Low- Versus High-dose Cyclophosphamide in Class III/IV Lupus Nephritis: A Retrospective Study from South Asia

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Abstract

Introduction: The comparative efficacy of low-dose cyclophosphamide (LD-CYC) and high-dose cyclophosphamide (HD-CYC) for treatment of lupus in South Asians is not well established. We aimed to compare treatment outcomes in South Asian patients with class III and IV lupus nephritis treated with either regimen. **Method:** This was a single-center, retrospective study conducted in Sri Lanka. Patients with biopsy-proven class III or IV lupus nephritis were recruited. The HD-CYC group was defined as having received ≥6 doses of 0.5–1 g/m^2 cyclophosphamide (CYC) followed by quarterly doses. The LD-CYC group was defined as having received six doses of 500 mg CYC at two-weekly intervals. The primary outcome was treatment failure defined as persistent nephrotic range proteinuria or renal impairment at 6 months. **Results:** Sixty-seven patients were recruited (HD-CYC 34, LD-CYC 33), all South Asian ethnicity. The HD-CYC group had received treatment between 2000 and 2013, and the LD-CYC group from 2013 onward. The HD-CYC and LD-CYC groups had 30/33 (90.9%) and 31/34 (91.2%) females, respectively. Nephrotic syndrome and nephrotic range proteinuria on presentation were seen in 22/33 (67%) and 20/32 (62%) in the HD-CYC and LD-CYC groups, respectively, and renal impairment was seen in 5/33 (15%) of the HD-CYC group and 7/32 (22%) of the LD-CYC group ($P > 0.05$). Treatment failure and complete or partial remission occurred in 7/34 (21%) and 28/34 (82%), respectively, of HD-CYC and 10/33 (30%) and 24/33 (73%), respectively, of LD-CYC ($P > 0.05$). Adverse events rates were similar. **Conclusion:** This study suggests that LD-CYC and HD-CYC induction is comparable in South Asian patients with class III and IV lupus nephritis.

Keywords: *Cyclophosphamide, high dose, low dose, lupus nephritis, South Asia, systemic lupus erythematosus*

Introduction

Lupus nephritis (LN) is one of the poorest prognostic factors in systemic lupus erythematosus (SLE).[1] Ethnic differences in prevalence and outcomes suggest that multiple biological and sociological factors contribute to the disease course. Asian SLE patients are known to have a higher incidence of renal involvement and more severe disease.[2] A combination of steroids and cyclophosphamide (CYC) is the gold-standard in treatment of LN with high disease activity.[3]

The Euro-Lupus Nephritis trial (ELNT), which was a European-based multicenter, prospective, randomized study, compared the then standard treatment of high-dose (HD) intravenous (IV) CYC and low-dose (LD) IV CYC as remission-inducing therapy in proliferative LN.[4,5] The study showed no difference in the rates of renal remission, treatment failure, or severe flares and a nonsignificant trend toward a reduction in adverse effects.[5] However, the patients included in the ELNT study were predominantly white Caucasians. The comparative efficacy of LD CYC in Asian populations has not been well investigated.[6] In particular, data from South Asian populations is scant. A recent systematic review from China suggests that both HD and LD regimens have similar efficacy outcomes.[7] However, data from a retrospective study done among Puerto Ricans and a prospective study among Indians showed poorer renal outcomes in patients treated with LD CYC.[8,11] While alternate treatment options such as mycophenolate and

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calcineurin inhibitors are becoming more popular, CYC is still commonly used, partly due to its lower cost.

The objective of our study was to compare the efficacy of LD- and HD-CYC in our population. The University Medical Unit, National Hospital of Sri Lanka, has been managing patients with LN since the 1980s. This cohort of patients includes those who received HD-CYC in accordance with the original National Institute of Health (NIH) trials and the evidence of Boumpas *et al*., [3,4] as well as those treated with LD CYC from 2013 onward, as in the ELNT.

Materials and Methods

The study was a single-center, retrospective, comparative study conducted in the University Medical Unit of the National Hospital of Sri Lanka. Patient data was collected between May 2017 and March 2020. The objective of the study was to compare the outcomes of LD-CYC and HD-CYC when used as induction therapy for class III and IV LN.

Outcome definitions

Outcomes were defined as follows:[5]

Treatment failure was defined as.

Absence of primary response to treatment within 6 months (primary outcome).

a. For those with a baseline serum creatinine (SCr) ≥1.3 mg/dl but ≤2.6 mg/dl, failure of the SCr to decrease to <1.3 mg/dl at 6 months
b. For those with a baseline SCr ≥2.6 mg/dl, failure of the SCr to improve by 50% at 6 months
c. For those with baseline 24-h urinary protein excretion ≥3 g/d, but with SCr <1.3 mg/dl, persistence of proteinuria ≥3 g/d at 6 months.

Severe renal flares were defined as

a. Renal impairment: An SLE-related sustained increase of >33% in S.Cr within a 1-month period after remission OR
b. Increase in proteinuria: Recurrence or appearance of 24-h urinary protein excretion ≥3 g.

Severe systemic flares were defined as cerebral lupus, thrombocytopenia <100,000/µl, hemolytic anemia, lupus pneumonitis, lupus myocarditis, extensive cutaneous vasculitis, or serositis requiring treatment with steroids equivalent to 1 mg/kg/d prednisolone or more or requiring a more aggressive nonsteroid-based immunosuppression.

For our analysis, data regarding flares and doubling of S.Cr over the lowest value reached during the period of follow-up were not counted as treatment failures. Complete remission (CR) was defined as proteinuria <1 g/d with inactive urine sediments and improved or stable renal functions. Partial remission (PR) was defined as a >50% decrease in proteinuria to <3 g/d with stable renal functions.

Inclusion and exclusion criteria

The inclusion criteria for the study were as follows (essential):[5]

1. Age ≥14 years
2. Biopsy-proven proliferative LN of class III or IV (±V) classification (World Health or International Society of Nephrology/Renal Pathology Society (ISN/RPS)
3. Proteinuria ≥500 mg in 24 h or urine protein creatinine ratio (UPCR) >0.5 mg/mg prior to induction of treatment
4. Received LD-CYC regimen for induction of treatment
   - Three daily pulses of 500–1000 mg of IV methylprednisolone, followed by oral glucocorticoid therapy at an initial dosage of 0.5–1 mg/kg/d of prednisolone (or equivalent) for 4 weeks tapered to doses of 5–7.5 mg/d during the maintenance phase AND
   - Six two-weekly doses of 500 mg of IV CYC
     OR HD-CYC
   - Three daily pulses of 500–1000 mg of IV methylprednisolone, followed by oral glucocorticoid therapy at an initial dosage of 0.5–1 mg/kg/d of prednisolone (or equivalent) for 4 weeks tapered to doses of 5–7.5 mg/d during the maintenance phase AND
     - Scheduled for eight or more IV CYC pulses within 1 year (six pulses given monthly, followed by two quarterly pulses at a starting dose of 0.5 g/m^2 of body surface area)
5. Patients should have been followed up for a minimum 6 months following the first dose of CYC, regardless of whether they received the LD regimen or the HD-CYC regimen.

Patients were categorized as LD-CYC or HD-CYC according to the treatment schedule received at the initial diagnosis. Outcomes were recorded only in relation to this first treatment regimen.

Sample size calculation

The sample size was calculated based on our primary objective to compare rates of treatment failure between the LD and HD groups. The sample size calculation relied on an expected failure rate of 15% for the HD treatment and a clinically acceptable margin of difference of 15% (i.e., a doubling of treatment failures was considered significant). These parameters were chosen based on the protocol of the ELNT.[5] Given a one-sided alpha error of 5% and keeping the statistical power to >80%, at least 33 patients were needed in one arm.[9]

All patients attending the rheumatology and renal clinics of the University Medical Unit of the National Hospital of Sri Lanka were assessed for suitability for recruitment. Sampling was by convenience sampling.

Data was collected retrospectively from the past medical records using an interviewer-administered data collection

form. This included data on the clinical, biochemical, and pathological features at presentation, clinical and biochemical responses to treatment, and adverse effects of treatment. Information was further corroborated by interview.

Continuous data was tested for normality using the Shapiro Wilk test. Parametric data was presented as mean ± standard deviation (SD) and nonparametric data as median with interquartile range (IQR). Qualitative or categorical variables were described as frequencies and percentages. For normally distributed data, means for the two groups were compared using Student's *t*-test. For nonparametric data, groups were compared using the Mann–Whitney U test or Kruskal–Wallis test, as appropriate. Proportions were compared using Chi-square (χ^2) test. Data was analyzed according to the treatment received, that is, HD- or LD-CYC.

A *P* value of <0.05 was accepted as statistically significant. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software (version 22).

Results

A total of 74 patients with class III and IV LN were considered for the study. Seven were excluded due to inadequate data or failure to meet the inclusion and exclusion criteria. Thirty-four had received HD-CYC and 33 had LD-CYC. The baseline characteristics of the two groups have been presented in in Table 1. The HD-CYC group had received treatment between 2000 and 2013, and the LD regimen comprised patients initiated on treatment between 2013 and 2019.

Clinical characteristics on presentation were similar between the two groups. Only one of the LD- group had class III LN compared to 7/34 having in the HD- group. Activity index on renal biopsy was available for 43 of 66 patients and the overall median for the sample was 9/24. Median activity index was higher in the LD-CYC group. Within treatment groups, 18/23 treated with the LD-CYC regimen as opposed to 7/20 treated with the HD-CYC had an activity index of greater than 9 and this difference was statistically different ($P < 0.005$). This implies more histologically active lupus in the LD group. The details regarding treatment received and outcomes are summarized in Table 2.

There was no significant difference between the numbers of patients affected by treatment failure (21% in the HD-CYC group vs. 30% in the LD-CYC group). Though fewer patients appeared to achieve remission (complete or partial) in the LD-CYC group (73% vs. 82%), this difference was not statistically different. To further improve comparability with the primary outcome of the LD group, we looked at a composite end point of absence of primary response, occurrence of severe renal flares within the first 2 years, and doubling of S.Cr over the lowest value achieved. There was no difference between the LD-CYC group (10/33) and the HD-CYC group (8/34) ($P = 0.3$). None of the clinical criteria or histological criteria correlated with treatment failure [Table 3]. Within the subgroup of patients with an activity index >9, 1/7 in the HD-CYC group compared to 7/18 in the LD-CYC group had treatment failure, but this difference did not reach significance ($P = 0.2$), perhaps due to inadequate numbers [Table 2].

Table 1: Baseline characteristics of patients with lupus nephritis included in the study

	High-dose cyclophosphamide treatment group (*n*=34)	Low-dose cyclophosphamide treatment group (*n*=33)	*P*
Age (years)	35 (29.5-40.5)	30 (27-37.5)	0.033*
Age at treatment (years)	24 (23.5-29)	28 (22-34)	0.008*
Females, *n* (%)	31 (91.2%)	30 (90.9%)	0.97
Renal histology (lupus class)	Class III- 7 Class IV- 27	Class III+V- 1 Class IV- 31 Class IV+V- 1	0.026*
Activity index (/24)	6 (3-12)	11 (7-13)	
Chronicity index (/12)	2 (1-2.25)	3 (1-4)	
Crescents (present)	6/17	14/23	0.12
Proteinuria, mg/24 h	3852 (2300-6210)	4100 (1492-6476)	0.57
Serum creatinine, mg/dl	0.85 (0.69-1.08)	0.95 (0.80-1.19)	0.92
Clinical presentation			
Nephrotic syndrome/nephrotic range proteinuria	23/33 (67%)	20/33 (61%)	0.72
Renal impairment	5/33 (15%)	7/32 (22%)	0.78
Hypertension	12/30 (40%)	10/30 (33%)	0.81
Active urinary sediment (>10 RBC/hpf)	17/32 (53%)	22/31 (71%)	0.34

NS=not significant, RBC=red blood cell. Continuous variables are presented as medians with interquartile range within parenthesis. Categorical data is presented as frequencies and percentages. *A *P*<0.05 was considered a significant difference between groups

Table 2: Comparison of treatment received and treatment outcomes in high-dose cyclophosphamide and low-dose cyclophosphamide treatment groups

	High-dose cyclophosphamide treatment group (*n*=34)	Low-dose cyclophosphamide treatment group (*n*=33)	*P*
CYC dose	750 mg (750-1000 mg)	500 mg	<0.0001
Number of pulses	6 (6-9) Maximum 18	6	<0.0001
Total CYC dose	4.5 g (4.5-7.75) Maximum 15 g	3 g	<0.0001
Maintenance			<0.02
MMF (*n*, dose)	20, 1.5 g/d (1.25-1.5)	31, 2 g/d (1.5-2)	
Azathioprine (*n*, dose)	14, 50 mg/d (25-62.5)	0	
Treatment failure (*n*, %)	7 (21%)	10 (30%)	0.46
Persistent renal impairment	1	1	0.20
Persistent nephrotic range proteinuria	6`	9	
Subgroup			
Activity index on biopsy >9	1 (*n*=7)	7 (*n*=18)	
Remission	28 (82.3%)	24 (72.7%)	0.64
Complete remission	26	24	
Partial remission	2	0	
Duration of follow-up (months)	134 (101-157)	25 (11-45)	<0.0001
Renal flare			
Nephrotic syndrome	10/34 (29.4%)	6/33 (18.2%)	0.63
One flare	6	6	0.50
Two flares	3	0	
Three flares	1	0	
Renal impairment	0/34	1/33 (3.2%)	
Non-renal flare (total)	7/34	5/33	
CNS	1/34	1/33	
ITP	4/34	2/33	
Hemolytic anemia	4/34	2/33	
Pneumonitis	0/34	1/33	
Myocarditis	0/34	0/33	
Skin	0/34	0/33	
Serositis	0/34	0/33	
Doubling of serum creatinine	1/34 (2.9%)	2/33 (3.2%)	0.71
End-stage kidney disease	2/34	1/33	0.53

CNS=central nervous system, CYC=cyclophosphamide, ITP=immune thrombocytopenia, MMF=mycophenolate mofetil, NS=not significant. Data of continuous variables is presented as medians with interquartile ranges in parenthesis. A *P*<0.05 was considered a significant difference between groups

The HD group in the ELNT trial received eight doses of CYC, the last two being quarterly doses. In our cohort, only 11 of 34 treated with the HD-CYC had received eight or more cycles.[5] Within the HD-CYC group, none of those receiving eight or more doses of CYC, compared to seven of those receiving less than eight doses of CYC, had treatment failure (P = 0.045). The difference in treatment failure rates did not appear to be significantly different between the LD-CYC group when compared with either the HD group that received ≥8 doses of CYC or the group that received less than eight doses. However, as numbers in these subgroups are small, results will need to be interpreted with caution.

Only 20 of the HD-CYC group received mycophenolate mofetil (MMF) as the maintenance therapy, as opposed to all the patients in LD-CYC. This likely reflects the change in choice of maintenance therapy over time.

The adverse effects within each treatment group are shown in Table 4. There appeared to be no difference in the number of significant side effects in either group. Nausea and vomiting appeared to be more in the HD-CYC group. Infections were observed among 10 of the HD-CYC group, three of whom had more than one episode of infection. One patient had experienced severe pneumonia requiring intensive care. Other infections included cystitis, tinea

Table 3: Association between clinical characteristics at presentation and treatment failure

	Treatment failure		*P*
	Yes	No	
Nephrotic syndrome			
Present	9	34	0.57
Absent	7	16	
Renal impairment			
Present	1	11	0.38
Absent	13	39	
Hypertension			
Present	4	18	0.82
Absent	9	28	
Active sediment			
Present	11	28	0.28
Absent	3	20	

P<0.05 was considered significant

Table 4: Adverse events experienced within two treatment groups

Adverse effect	High-dose cyclophosphamide treatment group (*n*=34)	Low-dose cyclophosphamide treatment group (*n*=33)
Infection	10	7
Cytopenias	1	2
Gonadotoxicity	5	5
Avascular necrosis of the hip	1	2
Diabetes mellitus	1	1
Ischemic cardiac disease	0	0
Nausea/vomiting	7	1
Hemorrhagic cystitis	0	0
Posterior reversible encephalopathy syndrome	0	2
Malignancy	0	0

corporis, onychomycosis, and multi-dermatomal shingles. Among the LD-CYC group, 7 experienced infections, with one experiencing two episodes of pyelonephritis. Infections among the others were pneumonia, shingles, and acute gastroenteritis.

Discussion

This study examined the hypothesis that HD-CYC and LD-CYC have similar outcomes in South Asian patients. Using retrospective data, it was suggested that both HD-CYC and LD-CYC therapies have comparable similar short-term outcomes in LN patients from a single center in Sri Lanka.

More than 62% of both groups in our cohort presented with nephrotic syndrome or nephrotic range proteinuria indicating severe disease, like the rates of nephrotic syndrome seen in the NIH cohorts.[4] Within our cohort, histological activity was more severe in the LD-CYC group and may reflect changes in CYC usage over time. Despite these differences in histological activity, there was no significant difference between the outcomes of the HD-CYC and LD-CYC groups. Notably, ELNT recruited patients with less-severe LN, with only 28% presenting with nephrotic syndrome.[5] The universal use of mycophenolate mofetil (MMF) maintenance in the LD-CYC group versus 20/34 in the HD-CYC group may have influenced the rates of relapses between the two arms. In the HD-CYC group, azathioprine doses were lower than those used in the ELNT and may have further increased risk of relapses.

The question of the efficacy of LD-CYC in non-European populations has been the subject of research worldwide. In the first phase of Abatacept and Cyclophosphamide combinations Efficacy and Safety Study (ACCESS), the placebo arm received a treatment course based on the ELNT and comprised six doses of LD-CYC followed by azathioprine.[10] The treatment group received abatacept in addition to the above. The primary outcome of CR at 24 weeks was 31% and 33%, respectively, in the treatment and placebo groups. Forty percent of the sample was African-American and 39% was Hispanic/Mestizo and, therefore, very different ethnically from the ELNT study population. The authors concluded that even in their ethnically diverse sample, the ELNT protocol appeared to have similar, if not superior, outcomes to HD-CYC and MMF-based regimens.

A systematic review comparing LD- and HD-CYC regimens among Chinese patients with LN described similar rates of PR and CR in both groups, with lower infection and menstrual disturbances in the LD group. This review studied only short-term effects but is reassuring in that early outcomes were similar.[7]

However, our study findings contrast with the only other study of its kind from South Asia. Mehra *et al.*[11] conducted a single-center, open-label, prospective, randomized controlled trial in India comparing remission rates achieved at 52 weeks with LD-CYC and HD-CYC in proliferative lupus. They defined CR as proteinuria <0.5 g, stable renal function, and inactive urinary sediments and PR as 50% reduction in proteinuria to subnephrotic range with stable renal function and inactive urinary sediments. In their study, the HD-CYC group received a median dose of 6 g (IQR 5.4–6.3 g), which was higher than that received in our HD-CYC group. Remission was significantly higher in the HD group (73%) compared to the LD (50%) group. During this 52-week follow-up, nine (24%) in the LD group compared to one (3%) in the HD group experienced relapse. While advising further studies, Mehra *et al*.[11]. suggested that HD-CYC may be a more efficacious treatment approach among Indian patients.

While this cohort of patients appeared to have less clinically severe LN (only 24% and 11% of patients in the LD-CYC and HD-CYC groups, respectively, having a UPCR >3 in the Indian cohort), our response rates appeared to be higher overall with no between-group difference. This may partly be due to the more generous definition of CR in our study. The definitions of PR and CR are very variable, but current data supports that achieving proteinuria <1 g/d is associated with very good outcomes, making this a practical goal.[12]

Gonadotoxicity, assessed in terms of transient amenorrhoea and premature menopause, was similar between the two groups, despite clear differences in the duration of follow-up. However, our cohort of patients is quite young, and it will be worthwhile obtaining further data on fertility and pregnancy outcomes prospectively.

The main strength of the study is the inclusion of patients with pathologically severe LN. The main limitations of our study are that data was collected retrospectively, with risk of bias. We believe that data regarding response and renal/non-renal relapses were obtained with good accuracy as these were based on objective documentation. In addition, these were two distinct cohorts treated at two different periods in time. For our earlier patients, HD-CYC was followed by maintenance therapy with azathioprine, compared to our current practice of MMF. It is now standard practise for all our lupus patients to be on hydroxychloroquine, known to increase renal remission, prevent relapses, and prevent progression to end-stage kidney disease. Furthermore, better supportive care with antiproteinuric agents and blood pressure control is to be expected over time. However, we believe that the effect on the primary outcome of treatment failure at 6 months would not have been impacted greatly by these changes. A prospective trial comparing HD- and LD-CYC in this population will be unethical due to possible toxicity of HD regimens. Therefore, the data we have collected, when analyzed with full understanding of its limitations, is very valuable. It is reassuring to know that, when considering the efficacy of CYC, the South Asian (Sri Lankan) cohort fares similarly to Caucasian populations on whom the bulk of research has been conducted and on whom evidence-based treatment guidance has been formulated.

Conclusions

Our study suggests that an LD-CYC regimen is as effective as HD-CYC in those of South Asian ethnicity. Well-designed local multicentre prospective studies are needed, so that we can better understand our patient cohort and how to treat them.

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Review Committee of the Sri Lanka Medical Association. Informed written consent was obtained from participants. For patients younger than 18 years of age, the informed consent of the accompanying parent or guardian was obtained.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Agarwal I, Kumar TS, Ranjini K, Kirubakaran C, Danda D. Clinical features and outcome of systemic lupus erythematosus. Indian Pediatr 2009;46:711-5.
2. Desmond Y, Chan TM. Lupus nepritis in Asia: Clincal features and management. Kidney Dis 2015;1:100-9.
3. Austin HA 3rd, Klippel JH, Balow JE, le Riche NG, Steinberg AD, Plotz PH, *et al*. Therapy of lupus nephritis. N Engl J Med 1986;314:614-9.
4. Boumpas DT, Austin HA 3rd, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, *et al*. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992;340:741-5.
5. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, *et al*. Immunosuppressive therapy in lupus nephritis: The Euro-Lupus nephritis trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.
6. Lewis MJ, Jawad AS. The effect of ethnicity and genetic ancestry on the epidemiology, clinical features and outcome of systemic lupus erythematosus. Rheumatology (Oxford) 2017;56(Suppl 1):i67-77.
7. Ming T, Song X, Dong L, Xin X, Dong J. Systematic evaluation of different doses of cyclophosphamide induction therapy for lupus nephritis. Medicine 2017;96:e9408.
8. Castro-Santana LE, Colón M, Molina MJ, Rodríguez VE, Mayor AM, Vilá LM. Efficacy of two cyclophosphamide regimens for the treatment of lupus nephritis in Puerto Ricans: Low versus standard dose. Ethn Dis 2010;20:S1-116-21.
9. Zhong B. How to calculate sample size in randomized controlled trial. J Thorac Dis 2009;1:51-4.
10. ACCESS Trial Group. Treatment of lupus nephritis with abatacept: The abatacept and cyclophosphamide combination efficacy and safety study. Arthritis Rheumatol 2014;66:3096–104.
11. Mehra S, Usdadiya JB, Jain VK, Misra DP, Negi VS. Comparing the efficacy of low-dose vs high-dose cyclophosphamide regimen as induction therapy in the treatment of proliferative lupus nephritis: A single center study. Rheumatol Int 2018;38:557–68.
12. Houssiau FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, *et al*. The 10-year follow-up data of the Euro-Lupus Nephritis trial comparing low-dose and high-dose intravenous cyclophosphamide. Ann Rheum Dis 2009;69:61–4.