ORIGINAL ARTICLE

Efficacy and Treatment-Related Complications of Low-Dose Versus Moderate-Dose Cyclophosphamide in the NIH Protocol in Initial Therapy of Proliferative Lupus Nephritis: A Retrospective Cohort Study

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Background: The National Institute of Health (NIH) regimen is established as the standard of care for induction therapy in cases of proliferative lupus nephritis (pLN). However, due to the variability of doses utilized in intravenous cyclophosphamide (CYC) treatment, ranging from 0.5 to 1 g/m^2, the differences between low and moderate doses of CYC in the NIH regimen have not been thoroughly examined.

Objection: The authors aimed to assess and compare the renal outcomes associated with low-dose and moderate-dose in the NIH regimen for the induction treatment of pLN.

Materials and Methods: A historical cohort study was conducted involving adult patients diagnosed with systemic lupus erythematosus with pLN, who underwent treatment according to the NIH regimen and were monitored for a minimum one year, from January 2015 to June 2021. Treatments were classified into two groups; (1) L-CYC with doses between 0.5 to 0.6 g/m^2; and (2) M-CYC, with dose of 0.6 to 0.75 g/m^2. Renal outcomes were compared between treatment groups, including rate of remission (complete and partial), time to remission, and complications.

Results: In the present study, 83 patients were included, 43 receiving L-CYC and 40 receiving M-CYC, with respective average doses of 0.52 g/m^2 and 0.69 g/m^2. At 12 months, there was no difference in renal remission rate between the two groups (90% in L-CYC vs. 92.5% in M-CYC, p=0.087). However, the time to remission in the M-CYC group was slightly shorter compared to the L-CYC group (6.5 vs. 7.3 months, p=0.19). Additionally, complication rates were found to be similar in both groups.

Conclusion: The efficacy of induction treatment for pLN with both L-CYC and M-CYC was comparable at one year. However, M-CYC may be considered the preferred initial therapy for pLN, as it was associated with a shorter time to remission without any difference in treatment-related complication rates.

Keywords: Cyclophosphamide; Lupus nephritis; Remission rate; Complication; Systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) is a connective tissue disease characterized by multi-systems involvement, predominantly affecting women of childbearing age. Renal involvement, known as lupus nephritis (LN), is a common presentation occurring in approximately 30% to 50% of SLE patients. Furthermore, LN represents a significant contributor to both morbidity and mortality within SLE patients[1,2]. According to the 2003 classification by the International Society of Nephrology/Renal Pathology Society (ISN/RPS), LN is classified into six classes, designated as I-VI[3]. Non-proliferative forms of LN include classes I, II and V, while, proliferative classes include classes III, IV and a mix of LN III or IV with class V. Proliferative classes are characterized by more pronounced inflammation and more significant potential to progress to end-stage kidney disease compared to non-proliferative classes[2,4].

The management of proliferative LN consists of two

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phases: induction and maintenance phase. The primary objective of therapy is to achieve clinical and renal remission and prevent disease relapse[1,5]. For cyclophosphamide, both the National Institute of Health (NIH) regimen, which involves six doses of intravenous cyclophosphamide (CYC) ranging from 0.5 to 1 g/m^2 monthly, and the Euro-Lupus Nephritis Trial (ELNT) regimen, comprising six doses of CYC (fixed 500 mg) intravenously administered biweekly, have been established as a standard-of-care protocol for LN induction[5,6]. Although current evidence shows the reduced-dose CYC (ELNT regimen) equivalent efficacy to the NIH regimen, the present study was performed mainly in White patients[6,7]. Moreover, the NIH regimens have been used in diverse ethnic populations and for all levels of disease severity[8,9]. Thus, the NIH regimen is the preferred agent for managing severe LN or aggressive disease.

CYC is an alkylating agent, and it is widely recognized that the administration of CYC is linked to dose-related risks such as cytopenia, infections, malignancy, and gonadal toxicity, which are particularly relevant in women of childbearing age. Consequently, modifications to the drug dosage have been implemented to mitigate its toxicity[10-12] or replaced by other immunosuppression agents such as mycophenolate mofetil or tacrolimus. Nonetheless, starting the initial treatment of LN, one should carefully consider between benefits and risks of disease progression and adverse events[5].

Induction therapy utilizing a modified NIH regimen, which administers a fixed dose 500 mg or 0.5 to 0.75 g/m^2 of CYC monthly, is adopted by medical centers to minimize cumulative exposure and reduce the risk of adverse events[10,13]. However, limited data exist regarding the comparative efficacy and adverse event profiles between a low-dose (0.5 to 0.6 g/m^2) and moderate-dose (0.6 to 0.75 g/m^2) CYC in modified NIH regimen. Thus, our study aimed to compare the efficacy and treatment-related complications of low-dose (L-CYC) and moderate-dose of CYC (M-CYC) in the induction phase of patient with proliferative LN.

Materials and Methods

This retrospective cohort study was conducted at a tertiary university hospital in Thailand. The inclusion criteria comprised adult SLE patients with proliferative LN, with or without biopsy-proven, who had undergone treatment with the NIH regimen for induction. The study period was between January 2014 and December 2020 with a follow-up period at least 1 year after the 6th dose of CYC induction therapy. Patients with loss of medical records, a history of kidney transplantation, and incomplete induction therapy were excluded from the present study.

Patient baseline demographic data, clinical features, laboratory results, medication, treatment regimen, and clinical outcomes were reviewed. Clinical data included age, sex, body weight, height, blood pressure, renal pathology, and extrarenal manifestations such as autoimmune hemolytic anemia. Laboratory results included complete blood count, BUN, serum creatinine, cholesterol, serum albumin, serum complement, urinalysis, and urine protein creatinine ratio. Clinical outcomes were categorized as complete remission or partial remission at 12 months. Treatment-related complications were recorded. The operating definitions used in this study are as follows:

Operational definitions

Adult SLE patients were defined as individuals aged 18 years old or over who the diagnosis criteria for SLE according to the American College of Rheumatology (ACR) criteria[14], Systemic Lupus International Collaborating Clinics (SLICC) criteria, or the new 2019 European League Against Rheumatism (EULAR) classification criteria[15].

Proliferative LN is defined as LN class III, IV, or a combination of class III or IV plus V according to ISN/RPS classification.

The estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2 is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Low-dose CYC is defined as induction average CYC dose between 0.5 to 0.6 g/m^2.

Moderate-dose CYC is defined as induction average CYC dose of 0.6 to 0.75 g/m^2.

Complete remission (CR) is defined as the return of serum creatinine to previous baseline level, along with a decline in urine proteinuria to <500 mg/day or urine protein creatinine ratio (UPCR) <0.5 g/g.

Partial remission (PR) is defined as an improvement in serum creatinine levels, although not returning to normal, along with a ≥50% decrease in UPCR. In case of nephrotic range proteinuria, improvement requires a ≥50% reduction in UPCR and UPCR <3 g/g.

Non-response (NR) is defined as UPCR >3 g/g and/or no improvement in serum creatinine levels.

Treatment-related complications are defined as any infections occurring during CYC treatment, including lung infection, gastrointestinal infection, urinary tract infection, mucocutaneous infection, and central nervous system infection, occurring within 12 months of treatment.

Statistical analysis

Descriptive data were expressed as percentages. The χ^2 or Fisher's exact test was used to compare categorical data between the two groups, as appropriate. Continuous variables were expressed as mean ± standard deviation or median (interquartile range, IQR) and compared between groups using the t-test or Mann-Whitney U test, as

appropriate. The probabilities of complete remission and partial remission were estimated using the Kaplan–Meier method and differences median time to remission between groups were assessed with the log-rank test.

The subsequent backward multivariate analysis included factors with $p<0.25$ by univariate Cox regression analysis as well as clinically important factors. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using STATA version 14.1 (College Station, Texas, USA).

Ethics approval and consent

This study was approved by the Khon Kaen University Ethics Committee of Khon Kaen University (No. HE641012). Due to the retrospective nature of the study, informed consent from the participants was not required, and the research posed no more than minimal risk to them. Patient data were maintained confidentially.

Results

Baseline patient characteristics

In the present study, 83 patients were included and divided into the L-CYC group (n=43) and M-CYC group (n=40). The overall mean age was 32.3±1.4 years. Females accounted for more than 80% of the patients and thirty-six (43.4%) were newly diagnosed with SLE with LN. Most patients underwent kidney biopsy, and approximately 70% of patients were classified as LN class IV. Patient characteristics and clinical data based on CYC dose are compared in Table 1. There was no significant difference in patient characteristics between the two groups, except for age and body weight, body surface area and the receiving of renin-angiotensin-aldosterone blockade.

Laboratory results and treatment profiles

In both the L-CYC and M-CYC groups, no significant differences were observed in hemoglobin levels, white blood cell count, or platelet count. However, In the L-CYC group, BUN tended to be higher and eGFR tended to be lower compared to the M-CYC group.

Parameters such as hypocomplementemia, active urinary sediment (including proteinuria or UPCI, maximum urinary RBC per high-power field), serum albumin, and cholesterol did not show significant differences between patients receiving L-CYC and those receiving M-CYC. The use of prior immunosuppressive agents, including CYC, mycophenolic acid, and calcineurin inhibitor did not differ between the two groups. However, a higher proportion of patient in the M-CYC group (82.5%) received angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB). The use of hydroxychloroquine (HCQ) and Trimethoprim/Sulfamethoxazole (TMP/SMX) were common among most patients in the study and was similar between both groups. All of this data is presented in Table 1.

Treatment outcomes

In the present study, there were 43 patients in the L-CYC group and 40 in the M-CYC group, with mean dosages of 0.52 g/m^2 and 0.69 g/m^2, respectively. The primary endpoint comparison between the two groups was illustrated using Kaplan-Maier curve with 6 and 12 months of follow-up for CR (Figure 1A) and both CR and PR (Figure 1B). No statistical significance was observed the two groups in CR ($p=0.16$) and both CR and PR ($p=0.08$). The M-CYC group tended to exhibit an earlier time-to-remission at 6 months of follow- up and showed a higher rate of CR (66.7%) and both CR and PR (85%). At 12 months, the L-CYC and M-CYC groups showed similar rated of CR and both CR and PR. However, a higher proportion of patients achieved CR and PR at 12 months of follow-up in the M-CYC group (92.5%) compared to those in the L-CYC group (87%), consistent with the results obtained from statistical analysis as shown in Table 2. In addition, the median time to remission in the M-CYC group was slightly shorter compared to the L-CYC group (6.5 vs. 7.3 months, $p=0.19$).

Treatment outcomes of lupus nephritis

In multivariate analysis, two factors significantly associated with both CR and PR in both groups were female (HR=2.96, 95% CI; 1.32 to 6.63) and newly diagnosed SLE/LN (HR=1.89, 95% CI; 1.08 to 3.32) as shown in Table 3. AIHA, eGFR, proteinuria and receiving moderate-dose CYC were not associated with CR and PR. We conduced a multivariate analysis of factors include gender, newly diagnosed SLE/LN, AIHA, eGFR, proteinuria, urinary RBC >20/hpf, and CYC (moderate dose) which may involve our primary outcome.

Treatment-related complications

In terms of secondary outcomes, treatment-related complications including infections occurring during CYC treatment (including respiratory infection, GI infection, urinary tract infection, mucocutaneous infection and CNS infection), and leukopenia did not differ between the L-CYC and M-CYC groups. The number of events over 12 months in the L-CYC and M-CYC regimens were 28 and 22, respectively ($p=0.139$). The third most common cause was urinary tract infection, upper respiratory infection and lower urinary tract infection (Table 4).

Discussion

Lupus nephritis is major organ involvement in patients with SLE and is notably associated with elevated morbidity

Table 1. Baseline patient characteristics

Parameters	Overall (n=83)	L-CYC (n=43)	M-CYC (n=40)	p-value
Age (years): mean± SD	32.3±1.4	35.6±13.5	28.8±10.9	0.007*
Gender (female): n (%)	73 (87.9)	36 (83.7)	37 (92.5)	0.22
Body weight (kg): mean ± SD	57±10.7	59.4±11.8	54.4±8.8	0.01*
BSA (kg/m^2): median (IQR)	1.55 (1.44 to 1.67)	1.57 (1.49 to 1.76)	1.54 (1.42 to 1.62)	0.04*
New diagnosis SLE: n (%)	36 (43.4)	19 (44.2)	17 (44.5)	0.87
Autoimmune hemolytic anemia	46 (55.4)	20 (46.5)	26 (65)	0.09
Muco-cutaneous lesion	39 (34.9)	14 (32.6)	15 (37.5)	0.64
Biopsy proven LN: n (%)	52 (62.6)	27 (62.8)	25 (62.5)	0.97
Class III ±V: n (%)		8 (30.67)	6 (24)	
Class IV ±V: n (%)		18 (69.23)	19 (76)	
SBP (mmHg): mean ± SD	133.4±18.7	133.6±18.5	133.4±19.1	0.54
DBP (mmHg): mean ± SD	80.3±13.4	78.6±14.1	81.7±12.7	0.82
Laboratory results:				
Hemoglobin(g/dL): mean ± SD	10.6±1.9	10.5±1.9	10.8±2.0	0.74
WBC (x103 cell/mm^3): mean ± SD	9.63±4.51	8.62±4.38	10.70±4.45	0.98
Platelet (x103 cell/mm^3): mean ± SD	258±103	250±99	266±107	0.75
BUN (mg/dL): median (IQR)	20 (13 to 33)	23 (16 to 38)	16 (12 to 27)	0.06
Serum creatinine (mg/dL): median (IQR)	0.9 (0.7 to 1.5)	1.0 (0.7 to 1.78)	0.84 (0.7 to 1.18)	0.12
eGFR (ml/min. 1.73 m^2): median (IQR)	79 (47 to 115)	72 (38 to 116)	92 (65 to 14)	0.07
Cholesterol (mg/dL): mean ± SD	292±117	303±131	281±100	0.21
Serum albumin (g/dL): mean ± SD	2.85±0.79	2.79±0.70	2.92±0.88	0.75
Low C3 and, or C4 levels: n (%)	57/75 (76)	29/39 (74.4)	28/36 (77.8)	0.72
Proteinuria (g/day) or UPCI: median (IQR)	3.5 (2 to 5.7)	4.2 (2 to 5.9)	2.9 (2 to 5.7)	0.49
Maximum urinary RBC/HPF (IQR)	10 (5 to 30)	10 (5 to 30)	10 (3 to 20)	0.26
Prior immunosuppression: n (%)				
Cyclophosphamide	15 (18.0)	11 (25.6)	4 (10.0)	0.06
Mycophenolic acid	31 (37.3)	12 (27.9)	19 (47.5)	0.06
Calcineurin inhibitor	9 (10.9)	3 (7.14)	6 (15.0)	0.25
Received ACEI/ARB	58 (69.9)	25 (58.1)	33 (82.5)	0.01*
Received HCQ	74 (90.2)	39 (92.7)	35 (87.5)	0.41
Received PJP prophylaxis	65 (78.3)	31 (72)	34 (85)	0.15
Dialysis needed	2 (2.4)	2 (4.7)	0	0.16

*p<0.05

ACEI=angiotensin-converting enzyme inhibitors; ARB=angiotensin receptor blockades; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; HCQ=Hydroxychloroquine; HPF=high power fields; PJP=Pneumocystis jiroveci pneumonia; RBC=red blood cell; SBP=systolic blood pressure; UPCI=urine protein creatinine index

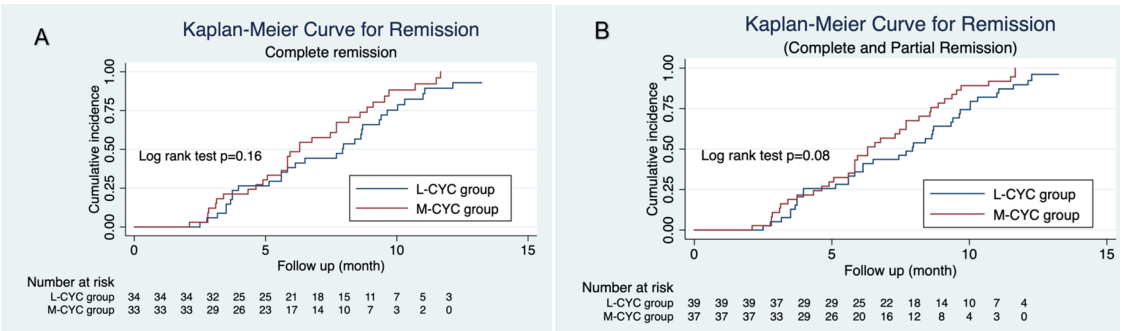

Figure 1. Kaplan-Meier curve for complete remission among lupus nephritis patients according to treatment groups. The log-rank test was used for analysis. There was no statistical significance in complete renal remission, with a p=0.16 (A), and combined complete and partial renal remission, with a p=0.08 (B), between the Low dose of cyclophosphamide (L-CYC) and Moderate dose of cyclophosphamide (M-CYC) groups.

Table 2. CR and both CR and PR in L-CYC Versus M-CYC at 6 months and 12 months

Efficacy	At 6 months			At 12 months		
	L- CYC	M- CYC	p-value	L- CYC	M-CYC	p-value
Complete remission	13 (52.0%)	16 (66.7%)	0.30	30 (69.7%)	31 (77.5%)	0.42
Complete & partial remission	14 (70.0%)	17 (85%)	0.25	37 (87.0%)	37 (92.5%)	0.34

L-CYC=low dose of cyclophosphamide; M-CYC=moderate dose of cyclophosphamide

Table 3. Univariate and multivariate analysis for complete and partial remission

Variables	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Gender (female)	1.89 (0.93 to 3.83)	0.07	2.96 (1.32 to 6.63)	0.008*
Age (year)	0.99 (0.97 to 1.01)	0.73		
New diagnosis SLE or LN	1.44 (0.90 to 2.29)	0.12	1.89 (1.08 to 3.32)	0.02*
Autoimmune hemolytic anemia	1.19 (0.75 to 1.89)	0.46	0.86 (0.49 to 1.49)	0.59
Serum creatinine (mg/dL)	0.93 (0.76 to 1.12)	0.43		
eGFR (ml/min/1.73 m^2)	1.00 (0.99 to 1.01)	0.63	1.00 (0.91 to 1.00)	0.74
Serum albumin (g/dL)	0.92 (0.67 to 1.24)	0.59		
Proteinuria (g/day)/UPCI	0.98 (0.90 to 1.07)	0.73	0.99 (0.91 to 1.09)	0.96
Urinary RBC >20/hpf	1.35 (0.82 to 2.22)	0.23	1.17 (0.67 to 2.05)	0.57
Normal complement	0.88 (0.50 to 1.55)	0.67		
Cyclophosphamide (moderate dose)	1.49 (0.94 to 2.38)	0.09	1.27 (0.71 to 2.24)	0.41

* $p<0.05$

LN=lupus nephritis; RBC=red blood cell; SLE=systemic lupus erythematosus; UPCI=urine protein creatinine index

Table 4. Number of treatment-related complications

Complications	L- CYC (n=43)	M-CYC (n=40)	Total
Urinary tract infection	13	10	26
Upper respiratory infection	3	3	6
Bacterial Pneumonia	3	1	4
Cellulitis	2	2	4
Gastrointestinal infection	2	1	3
Septicemia	0	1	1
Pulmonary tuberculosis	0	1	1
Leukopenia	5	3	8

and mortality rates, particularly among patients progressing to ESKD[16]. The primary objective of LN treatment is to induce renal remission and prevent relapse while minimizing complications associated with immunosuppressive therapy[1,2,5]. Our study compares the efficacy of low dose (0.5 to 0.6 g/m^2) and moderate dose (0.6 to 0.75 g/m^2) of cyclophosphamide in the modified NIH regimen for induction therapy of proliferative LN.

Our findings found that there was neither a statistically significant difference in CR and PR rates at 6 and 12 months of follow-up, nor in complication rates between the two groups. However, the M-CYC group, the mean dosage 0.69 g/m^2, demonstrated a trend toward earlier time-to-remission (6.3 vs. 7.5 months, p=0.09). The M-CYC group exhibited a higher CR rate and overall remission at 6 months after initial treatment compared to the L-CYC group, the mean dosage 0.52 g/m^2 (66.7% vs. 52%, and 70% vs. 85%, respectively). These finding are comparable with a prior study by Sigdel MR et al., which included patients with LN class III, IV, or mixed class V, similar to the present study, and reported a complete remission rate of 44% to 53.7% and an overall remission 82.9% of at 6 months with a fixed dose of 500 mg and 0.5 to 0.75 g/m^2 of cyclophosphamide monthly regimens[13]. In addition, the remission rate is quite similar with the efficacy of induction with mycophenolate mofetil which demonstrated by the Aspera Lupus Management Study (ALMS) group[8].

Clinical predictors indicative of ESKD development in lupus patients include male gender, concurrent with diabetes mellitus and hypertension, a low educational level, nephrotic range proteinuria, ineffective immunosuppressive agents, elevated serum creatine at the time of biopsy, absence of renal remission and repeat nephritis flares[17-20]. Based on the results, the M-CYC group, the response of induction to remission therapy is probably earlier than the L-CYC group. However, there is no statistical significance, In addition, the previous studies demonstrated initial response, which means remission by 6 months, as a predictor for favorable long-term renal outcomes[20-22]. Taken together, A moderate dose of cyclophosphamide in NIH regimen may be considered as induction therapy in proliferative LN in clinical practice generally.

Regarding the baseline patient characteristics, although the M-CYC group was younger, the difference may not be clinically significant, as all patients were adults. Similarly, while the M-CYC patients had a lower mean body weight, there is no evidence suggesting body weight influences the renal outcomes of proliferative LN. Notably, the majority of patients were female, consistently with generally observed female predominance in SLE cases, with female-to-male ratio of approximately 9:1[19,23]. ACEI and ARB are considered adjunctive management options as antiproteinuric drugs in LN.(5) Additionally, a previous study demonstrated that ACEIs/ARB reduced the risks of cardiovascular disease in patients with SLE[24]. In our study, although there was a significantly higher user rate of ACEI/ARB in the M-CYC group at 82.5% compared to 52.1% in L-CYC group, the effect of this medication in decreasing proteinuria may not directly influence the achievement of remission in LN.

At the 12 months, the complete remission rate in the M-CYC group and the L-CYC group increased to 77.5% vs. 70%, respectively, indicating some LN patient may require more than 6 months after initiating therapy to achieved remission. Therefore, clinicians should consider treatment response based on the trend of proteinuria improvement over time rather than rely on a single proteinuria value at a specific time. In multivariate analyses, newly diagnosed SLE with LN, classified as early onset LN, and female gender, are favorable factors associated with achieving CR and PR. This suggested that early onset of LN represents a positive prognostic factor for proliferative LN during induction therapy, while male gender is indicative of a potentially poorer prognosis. Previous studies have shown that delayed-onset LN is a risk factor for the relapse of LN[25]. Therefore, early onset LN serves not only as a reliable predictor for achieving renal remission but also as a predictor for the disease-free relapse.

For treatment-related complications, infection is an important concern in the management of LN treatment, with available data indicating notable variation of prevalence and clinical outcomes depending on factors such as the choice of immunosuppressive drugs, dosage and patient susceptibility including age, race, comorbidities[26]. Mehra S et al. demonstrated the overall incidence of adverse events and infections did not show a statistically significant difference between the groups receiving intravenous cyclophosphamide at a dosage of 500 mg monthly and 0.75 g/m^2 monthly[9]. Consistent with their findings, our study similarly observed no significant difference in overall treatment-related complications between low-dose and moderate-dose cyclophosphamide induction.

Our research represents the first study to investigate the efficacy of low and moderate doses of cyclophosphamide within the NIH protocol for induction therapy of proliferative LN. According to the ALMS trial, intravenous CYC, the median total dosage of CYC per infusion in the Asian were 0.785 g/m^2[8]. Thus, our findings suggest that moderate dose with approximately 0.7 g/m^2 of intravenous cyclophosphamide might be considered an appropriate dosage for induction proliferative LN in Asians. However, concerning the cumulative dose of CYC in some patients, i.e., younger patients with relapse proliferative LN, which cause gonadal toxicity and increases the potential risk of malignancy, the use of low dose of cyclophosphamide in NIH regimen sometimes should be considered with caution in delayed renal remission.

The present study has some limitations. Firstly, there were variations in certain baseline patient characteristics between two groups. Secondly, the pesent study population was relatively small, which may have impacted the statistical analysis. Further data collection with larger sample size would enhance the robustness of the findings. Thirdly, the retrospective nature of the present study and reliance on chart reviews introduce the potential for bias, including incomplete documentation in medical records or information bias. A prospective study would provide more reliable data. Finally, long-term complications such as gonadal toxicity and malignancy were not assessed.

Conclusion

The present study indicated that the efficacy of induction therapy for proliferative LN using both low and a moderate dose of cyclophosphamide within NIH regimen was comparable at one year. However, induction with a low dose of cyclophosphamide showed a tendency for slower remission. These results suggest that commencing therapy with a moderate dose of cyclophosphamide may be preferred for proliferative LN, as it could accelerate time-to-remission without increasing of treatment-related complications.

What is already known on this topic?

The NIH regimen, with an IVCY dose of 0.5 to 1 g/m^2, is the standard of care for induction therapy in cases of proliferative lupus nephritis. A modified NIH regimen, which administers 0.5 to 0.75 g/m^2 of CYC monthly, is commonly used in clinical practice to mitigate adverse events and cumulative dose.

What this study adds?

Moderate doses of 0.6 to 0.75 g/m^2 of cyclophosphamide in the NIH regimen are associated with a shorter time to remission without any difference in treatment-related complication rates, compared to low doses (0.5 to 0.6 g/m^2). Therefore, they may be considered the preferred initial therapy for proliferative lupus nephritis.

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Conflicts of interest

The authors declare no conflict of interest.

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