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Original Article

Efficacy and safety of cyclophosphamide combined with mycophenolate mofetil for induction treatment of class IV lupus nephritis

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Abstract: The present study aimed to evaluate the efficacy and safety of combination of cyclophosphamide (CTX) and mycophenolate mofetil (MMF) as induction treatment in Chinese patients with class IV lupus nephritis (LN). 82 patients were randomly divided into control (CTX, n=40) and test (CTX+MMF, n=42) groups, and they received monthly dose of 0.75 g/m^2 of body surface area of CTX and monthly dose of 0.4 g/m^2 CTX plus 1.0 g/d MMF, respectively. Patients were followed up for six months after treatment; and their efficacy rates, complete remission rates, adverse events, and certain indices in blood were compared between the two groups. Compared with the baseline levels, significant differences in the levels of hemoglobin, urinary proteins, albumin, serum creatinine, erythrocyte sedimentation rate, complement C3 and anti-dsDNA were observed after treatment in both groups (P<0.05). While the two groups did not differ significantly after treatment (P>0.05). There was a trend toward higher complete remission (54.8%) and efficacy rates (88.1%) after treatment in the test group without statistical significance. However, the incidence rate of gastrointestinal reactions (7.1%) and infections (11.9%) in the test group were significantly lower than the control group (P<0.05). The efficacy of lower dose of CTX combined with MMF as induction therapy for LN was not lower than the traditional treatment with CTX. Moreover, the low dose of CTX in combination with MMF could result in lesser adverse events and improved safety.

Keywords: Lupus nephritis, mycophenolate mofetil, cyclophosphamide, combination therapy

Introduction

Epidemiological studies have indicated that systemic lupus erythematosus (SLE) is a common and frequently-occurring disease with an incidence of 0.7/1000 in China, and lupus nephritis (LN) is the common cause of mortality in patients with SLE [1, 2]. According to the updated International Society of Pathology/Renal Pathology Society (ISN/RPS) classification of LN, LN is divided into six different types and diffuse proliferative LN (DPLN, class IV LN) is the predominant histological type [3]. Over the past 20 years, high dose of intravenous cyclophosphamide (CTX) therapy has widely been used for the treatment of class IV LN, which has shown significantly improved efficacy [4-6]. Until today, the combination therapy of steroids and CTX is still a classical regimen, but the overall efficacy is not so satisfactory [7]. Moreover, the use of CTX has been limited due to the potential adverse events (AEs) with the increases of dose. The severe AEs may include inhibition of bone marrow, gonadal inhibition, and serious infections [8, 9]. In recent years, mycophenolate mofetil (MMF) has been used to treat LN and is usually considered as a better alternative to CTX in clinical practice [10]. MMF combined with prednisolone could lead to an effective induction-maintenance treatment for DPLN, and MMF treatment was associated with similar recurrence rate and less AEs compared with CTX treatment [7, 11].

The inhibitory effects of CTX on cell differentiation and proliferation is mainly exerted by influencing the directional stem cells of the immune system, but direct effects on its effector cells are not observed [12, 13]. However, the similar inhibitory effects of MMF could be attributed to its selective inhibition of the activated T- and

Table 1. Comparison of the baseline information in the two groups (mean ± SD)

Variable	CTX group (n=40)	CTX+MMF group (n=42)	*P* value
Male:Female	3:37	4:38	1.000
Age (yr)	33.3±11.0	31.9±8.7	0.518
BMI (kg/m^2)	23.2±1.7	23.1±1.4	0.782
SBP (mmHg)	127.0±11.0	128.0±8.8	0.673
DBP (mmHg)	69.1±9.0	72.5±7.2	0.054
SLEDAI	13.8±3.0	14.1±3.2	0.631
Activity score	12.6±3.6	12.4±3.7	0.810
Chronicity score	2.7±2.1	2.5±1.9	0.650

BMI = body mass index; CTX = cyclophosphamide; DBP = diastolic blood pressure; MMF = mycophenolate mofetil; SBP = systolic blood pressure.

B-lymphocytes, expression of adhesion molecules, and protection of vascularendothelial cells [14, 15]. As both CTX and MMF are effective for treating LN, the present study involved the use of combination of reduced doses of MMF and CTX to treat class IV LN. Considering the differences in action sites of MMF and CTX, it was unknown whether this treatment regimen could display better efficacy and safety. Due to the lack of large-scale prospective clinical trials, this study on exploration of efficacy and safety profiles of reduced doses of CTX combined with MMF in the treatment of patients with class IV LN could provide foundations for further prospective, multi-centre, randomized controlled clinical trials.

Materials and methods

Study settings

This randomized, open-label study was conducted at the Department of Nephrology of the Third Xiangya Hospital, Central South University, Changsha, China from September 2007 to February 2012. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of the Third Xiangya Hospital. Written informed consent was obtained from all participants' guardians.

Subjects and selection criteria

Patients with the following criteria were included in the study: 1) male or female patients of 14 to 60 years of age (both inclusive), who could give written informed consent; 2) patients with SLE-Disease Activity Index (SLEDAI) of ≥12 [SLE as defined by the ACR guidelines]; 3) patients whose condition was diagnosed as SLE by light microscopy, immunofluorescence, and electron microscopy and blindly scored with respect to activity and chronicity; 4) patients who had histologically (renal biopsy) confirmed diagnosis of class IV LN, which corresponded to diffuse segment or global (IV-s of IV-G) lupus nephritis to the 2003 International Society of Nephrology/Renal Pathology Society Classfication [8]. Patients who met the following criteria were excluded from the study: 1) patients who were complicated by uncontrolled severe infections or neuropsychiatric lupus erythematosus; 2) patients with abnormal liver or kidney function (defined as >2 times of the normal values of transaminases or >265.2 μmol/L of serum creatinine (SCr) level); 3) patients with $<3\times10^9$/L of white blood cells (WBC) or $<50\times10^9$/L of platelets; 4) patients who received any cytotoxic or immunosuppressive drugs like CTX, tacrolimus, MMF, or cyclosporin A within 3 months prior to the study entry; 5) pregnant or lactating women; 6) patients with cerebrovascular disease, glucose metabolism disorder, or severe cardiopulmonary dysfunction.

Randomization

Based on lottery system, the patients were randomized either to the control (CTX, n=40) or test (CTX+MMF, n=42) groups.

Treatment regimen

Patients in the control group received CTX at a monthly dosage of 0.75 g/m^2 of body surface area, while the patients in the test group received CTX at a monthly small dose of 0.4 g/m^2 of body surface area plus MMF at a daily dosage of 1.0 g. In addition, prednisolone was started at a daily dose of 1.0 mg/kg for both groups, and then the dose was reduced gradually after four to eight weeks until completion of the treatment. All patients were followed up for 6 months after treatment. The dosages of MMF and CTX remained unchanged in the 6 months, except in patients who developed adverse effects of these drugs. The criteria for discontinuation of treatment and withdrawal from study included any of the following: Severe leukopenia (white blood cell count $<2\times10^9$/L), thrombocytopenia (platelet count $<50\times10^9$/L),

Table 2. Comparison of clinic indices before and after treatment

Index	Baseline CTX group (n=37)	CTX+MMF group (n=40)	*P* value	After six months of treatment CTX group (n=37)	CTX+MMF group (n=40)	*P* value
Hb (g/l)	85.2±21.1	81.8±17.9	0.445	124.4±14.5*	119.7±17.8*	0.217
Urinary proteins (g/24 h)	2.45±1.48	2.04±1.89	0.293	1.08±1.41*	0.54±1.17*	0.076
Alb (g/L)	25.0±2.5	25.2±4.0	0.872	35.5±2.2*	36.0±1.5*	0.197
SCr (mmol/L)	118.0±26.7	128.0±50.5	0.302	78.1±29.5*	70.3±23.8*	0.211
C3 (g/L)	0.27±0.10	0.31±0.08	0.054	0.77±0.05*	0.78±0.04*	0.334
ESR (mm/h)	70.9±11.9	67.9±14.4	0.322	29.0±5.04*	29.7±5.50*	0.563
Anti-ds-DNA (%)	64.9%	70.0%	0.631	32.4 %*	30.0%*	0.818

*$P<0.05$ vs. before treatment. Alb = serum albumin; C3 = complement C3; CTX = cyclophosphamide; ESR = erythrocyte sedimentation rate; Hb= hemoglobin.

no clinical or serologic improvement after 8 weeks of therapy, life-threatening complications (e.g., cerebral lupus, severe infection), pregnancy, or poor compliance.

Endpoint of the study

The differences in efficacy and complete remission between the two groups were considered as the primary endpoints of the study. Treatment outcome was defined as complete remission, partial remission, and no remission [11]. Complete remission was defined to have <0.3 g/24 h of urinary protein with ≥35 g/L of serum albumin (Alb) and normal SCr level. Partial remission was defined to have a urinary protein range of 0.3 to 2.9 g/24 h with an Alb concentration of ≥30 g/L, stable or improved renal function with reduction of proteinuria by >50%. Efficacy included complete remission and partial remission. No remission indicated ≥3.0 g/24 h of urinary protein with <30 g/L of Alb and no improvements in SCr concentration or >15% increase from its baseline value. The secondary endpoints involved the pre- and post-treatment differences in the levels of Hb, urinary proteins, Alb, SCr, erythrocyte sedimentation rate (ESR), complement C3and anti-dsDNA between the two groups. After treatment, these levels were also compared between the two groups. Other indices studied included the following: AEs during treatment, incidence of infections and gastrointestinal reactions, irregular menstruation for females (amenorrhea and abnormal menstrual cycles), WBC count of $<4\times10^9$/L, and abnormal liver functions.

Statistical analysis

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA), and all data were expressed as mean ± standard deviation (SD). Paired t-test was used to compare the paired data, and differences between the two groups were compared by t test. Differences of proportions were tested for statistical significance with the chi-square test. $P<0.05$ was considered statistically significant.

Results

Baseline characteristics

The diagnosis of class IV LN was confirmed from the clinical data and renal biopsy. The disease duration for all the patients ranged from 0.5 to 24 months, and the length of treatment was no less than six months. There were no significant differences in the baseline characteristics including sex ratio, age, body mass index, blood pressure, SLEDAI and activity and chronicity score between the two groups; which indicated that the patients in the two groups were comparably homogeneous (**Table 1**).

Comparison of clinical indices

The levels of Hb, urinary proteins, Alb, SCr, component C3, ESR and anti-dsDNA were compared between the two groups after six months of treatment. Though there were significant differences observed in these indices before and after treatment in the two groups ($P<0.05$), no significant differences were observed between the two groups after treatment for 6 months ($P>0.05$, **Table 2**).

Comparison of remission rate

After six months of treatment, the efficacy rates in the control and test groups were 77.5% and

Table 3. Comparison of efficacy and remission rates in the two groups (mean ± SD)

Group (n)	CTX group (40)	CTX+MMF group (42)	*P* value
Complete remission rate (%) (n)	45.0 (18)	54.8 (23)	0.377
Efficacy rate (%) (n)	77.5 (31)	88.1 (37)	0.202

CTX = cyclophosphamide; MMF = mycophenolate mofetil. MMF = mycophenolate mofetil; SCr = serum creatinine.

Table 4. Comparison of adverse events after treatment in the two groups (mean ± SD)

	CTX group	CTX+MMF group	*P* value
Gastrointestinal reactions (n = 40, 42)	9 (22.5%)	3 (7.1%)	0.049
Infections (n = 40, 42)	13 (32.5%)	5 (11.9%)	0.024
Irregular menstruation (n = 40-3, 42-4)	8 (21.6%)	4 (10.5%)	0.190
Elevated transaminase (n = 40, 42)	3 (7.5%)	2 (4.8%)	0.955
Leukopenia (n = 40, 42)	3 (7.5%)	2 (4.8%)	0.955

CTX = cyclophosphamide; MMF = mycophenolate mofetil.

88.1%, respectively. The complete remission rate in the test group was increased by 9.8% in comparison with that in the control group (54.8% vs. 45.0%). There were no significant differences observed between the two groups (**Table 3**).

Safety evaluation and comparison of adverse events

In the control group, one death was reported due to infection, and one patient left the study due to severe complications. One patient was withdrawn due to severe AE (leucopenia). In the test group, one patient died due to SLE and another was withdrawn from the study due to severe complications. In the control group, gastrointestinal reactions occurred in 9 patients, which included nausea, vomiting, and loss of appetite. In the test group, three patients reportedly had gastrointestinal reactions such as nausea and diarrhea. The incidence of gastrointestinal reactions in the test group was significantly lower than that in the control group ($P<0.05$). Infections were noted in 13 patients in the control groups: respiratory tract infection in seven patients, urinogenital system infection (including urinary tract infection and vaginitis) in four patients, respiratory tract infection combined with urinary tract infection in one patient, and respiratory tract infection combined with genital herpes virus infection in one patient. In the test group, five patients experienced infections: urinary tract infection in two patients, respiratory tract infection in two patients, and herpes virus infection in one patient. The occurrence of infections was reportedly lower in the test group than the control group ($P<0.05$). Eight females had irregular menstruation in the control group. Among them, two patients had menopause. Four patients in the test group had prolonged menstrual cycles, but none reported menopause. The other AEs in the two groups included mild leucopenia and transient elevated aminotransferase. Mild leucopenia presented in 3 patients in the control group and 2 in the test group. Transient elevated aminotransferase was found in 3 patients in the control group and 2 in the test group. No significant difference was observed for both (**Table 4**).

Discussion

In the early 1980s, the use of CTX had markedly improved the five-year survival rate of patients from 55% to 85% and also improved the long-term survival [4, 16]. However, due to the pathological types of kidney tissues, the therapeutic response for the treatment with CTX has shown great intersubject differences [3, 7, 17]. Some patients had not been sensitive to this therapy, and the LN remained unsatisfactorily controlled with a higher risk of recurrence [2, 6]. Moreover, their compliance could decrease due to the occurrence of severe AEs like infections, liver damage, and gonadal inhibition, etc. [2]. In recent years, MMF has been used in the treatment of LN and has usually been a better alternative to CTX in clinical practice [15]. In a multicentre, randomized controlled trial, Ong et al. [16] evaluated the efficacy of CTX and MMF in the induction treatment of class III and IV LN. The efficacy of both the drugs was similar, but the AEs were found to be dose related and the long-term use of MMF at a high dose could induce severe bacterial and viral infections [10, 18]. In 2007, a multitarget therapy was first introduced with the sug-

gestion to combine different immunosuppressive drugs for the multiple immune responses that could cause different tissue damages [19, 20]. A recent study had shown that MMF combined with tacrolimus was an effective treatment for refractory LN [17], while its long-term outcomes were needed to be further determined as it was difficult for most of the patient to accept due to the high cost of MMF and tacrolimus. In the present study, a combined therapy consisting of reduced doses of CTX and MMF was applied to observe their efficacy for the treatment of refractory LN. When compared with the baseline levels, significant differences in the levels of Hb, urinary proteins, Alb, SCr, ESR, complement C3 and anti-ds-DNA were observed after treatment in both the control and test groups ($P<0.05$), suggesting that these two regimens were effective in controlling the SLE activity. Nevertheless, there were no obvious differences after treatment between the two groups in these levels ($P>0.05$), which was mainly due to a short clinical observation of six months. The efficacy rate in the test group was increased by 10.6% in comparison with that in the control groups (77.5% vs. 88.1%). The complete remission rate in the test group was improved by 9.8% compared with the control group following the treatment for six months (45.0% vs. 54.8%). These findings suggest that the test group showed better efficacy for LN than the control group. However, there were no significant differences between the two groups in terms of efficacy and complete remission rates. This could be attributed to the limited number of clinical samples and short-term observation of this study. But the present study would certainly provide foundations for further prospective, multicentre, randomized controlled clinical trials with larger sample size. Because active LN requires long-term treatment with immunosuppressive drugs, it is always associated with severe complications [21, 22]. This could result in termination of treatment by patients in clinical practice [23]. In the current study, the AEs in the test group were lower than those in the control group, and the frequently occurred AEs were gastrointestinal reactions (nausea, vomiting, loss of appetite, and diarrhea) and infection. The incidence rate of gastrointestinal reactions was obviously lower in the test group than those in the control group (22.5% vs. 7.1%, $P<0.05$) and the most frequent infections in the study were urinogenital system infection, respiratory tract infection, and viral infection. In the control group, a patient died due to severe infection, while no death was reported in the test group. Per a reported study, the rate of infection was 31.3% in patients who received CTX at a monthly dose of 10 mg/kg for six months [24]. In the present study, the rate of infection for LN in the test group were markedly lower than those in the control group (32.5% vs. 11.9%, $P<0.05$), indicating that the AEs could be reduced in the test group with the decreased doses. The combination of reduced dose of CTX and MMF was much safer for the treatment of LN. Different degrees of menstrual disorders were reported in the two groups, which could partly be due to the disorders of the immune system and autoantibodies damage of the patients with SLE. Nevertheless, two cases had menopause in the control group, but none was observed in the test group. The menstrual disorders might also be due to the gonadal toxicity induced by CTX. Therefore, for females with fertility requirements, MMF alone or in combination with the reduced dose of CTX were recommended, while high dose of CTX should not be given priority. The other AEs in the test group included mild leucopenia and transient elevated aminotransferase, which did not require any special treatment for resolution. In conclusion, the efficacy of lower dose of CTX combined with MMF as induction therapy for LN was not lower than the traditional treatment with CTX. Moreover, the low-dose of CTX in combination with MMF could result in lesser AEs and improved safety. This combination would provide a new regimen for induction treatment of LN with more safety.

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Disclosure of conflict of interest

None.

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