Controlled trial of pulse versus continuous prednisolone and cyclophosphamide in the treatment of systemic vasculitis


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Summary

Although cyclophosphamide and prednisolone are effective in treating systemic vasculitis, the optimum treatment regimes and duration of treatment are unknown. We randomized 54 patients aged 15–70 years (median 57.5 years) with systemic vasculitis (classical polyarteritis \( n = 8 \), microscopic polyarteritis \( n = 17 \), Wegener’s granulomatosis \( n = 29 \)) to treatment with either pulse cyclophosphamide and prednisolone (PCYP) \( (n = 24) \) or continuous oral and prednisolone and cyclophosphamide, with the latter followed after a median of 3 months (range 1.5–10 months) by azathioprine (CCAZP) \( (n = 30) \). Patients on CCAZP were more likely to develop leucopenia \( (13/30) \) than patients on PCYP, \( (7/24) \) although the difference was not significant. The numbers of infective episodes during follow up were comparable in the two groups at 1.7/patient for PCYP and 1.66/patient for CCAZP. Overall, 26/30 patients (87%) treated with CCAZP developed treatment-related toxicity, as did 17/24 patients (71%) treated with PCYP. After a median follow-up of 40.4 months (range 0.7–64.8), there was no difference in the frequency of deaths (PCYP 5, CCAZP 4), relapses (PCYP 7, CCAZP 8), treatment failures (PCYP 4, CCAZP 4), improvement in disease activity scores or renal function. Survival at three years was 77% in patients treated with PCYP, and 90% in patients on CCAZP \( (p = 0.38) \). There was a tendency towards increased toxicity in patients treated with the continuous regimen.

Introduction

The prognosis of idiopathic systemic necrotizing vasculitis—Wegener’s granulomatosis (WG), classical polyarteritis nodosa (CPAN) and microscopic polyarteritis (MPA)—has been greatly improved by the addition of cyclophosphamide to steroid treatment.\(^1\)\(^\text{–}\)\(^6\) Recent studies show that over 80% of patients with WG and over 70% of patients with MPA survive for 5 years.\(^2\)\(^\text{–}\)\(^7\) This relates to an aggressive therapeutic approach, and it has been suggested that patients should be treated with cyclophosphamide for one year or even two years after remission is induced.\(^1\)\(^,\)\(^2\)\(^,\)\(^6\) The question of the optimum duration of treatment is important, as cyclophosphamide and steroids have substantial side-effects that have become more important as more patients survive their acute disease. On the one hand, an inadequate duration of treatment might be accompanied by relapses and organ damage from vasculitis; on the other hand overtreatment leads to a high drug toxicity. With the improved survival with current treatment, morbidity from haemorrhagic cystitis, bladder carcinoma and lymphoma has become an important clinical problem.\(^6,\)\(^\text{–}\)\(^8\)

There are no firm guidelines on the dose or optimum duration of treatment with cyclophosphamide, or on the least toxic way of administering this drug. There is now evidence that cyclophosphamide given as intermittent intravenous pulses together with steroids is of benefit in rheumatoid vasculitis,\(^9\) and studies in lupus nephritis have shown that a similar regime was more effective in preventing progression of renal disease, and was less toxic than when these drugs were given on an oral daily basis.\(^10\) Several uncontrolled studies have examined the value of
pulse intravenous cyclophosphamide in patients with
a systemic vasculitis, with conflicting results.\textsuperscript{11–15} To
address issues of toxicity, we embarked on a random-
ized controlled study to compare the effectiveness
and toxicity of our regime of pulse cyclophospham-
ide and prednisolone (PCYP) vs. continuous cyclo-
phosphamide (followed by azathioprine) and
prednisolone (CCAZP) in inducing and maintaining
remission in patients with primary systemic vas-
culitis.

\section*{Methods}

Patients aged 15–70 years with new-onset systemic
necrotizing vasculitis were recruited into the study.
The definitions used for categorizing patients as
WG, CPAN and MPA have been described in detail
by us\textsuperscript{16} and resemble those of the Chapel Hill
Consensus Meeting.\textsuperscript{17} The diagnosis in each patient
was established by histological evidence of a vascul-
itis, or radiological evidence of aneurysms in splanchic
or renal arteries in a patient with a multisystem disorder.
All patients had sera tested for anti-neutrophil cytoplasmic antibodies (ANCA), and
the antigenic specificity of these antibodies was
determined by ELISAs for anti-proteinase 3 (anti-PR3)
and anti-myeloperoxidase (anti-MPO) antibodies as
previously described.\textsuperscript{18,19} Remission was defined as
the absence of clinical symptoms of vasculitis, reso-
lution of pulmonary, renal or other organ changes
or stable changes consistent with scarring and stabil-
ization. Relapse was defined as the re-emergence of
new clinical symptoms attributable to vasculitis or
worsening of original manifestations after 4 weeks
of complete clinical remission had been achieved.
In all cases infection was excluded as the likely
cause of symptoms. Disease activity was also
assessed by the serum levels of C-reactive protein
(CRP) and von Willenbrand Factor (vWF). In addition,
disease activity was assessed prospectively using the
Birmingham Vasculitis Activity Score.\textsuperscript{20} This was not,
however, used to change therapy, as the score was
in the process of being validated. For analysis of the
trial data, complete remission was defined as the
absence of any active disease for at least one month,
i.e a BVAS score of 0–1. Partial remission was
defined as a >50% reduction in disease activity as
measured by BVAS. Relapse was defined as a rise
in BVAS score.

\section*{Study protocol}

The trial protocol had institutional ethical approval,
and informed consent was obtained from each
patient before enrolment into the study. The primary
endpoint of the study was drug toxicity, and the
secondary endpoints were survival and relapses.

\section*{Randomization}

Patients were randomly assigned to either the con-
tinuous or pulse regime by computer-generated
random numbers held in sealed envelopes. The
randomization was stratified for renal function (serum
creatinine <250, 251–500, >500 \(\mu\text{mol/l}\)).

\section*{Treatment}

The pulse cyclophosphamide and prednisolone
regime has been previously reported in detail\textsuperscript{7,16} and
is summarized, together with the continuous treat-
ment regime, in the Appendix. In the continuous arm
of the trial (CCAZP), initial treatment was with
a tapering dose of oral prednisolone starting at
0.85 \(\text{mg/kg}\) and cyclophosphamide. The cyclophos-
phamide was given until a clinical decision that
remission had been achieved, at which time it was
stopped and azathioprine started. In the pulse regime
(PCYP), cyclophosphamide and methylprednisolone
were given intravenously at 0, 2 and 4 weeks.
Thereafter, the same dose of these agents was given
as oral pulses over a 3-day period, and the interval
between pulses was gradually increased. The proto-
col allowed escalation of immunosuppressive treat-
ment for severe or life-threatening disease.

\section*{Statistics}

Differences in clinical and laboratory variables
between the treatment groups were tested for signifi-
cance with Fisher’s exact test for discrete variables,
and by the Wilcoxon rank sum test for continuous
variables. Survival was analyzed by the Kaplan-Meier
life-table method and the treatment groups were
compared by the log rank test.

\section*{Results}

\subsection*{Clinical data}

These are summarized in Table 1. Twenty-four
patients were randomized to PCYP (CPAN \(n=3\), WG
\(n=16\), MPA \(n=5\)) and 30 patients to CCAZP (CPAN
\(n=5\), WG \(n=13\), MPA \(n=12\)). Patients treated with
CCAZP were slightly older (median age 62, range
15–70 years) than patients treated with PCYP (median
age 47, range 22–70 years) (\(p=0.1\)) and had worse
renal function at diagnosis (median serum creatin-
ine 234, range 60–1082 \(\mu\text{mol/l}\) vs. 139, range
72–1255 \(\mu\text{mol/l}\) (\(p=0.3\)). In patients treated with
CCAZP, the median duration of treatment with
cyclophosphamide was 3 months (range 1.5–10
months) after which azathioprine was started.
Of the 54 patients, 39 had antibodies to neutrophil cytoplasmic antibodies (ANCA) and 15 were ANCA-negative by immunofluorescence. Data on ANCA specificity at diagnosis were obtained by ELISA in 50 patients and are summarized in Table 2. Of patients with WG, 65% had anti-proteinase 3 (PR3) antibodies, as did 19% of patients with MPA and 13% of patients with CPAN. Anti-myeloperoxidase (MPO) antibodies were found in 50% of patients with MPA 25% of patients with CPAN and 4% of patients with WG. Overall 26% of patients were negative for ANCA by indirect immunofluorescence and by ELISA.

**Follow-up data**

**Toxicity and complications**

There was slightly more leucopenia (13/30 vs. 7/24, \(p=0.39\)) in patients treated with CCAZP than in patients treated with PCYP. The incidence of infective episodes per patient was comparable in the two groups, (1.70/patient for PCYP; 1.66/patient for CCAZP) (Table 3). The other toxicities seen were all in patients treated with CCAZP, and these were thrombocytopenia (platelet count \(<100 \times 10^9/l\)) in three patients, steroid-induced diabetes in one patient, osteoporosis in one patient and a basal-cell carcinoma in one patient. Two patients in the CCAZP group died from septicaemia, one from a pancreatitis and one from a bronchial neoplasm.

**Remission and relapse**

Using BVAS score and the definitions in the methods, 8 (33.3%) patients treated with PCYP and 7 (23.3%) treated with CCAZP went onto complete remission. Partial remission was achieved in 12 (50%) patients treated with PCYP and in 19 (63.3%) patients on CCAZP (Table 4). Of eight patients with a serum creatinine higher than 500 \(\mu\)mol/l treated with PCYP, two died, renal function improved in five and remained unchanged in one. In 10 patients with the same degree of renal failure treated with CCAZP, one died and renal function improved in nine. After a median follow up of 40.4 months, comparable proportions of patients died, relapsed or developed end-stage renal failure in the two treatment groups (Table 4 and Figure 1). The median rise in BVAS at relapse was 6 (range 1–17). The three-year patient survival of 77% in patients on PCYP did not differ significantly from that of 90% in patients treated with CCAZP, \((p=0.38)\) (Figure 1). There were no significant differences between the two treatment groups in the serum creatinine (Figure 2), disease activity scores (Birmingham vasculitis activity score) (Figure 3), CRP and vWF (data not shown) at follow-up. The rate of fall of disease activity and serum creatinine was most marked in the first 3 months of therapy.

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**Table 1** Clinical data

<table>
<thead>
<tr>
<th>Treatment regime</th>
<th>Age (years)</th>
<th>SEX</th>
<th>MPA</th>
<th>CPAN</th>
<th>WG</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCYP</td>
<td>47 (22–70)</td>
<td>17:7</td>
<td>5</td>
<td>3</td>
<td>16</td>
<td>35.1 (0.7–63.6)</td>
</tr>
<tr>
<td>CCAZP</td>
<td>62 (15–70)</td>
<td>18:12</td>
<td>12</td>
<td>5</td>
<td>13</td>
<td>42.5 (2.5–54.8)</td>
</tr>
<tr>
<td>(p)</td>
<td>0.1</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Table 2** ANCA data at entry

<table>
<thead>
<tr>
<th>Disease</th>
<th>Patients tested (n)</th>
<th>Immunofluorescence</th>
<th>ELISA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>WG</td>
<td>29</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>MPA</td>
<td>17</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>CPAN</td>
<td>8</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
Table 4 Follow-up data

<table>
<thead>
<tr>
<th></th>
<th>PCYP ((n = 24))</th>
<th>CCAZP ((n = 30))</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (months and range)</td>
<td>35.1 (0.7–63.6)</td>
<td>42.5 (2.5–64.8)</td>
<td>0.32</td>
</tr>
<tr>
<td>Partial remission ((&gt; 50% \text{ reduction in disease activity}))</td>
<td>12 (50)</td>
<td>19 (63.3)</td>
<td></td>
</tr>
<tr>
<td>Complete remission ((\text{Disease activity} = 0))</td>
<td>8 (33.3)</td>
<td>7 (23.3)</td>
<td>0.69</td>
</tr>
<tr>
<td>Treatment failure ((\text{Disease activity} &gt; 50%))</td>
<td>4 (16.6)</td>
<td>4 (13.3)</td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>5 (20.8)</td>
<td>4 (13.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Relapse</td>
<td>7 (29.6)</td>
<td>8 (26.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>2 (8.3)</td>
<td>3 (10)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Disease activity as measured by BVAS. Data are numbers (percentages).

**Figure 1.** Kaplan-Meier estimates of survival according to treatment group \((p = 0.38)\).

**Figure 2.** Boxplot of serum creatinine with time of follow-up, showing the median and interquartile range. The whiskers extend to the upper and lower adjacent values. There were no differences between PCYP and CCAZP in the serum creatinine.

**Escalation treatment**

This was allowed in the protocol as clinically indicated. It was used in 31 patients in total. In patients treated with PCYP, eight received plasma exchange, five intravenous methylprednisolone and eight intravenous immunoglobulin. In addition, 13 patients were given continuous oral prednisolone. In patients on CCAZP, 12 received plasma exchange, eight intravenous methylprednisolone and five intravenous immunoglobulin.

**Deaths**

Septicaemia was the cause of death in two patients in the CCAZP group, while pancreatitis and bronchial neoplasm accounted for the two other deaths in this group. In the pulse group, two patients died early (within 3 months) with active vasculitis. Of the later deaths, two were from myocardial ischaemia and one from a pulmonary embolus.

**Discussion**

The key clinical question addressed was whether pulse cyclophosphamide was less toxic than continuous oral cyclophosphamide and azathioprine in treating vasculitis. In order to detect a reduction in toxicity from 70 to 40%, with a power of 80% and a significance at the 5% level, 42 patients would be required in each treatment arm. Because the trial was small, although no statistically significant differences in toxicity were detected, smaller differences that might be important could exist between the treatments.

The present study included patients with Wegener’s granulomatosis and microscopic polyarteritis, which are primary systemic vasculitides with predominant small-vessel involvement, as well as classical polyarteritis with medium-vessel involvement. At the time the study was started, microscopic
Treating systemic vasculitis

Cyclophosphamide and prednisolone, with or without azathioprine. Steroids and cyclophosphamide are widely used for remission induction in systemic vasculitis, with the steroids being tapered and cyclophosphamide maintained for a variable period after remission is induced.1,6 Although leading to long-term remissions in what were once usually fatal diseases,1 this regime is not supported by controlled study. The early NIH studies by Fauci et al.1 recommended treatment with oral cyclophosphamide for one year after remission had been induced. As more patients survive in systemic vasculitis, a major problem now is the long-term toxicity of continuous oral cyclophosphamide and also of prednisolone. In their long-term follow-up report of patients with Wegener’s granulomatosis treated in this way, Hoffman et al.6 found that drug-related toxicity had become a major cause of morbidity. Forty-three percent of patients developed cyclophosphamide-induced cystitis, 2.8% a bladder cancer, 2% lymphomas, 2% myelodysplasia and 57% of the women, ovarian failure. Overall there was a 2.4-fold increase in malignancies, a 33-fold excess risk of bladder cancer and an 11-fold excess risk of lymphoma, compared with age-matched controls. Despite this very significant treatment toxicity from cyclophosphamide, the patients still had active disease for 54% of the total time of follow-up, and there is the additional toxicity from prednisolone.

The main justification for the present study was to find safer therapies for the treatment of vasculitis. In uncontrolled studies in the UK, cyclophosphamide has been substituted by azathioprine for the maintenance of remission3,4,7 to minimize cyclophosphamide toxicity, and this regime was used in one arm of the present study. Whether prednisolone and long-term cyclophosphamide, or prednisolone and cyclophosphamide with conversion to azathioprine when remission is induced, are comparable in terms of efficacy and toxicity is not known, and is currently being investigated by the multicenter ECSYVASPIATIAL trial.22 The pulse regime in this study has been used in the UK for the treatment of rheumatoid vasculitis9 and systemic vasculitis.7 The initial three pulses are given intravenously and subsequently by mouth. The rationale was that by giving both prednisolone and cyclophosphamide intermittently, overall toxicity from immunosuppression would be diminished. This differs from other pulse regimes used in systemic vasculitis in which cyclophosphamide is given intermittently intravenously and the steroids administered continuously.11–15 These regimes have also not been validated in a controlled trial. Our study set out to compare a continuous regime which was being used in the UK with our pulse regime. We did not set out to...
determine whether cyclophosphamide given intermittently intravenously was as safe and as effective as cyclophosphamide given continuously on a background of the same dose of continuous prednisolone. This is a valid question which must be determined separately by controlled study. We accept that steroid dosages in the two regimes in the present study differed and that this might have contributed to the differences seen.

Previous studies in lupus nephritis showed that pulse cyclophosphamide was as effective in improving and stabilizing renal function and less toxic than continuous oral cyclophosphamide. Uncontrolled studies of pulse cyclophosphamide, usually with daily prednisolone, in patients with systemic vasculitis, have yielded contradictory findings. Early studies in systemic rheumatoid vasculitis suggested that an initial three-weekly pulse regime was more effective than continuous oral treatment with these agents. Falk et al. in a retrospective study in patients with ANCA-positive glomerulonephritis and systemic vasculitis, showed that monthly intravenous cyclophosphamide for 6 months, and continuous oral prednisolone (15 patients) was as effective as continuous oral cyclophosphamide and prednisolone (30 patients) in terms of renal and patient survival. Similarly, Haubitz et al. found that all eight patients with Wegener’s granulomatosis treated with monthly intravenous cyclophosphamide and oral daily prednisolone went into remission, and that drug toxicity was less than in 15 patients treated with continuous oral cyclophosphamide and prednisolone. By contrast Hoffman et al. found that only 2/11 (18%) patients with Wegener’s granulomatosis treated with monthly pulse cyclophosphamide and oral daily prednisolone achieved sustained remission. A similar disappointing outcome was observed by Steppat and Gross and by Reinhold-Keller et al. In the latter study of 43 patients, only seven were new patients, and overall 42% of the whole group responded to treatment with pulse cyclophosphamide. The non-responders had more severe disease, were less likely to have disease restricted to the upper respiratory tract, and were also more likely to have higher ANCA titres than were responders. The above studies, although uncontrolled, led to a widespread perception that pulse cyclophosphamide was less effective than continuous cyclophosphamide, especially in patients with severe disease.

In the present study, patients treated with pulse PCYP had fewer episodes of leucopenia than patients treated with CCAZP, although the differences were not significant. The incidence of infection was comparable with the two treatment regimes. There were no episodes of haemorrhagic cystitis. It is likely that some of the toxicity seen in the CCAZP-treated patients was due to azathioprine. With the limitations imposed by the number of patients in each treatment group, we found that pulse cyclophosphamide and steroids were as effective in inducing remission (as assessed by BVAS and CRP and improving renal function) as continuous cyclophosphamide and steroids. Improvement of renal function was comparable between the two treatments in patients with initial severe renal impairment. Survival did not differ significantly between treatment regimes, with 77% of patients treated with PCYP and 90% of patients treated with CCAZP surviving for 3 years. The overall survival in this study is comparable to that of other studies of patients with a vasculitis treated with continuous oral prednisolone and long-term oral cyclophosphamide. The data from this study suggest that prednisolone and short-term cyclophosphamide with conversion to azathioprine on remission, or pulse cyclophosphamide and prednisolone, is no less effective in treating vasculitis than the long-term cyclophosphamide used in other studies. We also believe that these regimes are likely to be less toxic than long-term continuous oral cyclophosphamide. The ECSYSVASCTRIAL group is currently comparing continuous oral prednisolone and long-term cyclophosphamide with continuous oral prednisolone and cyclophosphamide with early conversion to azathioprine on remission. A further question that needs to be addressed is whether pulse cyclophosphamide is as effective and less toxic than continuous oral cyclophosphamide when given on a background of the same dose of continuous oral prednisolone.

In any controlled trial of therapy the question of escalation treatment poses difficulties in the analysis of the efficacy of trial agents. In a recent round-table discussion by participants from 15 European centres, all used additional therapy in the form of intravenous methylprednisolone, plasma exchange or intravenous immunoglobulin for patients with severe vasculitis. In the present study, escalation treatment was used in slightly more patients treated with PCYP (15/24) than in patients treated with CCAZP (16/30). Together with the requirement for continuous oral prednisolone in 13 patients treated with PCYP, this does suggest that this regime was less effective in treating vasculitis than CCAZP. Clearly the use of additional treatment could obscure differences between the two treatments studied, but it would be impossible to deny patients accepted additional therapies in the presence of potentially life-threatening disease. Relapses in the short term were comparable in the two treatment regimes. Two recent studies have highlighted the problem of relapses in patients with a systemic vasculitis. This has become apparent as more patients survive their acute illness. The study of Gordon et al. reported a relapse rate of 70%
over a 10-year period in patients with Wegener's granulomatosis, classical polyarteritis and microscopic polyarteritis. In a long-term study of Wegener's granulomatosis, Hoffman et al. found that 50% of remissions were followed by one or more relapses. 

Explanations of the apparent effectiveness of our pulse regime as compared with previously reported studies include differences in the dose interval. Our regime provides the first three doses at two-weekly intervals, whereas in the other regimes cyclophosphamide was given monthly. 11–15 In addition, in our study prednisolone was given as pulses, whilst in previous studies it was given continuously. 11–15 Finally, our study was of new patients with a vasculitis, while in some of the previous studies the majority of patients had long-standing vasculitis and had already received treatment with continuous oral cyclophosphamide. 14,15 Cyclophosphamide is effective in inducing remission, but a significant percentage of patients will relapse when it is discontinued, and in a proportion of patients the relapse may occur whilst on cyclophosphamide. 6,9 Cyclophosphamide may well be less effective in maintaining remission than in inducing it. The slow rate of improvement in the activity score after the marked change in the first 3 months is consistent with this. Presently, there is no controlled trial to confirm or refute the possibility that a smaller percentage of patients would relapse with long-term continuous oral cyclophosphamide than with the regimes used in the present study. As more patients survive their acute illness, the burden from serious cyclophosphamide-related toxicity becomes a major concern, and there is a need for controlled trials to find safer and at least equally effective ways of maintaining remission.

In the present study, 84% of patients survived for a year and the majority of these were in remission by 6 months. The French group, (Guillevin et al. submitted for publication), reached essentially the same conclusion despite a different approach. The longer-term control of disease does not appear as good with either regime. The major challenge is the development of more effective and less toxic regimes for the maintenance of remission.

Acknowledgements

We are grateful to Ms. Janet Dunn, Senior Statistician, CRC Trials unit for advice.

References

Appendix I

Continuous cyclophosphamide, prednisolone and azathioprine protocol

**Induction phase 0–12 weeks**

1) Cyclophosphamide 2 mg/kg/day
   (Dosage reduction for renal failure – serum creatinine < 250 µmol/l: 2 mg/kg; 251–500: 1.75 mg/kg; 500: 1.5 mg/kg).
2) Prednisolone—maximum dose 60 mg/day.

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2</td>
<td>0.85</td>
</tr>
<tr>
<td>3–6</td>
<td>0.65</td>
</tr>
<tr>
<td>7–12</td>
<td>0.5</td>
</tr>
<tr>
<td>13–20</td>
<td>0.3</td>
</tr>
<tr>
<td>21–28</td>
<td>0.2</td>
</tr>
<tr>
<td>29–36</td>
<td>0.15</td>
</tr>
<tr>
<td>37–44</td>
<td>0.15/0.07</td>
</tr>
<tr>
<td>45–78</td>
<td>0.15/0</td>
</tr>
</tbody>
</table>

**Remission phase 13–52 Weeks**

1) Azathioprine 1.5 mg/kg/day.
2) Prednisolone reduce as per protocol above.

**Maintenance phase**

1) Prednisolone 0.15 mg/kg alternate days.

**Protocol for the treatment of vasculitis with intermittent pulses of cyclophosphamide and prednisolone**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time (week)</th>
<th>Pulse number</th>
<th>Route</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td>0,2,4</td>
<td>1–3</td>
<td>iv</td>
<td>15 mg/kg x 1</td>
</tr>
<tr>
<td></td>
<td>7,10,13,17,21,25</td>
<td>4–9</td>
<td>oral</td>
<td>5 mg/kg x 3</td>
</tr>
<tr>
<td><strong>Remission</strong></td>
<td>30,35,40,46,52</td>
<td>10–14</td>
<td>oral</td>
<td>5 mg/kg x 3</td>
</tr>
<tr>
<td><strong>Consolidation</strong></td>
<td>58,64,70,76</td>
<td>15–21</td>
<td>oral</td>
<td>5 mg/kg x 3</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>Oral prednisolone, 0.15 mg/kg alternate days.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MESNA is to be given in 3 oral doses totalling 75% of the dose of cyclophosphamide for every dose of intravenous cyclophosphamide.

**Dose adjustments** are advised for the following reasons:

1) **Maximum doses**: The maximum bolus dose of cyclophosphamide, regardless of weight, will be 1000 mg. The maximum bolus dose of prednisolone regardless of weight will be 1000 mg.
2) **Cytopenia prior to bolus therapy:** Delay bolus until count restored to above lower limit of normal (WCC > 3.5 or neutrophil count > 2.0, platelets > 140). If cytopaenia recurs, reduce cyclophosphamide bolus by 25%.

3) **Renal failure on bolus therapy:** reduce as follows.

<table>
<thead>
<tr>
<th>Serum creatinine</th>
<th>Cyclo dose</th>
<th>Pred dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 150</td>
<td>15 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>150–250</td>
<td>10 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>251–500</td>
<td>7.5 mg/kg</td>
<td>10 mg/kg</td>
</tr>
<tr>
<td>&gt; 500</td>
<td>5 mg/kg</td>
<td>7 mg/kg</td>
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</table>