CONCISE REPORT

Combined intravenous methotrexate and cyclophosphamide for refractory childhood lupus nephritis

T J A Lehman, B S Edelleit, K B Onel

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Objective: To evaluate the efficacy and safety of combining monthly intravenous methotrexate (IV MTX) with monthly IV cyclophosphamide (CYTX; given on the same day) for the treatment of children who develop recurrent diffuse proliferative glomerulonephritis secondary to systemic lupus erythematosus during or after the standard 3 year course of IV CYTX.

Methods: Five children were treated with nine monthly doses of IV CYTX (750–1000 mg/m²/month) and IV MTX (50–300 mg/m²/month) given on the same day. Their clinical and laboratory measurements were collected every other week throughout the nine months.

Results: All children improved dramatically. SLEDAI scores decreased from an average of 13.8 to 4.4, mean (SD) serum creatinine level fell from 100 (60) to 80 (40) µmol/l, and serum albumin rose from 28 (11) g/l to 41 (6) g/l, while the mean (SD) C3 level increased from 0.5 (0.1) g/l to 0.9 (0.4) g/l. Clinical improvement persisted after 4 years' follow up despite discontinuing MTX and CYTX after 9 months. The average daily dose of corticosteroids has been reduced from 27.6 mg/day at the start of treatment to 12.5 mg/day at follow up.

Conclusion: Combined IV MTX and IV CYTX treatment effectively controls recurrent or refractory lupus nephritis in children with significant disease activity after treatment with IV CYTX alone.

The prognosis of children with systemic lupus erythematosus (SLE) has dramatically improved with the introduction of systematic intravenous cyclophosphamide (IV CYTX) treatment.^{1–3} In our experience, 6/42 children with biopsy proven diffuse proliferative glomerulonephritis (DPGN) have relapsed after a three year course of IV CYTX.^{1,2} These children experienced recurrent nephritis a mean (SD) of 24 (33) months (range 1–72) after completion of the standard 3 year IV CYTX regimen. One additional child developed DPGN while receiving IV CYTX every 3 months (after completing the initial course of monthly IV CYTX, which was started in her case to treat pulmonary haemorrhage).

Before the use of combined IV CYTX and IV methotrexate (MTX) two children with recurrent DPGN were treated with a second 3 year course of IV CYTX (total dosage >34 g/m²). Although the nephritis resolved in both cases, one child developed a renal papillary cell carcinoma and one remains amenorrhoeic 6 years after her last dose of CYTX. Our goal in using combined IV CYTX (up to 1 g/m²) and intravenous methotrexate (IV MTX) (up to 300 mg/m²) was to obtain more substantial immunosuppression in a shorter period with less likelihood of long term toxicity.

METHODS

All five treated children fulfilled the American College of Rheumatology criteria for a definite diagnosis of SLE.⁴ 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.² 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.² 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

Table 1 Results of treatment

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

Results are shown as mean (SD).

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.^{5–7} 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.^{1–8–9} Systematic use of a 3 year course of IV CYTX has been very successful for most children with DPGN.² However, in our experience recurrent DPGN related disease activity has occurred in 6/42 children (14%) who completed three years of IV CYTX.

Figure 1 Average SLEDAI score before and after treatment. **Figure 2** Change in daily prednisone dose before and after treatment.

Before this study there were no reports of consistently successful treatment for children with recurrent disease after completion of systematic IV CYTX treatment. Our experience showed that repeated treatment with a further 36 month course of IV CYTX alone carried an unacceptable risk of long term toxicity. We chose to combine IV CYTX and IV MTX after the oncologists' precept that combining two drugs with different dose limiting toxicities and mechanisms of action should have a synergistic effect without a corresponding increase in treatment related toxicity.¹⁰ Our findings suggest this is true in SLE as well.

Autologous bone marrow transplantation,^{11–12} and high dose IV CYTX ablation,^{13–14} have been suggested for patients with severe SLE. Both have significant morbidity and mortality. The children in our study experienced long term remission without toxicity comparable to these treatments.

All the children in this group were expected to progress to renal failure and dialysis without aggressive intervention. After combined IV CYTX and IV MTX treatment four improved dramatically and the fifth stabilised. Our results suggest that more careful consideration should be given to the use of combined agent regimens in the treatment of children with DPGN. Such regimens may result in greater efficacy and lower toxicity.

Authors' affiliations

T J A Lehman, K B Onel, B S Edelheit, Division of Paediatric Rheumatology, Hospital for Special Surgery, and Department of Paediatrics, Sanford Weill Medical College of Cornell University, USA

Correspondence to: Dr T J A Lehman MD, Hospital for Special Surgery, 535 E 70th St, New York, NY 10021, USA; goldscout@aol.com

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