme was set up for children receiving much larger doses of cyclophosphamide than we normally prescribe, but it should be considered when very young women are likely to require substantial cumulative doses of cyclophosphamide. As above, it is best undertaken before patients have received any cyclophosphamide.

**For ovarian cyopreservation in young women** (This programme is experimental) contact Prof Richard Anderson (Gynaecology RIE) bleep #6841 Sec 22444, or Dr Hamish Wallace (Oncology RHSC) 20426.

## Newer Treatments for SLE

Several biological agents are currently being tested for their promise in SLE. Contact Dr David Kluth about most of these.

**Rituximab** - anti-CD20 antibody with proven effects in some autoantibody-associated conditions. However efficacy probably not due solely to reduction in antibody titres. Given as IV infusion of 1000mg on two occasions two weeks apart. Before starting treatment check CD19 count (B cell marker; haematology at WGH) and immunoglobulins. During infusion the patient's vital signs (bp, pulse, respiration and temperature) should be monitored every 15 minutes for the first hour, and then if stable, hourly until infusion stops. **First infusion:** 50mg/h for first 30 min, escalate in 50mg/hr increments every 30 min to max of 400mg/h. **Subsequent infusions:** Initial rate 100mg/h for first 30 min, escalated by 100mg/h every 30 min to max 400mg/hr.

- Elderly patients may require a slower infusion rate.
- If a patient develops severe cytokine release syndrome the infusion should be stopped. On resolution, the infusion can be resumed at not more than one-half the previous rate. Mild to moderate infusion-related reactions usually respond to a reduction in infusion rate.
- Anaphylactic reactions can occur to this humanised mouse antibody CD19 count is checked before second infusion and at 2 weekly intervals for next 6-8 weeks.

## Patient information

Information for patients on [SLE](#) in general, or on [lupus affecting the kidneys](#) - from [EdRenINFO](#)

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