Clin Rheumatol (2014) 33:939–945
DOI 10.1007/s10067-014-2590-6

ORIGINAL ARTICLE

Short-interval lower-dose intravenous cyclophosphamide as induction and maintenance therapy for lupus nephritis: a prospective observational study

X. W. Zhang · Chun Li · X. X. Ma · J. X. Zhao · Yuan An · Shuang Liu · Yan Li · Z. G. Li

Received: 1 March 2014 / Revised: 18 March 2014 / Accepted: 22 March 2014 / Published online: 18 April 2014

Abstract Cyclophosphamide (CYC) has long been considered a gold standard in inducing renal remission and preventing renal flares for patients with systemic lupus erythematosus (SLE). However, the rational use of CYC has not reached a consensus, such as the timing and length of treatment, the route of administration, and the ideal dosage. The objective of this study was to assess the efficacy and safety of short-interval lower-dose (SILD) intravenous (IV) CYC in the treatment of SLE. A total of 225 patients with lupus nephritis were randomly assigned to a 1-year trial, either the SILD group (12 fortnightly pulses at a fixed dose of 400 mg followed by 6 monthly pulses) or high-dose (HD) group (6 monthly pulses followed by two quarterly pulses at a dose of 0.5~1.0 g/m^2). At 6 months of treatment, 28 % (30/107) of patients in the SILD group reached a complete remission (CR), and 51.4 % (55/107) were in partial remission (PR), as compared with 32.7 % (35/107) and 45.8 % (49/107) in the HD group, respectively. Serum albumin, 24-h urinary protein, and the scores of disease activity were significantly improved in both groups at 6 months and maintained at the end of clinical trial. However, the SILD group showed much less menstrual disturbances (11.5 %), gastrointestinal adverse effects (5.3 %), and leukopenia (9.7 %) than the HD group (28.6, 26.8, and 19.8 %, respectively) at the end of clinical trial. The efficacy of the short-interval lower-dose (SILD) IV CYC regimen in the treatment of lupus nephritis is equivalent to that of the high-dose (HD) regimen, whereas the incidence of adverse events is much lower in the SILD group.

Keywords Cyclophosphamide · Lupus nephritis · Menstrual disturbance

Introduction

Systemic lupus erythematosus (SLE) is a complicated autoimmune disease with a diversity of clinical features, courses, and prognosis. Among the various organs affected in SLE, the kidney appears to be one of the most common, and at the same time, a more serious complication. Up to two thirds of patients with SLE have renal diseases at some stage of their illness. The risk of progression to end-stage renal failure in lupus nephritis (LN) is 10–15 %[1]. The therapeutic goals for LN are preserving renal function by initially inducing remission of nephritis and then preventing subsequent renal flares.

Cyclophosphamide (CYC) remains the "gold standard" treatment for severe organ-threatening SLE, especially when the renal and central nervous system functions are severely compromised. In the 1970s, Donadio et al. showed that SLE patients with proliferative nephritis who received steroids combined with oral administration of CYC were more likely to have a stable renal function than those treated with prednisone alone [2]. High-dose intravenous (IV) CYC in combination with glucocorticoids has become the standard routine therapy of LN, which has dramatically improved the prognosis. However, the adverse effects, including infection, bone marrow suppression, and gonadal toxicity, have limited the long-term use of this therapeutic regimen. Patients are increasingly reluctant to take such risks. Lower-dose IV

Dr. Chun Li and Dr. Xuewu Zhang contributed equally to this article.

X. W. Zhang · C. Li · X. X. Ma · Y. An · S. Liu · Y. Li · Z. G. Li (✉)
Department of Rheumatology and Immunology, Peking University People's Hospital, 11 South Xizhimen Street, Beijing 100044, People's Republic of China
e-mail: li99@bjmu.edu.cn

J. X. Zhao
Department of Rheumatology and Immunology, Peking University Third Hospital, 49 North Garden Rd., Beijing 100191, China

CYC (0.5 g as a fixed dosage) regimen—as proposed by the Euro-Lupus Nephritis Trial—has been demonstrated to be efficacious. In addition, the rate of severe adverse events was much lower [3]. However, both regimens present a high relapse rate, and some patients fail to respond to the treatment [4, 5]. These phenomena probably attributed to the longer interval of the high-dose IV CYC regimen or the shorter duration of the lower-dose regimen (only 3 months). Moreover, due to the high costs of mycophenolate mofetil, IV CYC still holds on to a dominant position of induction and maintenance therapy for LN. This prompted us to find an ideal dosage and duration for IV CYC treatment in this study.

We hypothesized that short interval with prolonged exposure of lower-dose CYC (12 fortnightly IV CYC pulses at a fixed dose of 400 mg for 6 months and followed by 6 monthly pulses) may be beneficial to those refractory patients.

Patients and methods

The study was approved by the Ethics Committee of Peking University People's Hospital (FWA00001384). All study subjects signed the informed consent agreement.

Patients

Two hundred twenty-five patients with LN were enrolled from January 2004 to June 2012. All patients had met the following study criteria: (1) a definite diagnosis of SLE according to the 1997 American College of Rheumatology (ACR) criteria [6], (2) female, (3) age ≥16 years old, (4) biopsy-proven proliferative lupus glomerulonephritis (World Health organization class III and IV), and (5) proteinuria ≥500 mg in 24 h. Patients who had abnormal menstruation, or had taken prednisolone ≥15 mg/day (or equivalent) or CYC during the previous month were excluded (except using glucocorticoids for a maximum of 10 days before referral). Other exclusion criteria were pregnancy, malignancy, gynecological disease, diabetes mellitus, and patients who received methylprednisolone pulse therapy.

Immunosuppressive treatment and study protocol

One hundred thirteen patients were assigned to the short-interval lower-dose (SILD) group and received 12 fortnightly IV CYC pulses at a fixed dose of 400 mg; subsequent doses were decreased to 400 mg monthly for 6 months as well. On the other hand, 112 patients were assigned to the high-dose (HD) group and received 8 IV CYC pulses within a year (6 monthly pulses followed by 2 quarterly pulses). The former 6 pulses were at a dose of 500 mg/m^2 of body surface area, and the subsequent doses were increased by 250 mg according to the white blood cell (WBC) count nadir measured on day 14 [7], up to a maximum of 1,500 mg per pulse. The initial dosage of prednisone (or equivalent) for all the patients was 0.5~1 mg/kg per day for 4 weeks. After 4 weeks, the dosage of prednisolone was tapered by 2.5 mg every 2 weeks. Low-dose prednisone therapy (5~7.5 mg of prednisone per day) was maintained in the remaining time.

Patients with hypertension were treated primarily with angiotensin-converting enzyme inhibitors (ACEI) unless contraindicated.

Efficacy and safety assessments

The primary end point was the remission of LN (includes complete and partial remission) at the 6th month. A complete remission (CR) was defined as a value for urinary protein excretion that was less than 0.3 g per 24 h, with normal urinary sediment and serum albumin (ALB) concentration, and values for both serum creatinine (sCr) and creatinine clearance that were 15 % or less above the baseline values. A partial remission (PR) was defined as a value for urinary protein excretion that was 0.3–2.9 g per 24 h, with an ALB concentration of at least 3.0 g/dL and stable renal function.

Treatment failure was defined as a value for urinary protein excretion that remained at or above 3 g per 24 h, or a value of 0.3–2.9 g per 24 h but with an ALB concentration of less than 3.0 g/dL, an increase in the sCr concentration greater than or equal to 0.6 mg/dL (50 μmol/L), or a value for creatinine clearance that was more than 15 % above the baseline value, or the discontinuation of treatment due to side effects [8].

Secondary end point included death, elevation of systemic lupus erythematosus disease activity index (SLEDAI) score, commencement of permanent dialysis and kidney transplantation.

All patients were to be seen at regular intervals of 3 months or more frequently if medically indicated. Complete history inquiry, physical examination, and routine laboratory tests [complete blood count, erythrocyte sedimentation rate (ESR), sCr, ALB, 24-h urinary protein, immunoglobulin (Ig), C3, C4, ANA, and anti-double-stranded DNA (dsDNA) antibody] were performed and collected at the 6th month and at the end of clinical trial.

A nadir of WBC count lower than 3.0×10^9/L or a WBC count that could not recover after a month of symptomatic treatment would be an indication to withdraw a patient from the study to ensure the safety of the patient. What is more, the patients would be withdrawn if their liver function indices were twofold higher than the normal range during the trial and unrecovered after symptomatic treatment for 1 month. Anti-infective drugs were administered when infection occurred.

Table 1 Characteristics of the study subjects at baseline

Clinical data	Short-interval lower-dose (n=113)	High-dose (n=112)	P value
Age, years (SD)	31.6 (9.0)	31.7 (10.1)	0.948
History, years (range)	0.75 (0.13–5)	0.92 (0.25–4)	0.962
SLEDAI (SD)	15.5 (7.1)	14.2 (5.9)	0.476
Serum creatinine, μmol/L (SD)	81.3 (62.1)	74.9 (36.0)	0.371
Creatinine clearance, mL/min (SD)	112 (41)	104 (38)	0.403
Serum albumin, mg/dL (SD)	29.4 (4.7)	27.5 (6.4)	0.110
24-h urinary protein, g (SD)	2.68 (2.41)	3.23 (2.90)	0.310
WBC, $\times 10^9$/L (SD)	6.07 (3.02)	5.60 (3.12)	0.441
Hb, $\times 10^{12}$/L (SD)	103.2 (20.5)	101.4 (20.8)	0.659
PLT, $\times 10^9$/L (SD)	157.7 (84.2)	155.2 (85.7)	0.883
ESR, mm/1 h (SD)	48.4 (35.4)	53.5 (31.5)	0.473
IgG, g/L (SD)	16.3 (8.5)	14.2 (7.5)	0.191
IgA, g/L (SD)	3.42 (3.17)	3.13 (1.65)	0.562
IgM, g/L (SD)	1.38 (0.58)	1.31 (0.86)	0.709
C3, g/L (SD)	0.46 (0.28)	0.44 (0.21)	0.733
C4, g/L (SD)	0.10 (0.08)	0.12 (0.15)	0.402
WHO class nephritis, no. patients (%)			
Class III	28 (24.8)	30 (26.8)	0.731
Class IV	85 (75.2)	82 (73.2)	0.731
Activity index (SD)	7.3 (2.6)	7.5 (2.3)	0.795
Chronicity index (SD)	2.1 (1.0)	1.6 (1.0)	0.162

SLEDAI systemic lupus erythematosus disease activity index, *WBC* white blood cell, *PLT* platelet, *RBC* red blood cell, *ESR* erythrocyte sedimentation rate, *Ig* immunoglobulin, *C3* complement 3, *C4* complement 4

Statistical analysis

Consecutive data were compared within and between the two groups by repeated measures analysis of variance. Unpaired t tests or Mann–Whitney U tests were used for between-group comparisons, and paired t test was used for within-group comparisons. Categorical groups were compared by chi-square test and Fisher's exact test. Statistical analyses were performed with the use of SPSS for Windows 16.0. Statistical significance was indicated by two-sided P values <0.05.

Results

Baseline data and treatment

One hundred thirteen patients were assigned to the SILD IV CYC group and 112 to the HD IV CYC group. The clinical characteristics of patients between the two groups did not differ significantly at baseline (Table 1).

As shown in Fig. 1, six patients of the SILD group dropped from the trial for the following reasons: lost to follow-up (n=

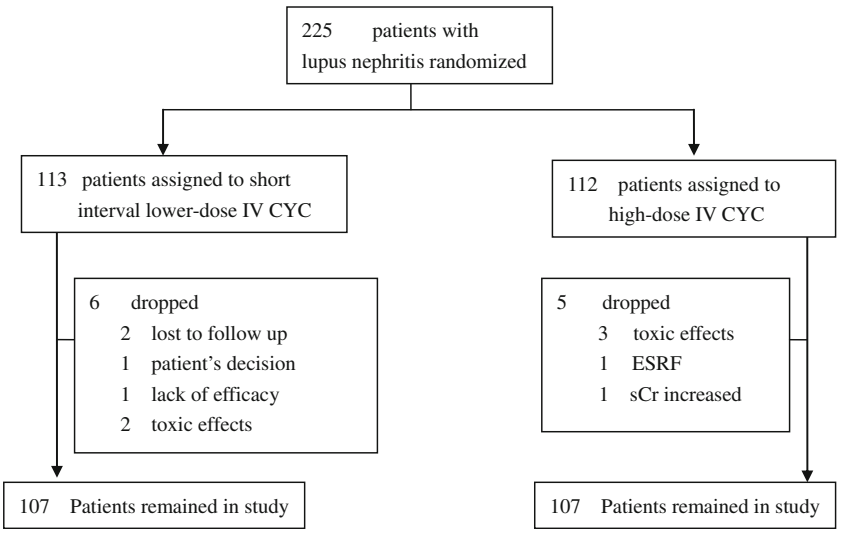

Fig. 1 Patients randomized in the trial to short-interval lower-dose intravenous (IV) cyclophosphamide (CYC) and high-dose IV CYC. *ESRF* end-stage renal failure

Table 2 Outcome of treatment

Variable	SILD (n=107)		HD (n=107)		Difference between groups	P value
	n	%	n	%		
Complete remission	30	28.0	35	32.7	0.801 (0.447–1.437)	0.457
Partial remission	55	51.4	49	45.8	1.252 (0.732–2.142)	0.412
Treatment failure	17	15.9	16	15.0	1.074 (0.511–2.257)	0.850
Relapse	5	4.7	7	6.5	0.700 (0.215–2.280)	0.552

2), patient's decision (n=1), lack of efficiency (n=1), and toxic effects (n=2). Besides, five patients of the HD group dropped from the trial for the following reasons: end-stage renal failure (n=1), toxic effects (n=3), and serum creatinine (sCr) continuing to be higher than normal (n=1). Patients who did not achieve 3-month regular follow-up were not analyzed.

Outcome of treatment

Remission occurred in 79.4 % of patients (85/107) in the SILD group and 84 (78.5 %) in the HD group (P=0.867). The incidences of CR or PR were similar in the two groups (Table 2). The mean time of CR was 4.61±2.80 months for the SILD group and 4.00±2.89 months for the HD group (P=0.633).

The proportion of patients with high serum anti-dsDNA antibody concentrations was reduced from 58.4 to 23.0 and 12.4 % after 6 and 12 months of treatment in the SILD group. In the HD group, the proportion was reduced from 54.5 to 18.8 and 14.3 %.

Serial values for SLEDAI score, ALB and sCr concentrations, and urinary protein excretion per 24 h were similar in both groups (Fig. 2). The SLEDAI score decreased from 15.5 ±7.1 at baseline to 4.4±2.8 at 6 months in the SILD group (95 % confidence interval (CI), 7.7–12.9; P=0.000), and from 14.2±5.9 at baseline to 5.0±4.0 at 6 months (95 % CI, 6.9–10.2; P=0.000) in the HD group, respectively. From baseline to 6 months, urinary protein excretion per 24 h decreased from 2.68±2.41 to 0.75±0.82 g in the SILD group and from 3.23± 2.90 to 1.1±1.8 g in the HD group. The ALB concentration increased from a baseline of 29.4±4.7 to 40.3±3.6 g/L at 6 months in the SILD group and from 27.5±6.4 to 37.2± 6.4 g/L in the HD group. There was no significant difference in the serum creatinine between groups at the end of 6 months (mean serum creatinine was 57.3±16.1 and 74.8±27.5 μmol/L in the SILD and HD groups, respectively). At 12 months, SLEDAI score, 24 h urinary

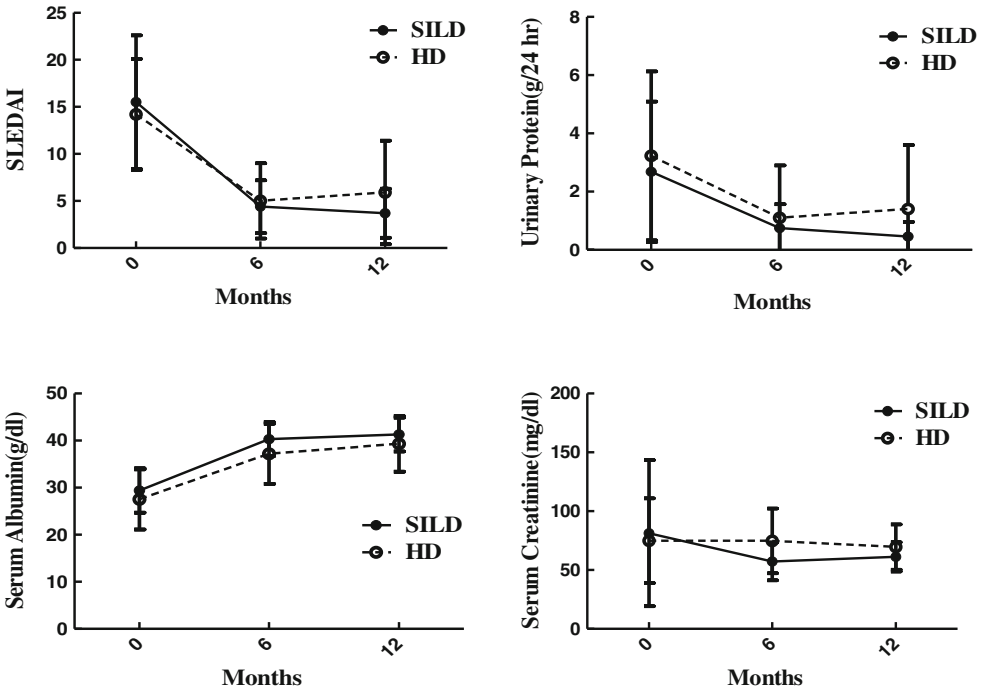

Fig. 2 Mean (±SD) SLEDAI, urinary protein excretion, serum albumin, and serum creatinine in patients with lupus nephritis. The mean SLEDAI was significantly lower than the baseline value after 6 months of therapy in the HD group and in the SILD group, and it remained significantly lower after 12 months in the two groups. Urinary protein excretion was significantly lower than the baseline value after 6 months of therapy in the SILD group and in the HD group, and it remained significantly lower after 12 months in the two groups. The mean serum albumin concentration was significantly higher than the baseline value after 6 and 12 months in both groups. *P<0.05 vs baseline value

Table 3 Secondary end point

Parameter	SILD	HD
Mean change in SLEDAI score (SD)[a,b]	11.8 (7.7)	9.9 (7.0)
Mean change in C3, mg/dL (SD)[a,b]	0.37 (0.13)	0.20 (0.10)
Mean change in C4, mg/dL (SD)[a,b]	0.07 (0.06)	0.13 (0.04)
No. deaths (%)	0 (0)	0 (0)
Permanent dialysis, no. (%)[b]	1 (0.9)	1 (0.9)

SLEDAI systemic lupus erythematosus disease activity

[a] Change at 6 months from baseline value

[b] *P* value not significant for comparison between groups

protein excretion, and ALB were sustained. There was no statistical difference between the two groups regarding the concentration of sCr at the end of trial.

Other indicators of SLE and LN activity had some improvement including the serum concentration of C3 and C4 within groups. However, there was no significant difference of these parameters between the two groups (Table 3).

There was one end-stage renal failure (ESRF) in each group. One patient in the SILD group developed ESRF. The patient started hemodialysis 4 months after recruitment. The other from the HD group went into ESRF 2 months after recruitment and dropped from the clinical trial.

Adverse events

All adverse events occurring between study inclusion and last follow-up visit were recorded (Table 4). Menstrual cycle disturbances occurred in both regimens. At month 12, 11.5 % of patients in the SILD group had menstrual disturbance, compared with 28.6 % in the HD group (P=0.001). The gastrointestinal adverse effects (nausea or vomiting) occurred more frequently in the HD group than in the SILD group (26.8 vs 5.3 %; P=0.000). Leukopenia (defined as WBC count of less than 3.5×10^9/L) occurred more frequently in the HD group (19.8 %) compared with the SILD group (9.7 %; P=0.036). One patient in the HD group withdrew from the study for continuing leukopenia; the others recovered to the normal level in a short period of time.

Table 4 Adverse events

Adverse event	SILD (n=113)	HD (n=112)	P value
Menstrual disturbance	13	32	0.001*
Nausea or vomiting	6	30	0.000*
Infection	20	25	0.386
Herpes zoster	5	7	0.542
Urinary tract infection	8	6	0.605
Upper respiratory tract infection	7	10	0.438
Pneumonia	0	2	0.247
Leukopenia	11	22	0.036
End-stage renal disease	1	1	1.000
Doubling of serum creatinine level	1	1	1.000
Drug-induced hepatitis	3	6	0.333

*P<0.05

Infectious events included herpes zoster, pneumonia, urinary tract infection, upper respiratory tract infection, and so on. The incidence of infections were 17.7 % of the SILD group and 22.3 % of the HD group (P=0.386). The rate of pneumonia was higher in the HD group, but the differences did not reach statistical significance. In addition, the occurrence of urinary infection and herpes zoster of these two groups were similar with each other (Table 4). All infected patients were convalesced after the treatment of antibiotic or antiviral agents, so there was no influence on the therapy of LN.

As indicated in Table 4, one patient in the HD group and one patient in the SILD group had progressed to ESRF and currently undergoing dialysis. Two patients, also one in the HD group and one in the SILD group, had been censored because of doubling of sCr level.

Discussion

We report a prospective 1-year follow-up study comparing the efficacy and safety of two IV CYC regimens. In this patient population, we confirm that the efficacy and kinetics of the initial response between the two groups appear to be comparable. Side effects were less common in the SILD group. Recently, there has been still a lot of controversy over the best IV CYC regimen for patients with SLE. Though high-dose IV CYC in combination with glucocorticoids viewed as the most effective immunosuppressive medication for LN, no final conclusion has yet been reached on this matter so far. With development of further research into this issue, several investigators have raised concerns about the high-dose CYC regimen for the treatment of SLE, especially the risks of infection and ovarian failure [9, 10]. Meanwhile, other researchers put forward a question on whether the patients with mild damage should use this regimen or not.

On the other hand, the regimen of low-dose IV CYC has become more and more popular in recent years. Many studies have come to the conclusion that the effect of the low-dose therapy is comparable with the recommended high-dose regimen and with a considerably low incidence of infections [3, 11–13]. However, our results showed that the incidence of infections between the two groups had no notable differences. As indicated in Fig. 2, the level of 24-h urinary protein in both groups experienced a similar decrease after 1 year of treatment. But we also observed that there were cases in both groups whose 24-h urinary protein were not reduced to the

normal range, in spite of an obvious decrease after the treatment of 6 months. It revealed that the treatment duration of 6 months was not enough to control renal damage efficiently in neither of the groups. The relapse rate was high when CYC were ceased after 6 months of treatment reported by other studies. In our study, although we cut down the dose of CYC to 400 mg monthly after 6 months, the SILD regimen was still very effective in reducing the proteinuria and improving the renal function. In the meantime, the positive rate of anti-dsDNA antibody was reduced to 23.0 % (SILD group) and 18.8 % (HD group) after 6 months of therapy. After 1 year of treatment, the positive rate of anti-dsDNA antibody was continuously decreased to 12.4 % (SILD group) and 14.3 % (HD group), respectively. From our data, the SILD regimen seems to be more efficient in reducing the positive rate of anti-dsDNA antibody than the HD regimen.

Many studies have come up with several different regimens for remission-maintaining treatment followed by azathioprine (AZA), mycophenolate mofetil (MMF), and oral or IV CYC [5, 14–16]. And the MMF regimen seems to be the most effective one; however, there would be limitations in long-term using of MMF because of its high expense in developing countries. Based on our daily clinical observations, we concluded that it was essential for the SLE patients to receive an IV CYC regimen intermittently with better effect and lower relapse rate for more than 1 year, especially for those severe LN patients with dissatisfactory pathology type [17–23]. Therefore, we are planning to follow and administer these patients 400 mg every 2 or 3 months in order to reach the better effect, lower relapse rate, as well as to reduce the dose of prednisone as early as possible.

CYC is a cyclical non-specific alkylating agent, which inhibits DNA replication and initiates cell death. CYC may affect all the components of cellular and humoral immunity, and may reduce the production of immunoglobulins and the concentration of the immunoglobulins in the serum. It is very important to take into account the potential of bone marrow suppression caused by pulse therapy of CYC. In recent years, many studies have showed that CYC may cause leukopenia, thrombocytopenia, and erythropenia. The WBC count showed a saw-tooth pattern with IV CYC as it reached a nadir approximately 2 weeks following administration [24]. Our data showed that the SILD IV CYC would keep the WBC counts at relatively low levels. These findings provide strong evidence for the SILD IV CYC regimen, but we cannot infer the real changes of the lymphocyte function only owing to WBC of the peripheral blood, so further research is needed.

Gonadal toxicity remains an important issue contributing to significant physical and emotional consequences in young women patients with SLE. Studies have reported ovarian insufficiency in 10–83 % of female SLE patients treated with CYC, depending primarily on the subject's age at initiation of treatment and cumulative CYC dose [25–27]. Medeiros et al. showed that SLE patients treated with a cumulative CYC dose of greater than 10 g had a 3.2 times higher risk of developing ovarian insufficiency than patients receiving a cumulative dose lower than 10 g [28]. Our results showed that 28.6 % of patients with premature cessation of menses following high-dose CYC were consistent with previous reports. However, it was significantly lower in the SILD group. One explanation is the cumulative dose that is lower in the SILD group; another possibility is that the lower dosage in one administration may lead to lower toxicity in menstruation.

In conclusion, the efficacy of SILD IV CYC regimen in the treatment of LN is similar to that of the HD regimen, but the incidence of menstrual disturbances, gastrointestinal adverse effects, and leukopenia is much lower in the SILD IV CYC group than the standard therapeutic regimen.

Acknowledgments We thank all the patients, doctors, and nurses who took part in this study.

Disclosures None.

References

1. Cameron JS (1999) Lupus nephritis. J Am Soc Nephrol 10:413–424
2. Donadio JV Jr, Holley KE, Ferguson RH, Ilstrup DM (1978) Treatment of diffuse proliferative lupus nephritis with prednisone and combined prednisone and cyclophosphamide. N Engl J Med 299:1151–1155
3. Houssiau FA, Vasconcelos C, D'Cruz D et al (2002) Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 46:2121–2131
4. Mok CC, Ho CT, Chan KW, Lau CS, Wong RW (2002) Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. Arthritis Rheum 46:1003–1013
5. Yee CS, Gordon C, Dostal C et al (2004) EULAR randomised controlled trial of pulse cyclophosphamide and methylprednisolone versus continuous cyclophosphamide and prednisolone followed by azathioprine and prednisolone in lupus nephritis. Ann Rheum Dis 63:525–529
6. Hochberg MC (1997) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725
7. Balow JE, Boumpas DT, Fessler BJ, Austin HA 3rd (1996) Management of lupus nephritis. Kidney Int Suppl 53:S88–S92
8. Chan TM, Li FK, Tang CS et al (2000) Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 343:1156–1162
9. Chan TM, Li FK, Wong RW, Wong KL, Chan KW, Cheng IK (1995) Sequential therapy for diffuse proliferative and membranous lupus nephritis: cyclophosphamide and prednisolone followed by azathioprine and prednisolone. Nephron 71:321–327
10. Boumpas DT, Austin HA 3rd, Vaughn EM et al (1992) Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 340:741–745

11. Martin-Suarez I, D'Cruz D, Mansoor M, Fernandes AP, Khamashta MA, Hughes GR (1997) Immunosuppressive treatment in severe connective tissue diseases: effects of low dose intravenous cyclophosphamide. Ann Rheum Dis 56:481–487
12. Stojanovich L, Stojanovich R, Kostich V, Dzjolich E (2003) Neuropsychiatric lupus favourable response to low dose i.v. cyclophosphamide and prednisolone (pilot study). Lupus 12:3–7
13. Houssiau FA, Vasconcelos C, D'Cruz D et al (2004) Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. Arthritis Rheum 50:3934–3940
14. Takada K, Illei GG, Boumpas DT (2001) Cyclophosphamide for the treatment of systemic lupus erythematosus. Lupus 10:154–161
15. Mok CC, Ho CT, Siu YP et al (2001) Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide-containing regimens. Am J Kidney Dis 38:256–264
16. Dooley MA, Jayne D, Ginzler EM et al (2011) Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med 365:1886–1895
17. Pistiner M, Wallace DJ, Nessim S, Metzger AL, Klinenberg JR (1991) Lupus erythematosus in the 1980s: a survey of 570 patients. Semin Arthritis Rheum 21:55–64
18. Lee P, Urowitz MB, Bookman AA et al (1977) Systemic lupus erythematosus. A review of 110 cases with reference to nephritis, the nervous system, infections, aseptic necrosis and prognosis. Q J Med 46:1–32
19. Wallace DJ, Podell T, Weiner J, Klinenberg JR, Forouzesh S, Dubois EL (1981) Systemic lupus erythematosus—survival patterns. Experience with 609 patients. JAMA 245:934–938
20. Esdaile JM, Levinton C, Federgreen W, Hayslett JP, Kashgarian M (1989) The clinical and renal biopsy predictors of long-term outcome in lupus nephritis: a study of 87 patients and review of the literature. Q J Med 72:779–833
21. Gruppo Italiano per lo Studio della Nefrite Lupica (GISNEL) (1992) Lupus nephritis: prognostic factors and probability of maintaining life-supporting renal function 10 years after the diagnosis.
22. Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE (1994) Predicting renal outcomes in severe lupus nephritis: contributions of clinical and histologic data. Kidney Int 45:544–550
23. Lim CS, Chin HJ, Jung YC et al (1999) Prognostic factors of diffuse proliferative lupus nephritis. Clin Nephrol 52:139–147
24. Ong LM, Hooi LS, Lim TO et al (2005) Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrol (Carlton) 10:504–510
25. Katsifis GE, Tzioufas AG (2004) Ovarian failure in systemic lupus erythematosus patients treated with pulsed intravenous cyclophosphamide. Lupus 13:673–678
26. Huong DL, Amoura Z, Duhaut P et al (2002) Risk of ovarian failure and fertility after intravenous cyclophosphamide. A study in 84 patients. J Rheumatol 29:2571–2576
27. Harward LE, Mitchell K, Pieper C, Copland S, Criscione-Schreiber LG, Clowse ME (2013) The impact of cyclophosphamide on menstruation and pregnancy in women with rheumatologic disease. Lupus 22:81–86
28. Medeiros MM, Silveira VA, Menezes AP, Carvalho RC (2001) Risk factors for ovarian failure in patients with systemic lupus erythematosus. Braz J Med Biol Res 34:1561–1568