Combined intravenous methotrexate and cyclophosphamide for refractory childhood lupus nephritis

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METHODS
All five treated children fulfilled the American College of Rheumatology criteria for a definite diagnosis of SLE. All had renal biopsy proven class IV DPGN. Initial treatment was 750–1000 mg/m² of IV CYTX per dose given monthly for 7 months and then every 3 months for an additional 30 months (17 total doses over 36 months according to our published protocol) for all children. Four children had completed this regimen. The fifth child had received 11 doses of IV CYTX (monthly×7 doses and every 3 months×4) before developing DPGN.

All children were selected for combined IV CYTX and IV MTX treatment because of new (one case) or recurrent (four cases) worsening of haematuria and proteinuria with decreasing serum albumin, haemoglobin, and serum complement C3 and C4 levels, unresponsive to doubling the daily prednisone dosage. Before starting combined IV CYTX and IV MTX treatment all children were given folic acid 1 mg daily, which was continued throughout. Informed consent was obtained in all cases.

Treatment was begun with IV CYTX at 750–1000 mg/m² in 150 ml D5W over 1 hour. Four hours later patients received IV MTX 50 mg/m² in 100 ml D5W over 4 hours. IV CYTX was continued at the maximum dose tolerated during the initial treatment with IV CYTX alone. The IV MTX dosage was increased to 100 mg/m², then 150 mg/m², and then 300 mg/m² as tolerated by each child. If the absolute neutrophil count fell below 0.5×10⁹ neutrophils/l 10–14 days after treatment, the next dose of IV MTX was reduced by 25% and the lower dose was maintained for the remainder of the study. No child received more than 300 mg/m² of IV MTX. The IV CYTX dose was held constant throughout.

Treatment with combined IV CYTX and IV MTX was continued at monthly intervals for 9 months. All children were observed in the hospital for at least 12 hours before IV CYTX and IV MTX for evidence of fever, irregular vital signs, or other findings suggesting infection. Samples were obtained for complete blood count (CBC), erythrocyte sedimentation rate (ESR), Na, K, Cl, CO₂, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (Cr), antinuclear antibodies (ANA), C3, and C4 at the time of admission. Twenty four hour urine for protein, Cr, and CrCl was also obtained. All children were treated in hospital and received intravenous hydration (2 l/m²/24 h D5 0.5 NS) for 12 hours before and 24 hours after IV CYTX, and intravenous MESNA for 12 hours after the IV CYTX.

Fourteen days after combined

**Abbreviations:** ALT, alanine aminotransferase; ANA, antinuclear antibodies; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine; CYTX, cyclophosphamide; DPGN, diffuse proliferative glomerulonephritis; ESR, erythrocyte sedimentation rate; IV, intravenous; MTX, methotrexate; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index
IV CYTX and IV MTX all children were evaluated in the outpatient department and the determination of CBC, ESR, Na, K, Cl, CO₂, BUN, AST, ALT, Cr, ANA, C₃, and C₄ repeated.

Because of the small sample size statistical analysis was performed using one tailed t-tests. This was consistent with our hypothesis that IV CYTX and IV MTX treatment would be associated with improvement.

RESULTS

Table 1 shows that all children improved with combined IV CYTX and IV MTX treatment. There were statistically significant reductions in the mean SLE disease activity index (SLEDAI) score (fig 1) and mean daily prednisone dose (fig 2) and statistically significant increases in mean serum albumin, total protein, and serum C₃ level. The mean serum creatinine level remained in the normal range.

Side effects of combined IV CYTX and IV MTX treatment included leucopenia in 4/5 and mild mucositis 2/5 children. The leucopenia occurred at an MTX dose of 150 mg/m² in two children and at 300 mg/m² in two others. In all cases the leucopenia resolved when the dose was reduced. One child required IV acyclovir because of recurring Herpes zoster infection. Two children required admission for observation because of fever and neutropenia between treatments with IV CYTX and IV MTX but were without infection.

All children completed nine treatments with combined IV CYTX and IV MTX. All remain stable a mean of 4 years (range 1–10) after treatment, without recurrent active nephritis or evidence of IV CYTX and IV MTX related toxicity.

DISCUSSION

DPGN secondary to SLE is a severe life threatening condition. Over the past 20 years the prognosis for children with DPGN has dramatically improved. This is due in part to the advent of improved paediatric intensive care units, improved antibiotic regimens, and the systematic use of IV CYTX. Systematic use of a 3 year course of IV CYTX has dramatically improved. This is due in part to occurred in 6/42 children (14%) who completed three years of our experience recurrent DPGN related disease activity has been very successful for most children with DPGN. However, in our experience recurrent DPGN related disease activity has occurred in 6/42 children (14%) who completed three years of IV CYTX.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Paired t test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLEDAI</td>
<td>13.8 (7.0)</td>
<td>4.4 (3.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>28 (11)</td>
<td>41 (6)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>52 (12)</td>
<td>67 (7)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>C₃ (g/l)</td>
<td>0.5 (0.1)</td>
<td>0.9 (0.4)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>Serum creatinine (μmol/l)</td>
<td>100 (60)</td>
<td>80 (40)</td>
<td>NS</td>
</tr>
<tr>
<td>Prednisone (mg/day)</td>
<td>27.6 (7.8)</td>
<td>12.5 (5.0)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Results are shown as mean (SD).

REFERENCES

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