ORIGINAL ARTICLE

Treatment and Renal Outcome of Lupus Nephritis: Single Center Experience

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Summary

Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease with renal involvement being one of the most frequent and serious manifestations of the disease. The aim of the study is to analyze the treatment and renal outcome of patients with lupus nephritis (LN) WHO class III and IV on cyclophosphamide (CYC). We retrospectively identified 41 patients with biopsy proven LN who was given either oral or intravenous CYC. The male: female ratio was 4:37; with a mean age of 31.7 ± 9.8 years at presentation. 36 patients (87.8%) had LN class IV and only five patients (12.2%) with LN class III. The mean serum creatinine at presentation was 87.4 ± 37.2 μmol/L with mean follow-up of 84 ± 78 months. A total of 30 patients (73.2%) completed 12 courses of IV CYC and one patient (2.4%) completed three months of oral CYC. 71.0% (n=22) had complete response (CR), 25.8% (n=8) had partial response and 3.2% (n=1) had no response (NR). Of the remaining 11 patients, two patients (4.9%) died during the treatment, three patients (7.3%) defaulted treatment and five patients (12.2%) are still receiving on-going treatment. Presence of hypertension ($p<0.003$) and evidence of chronicity on renal biopsy ($p<0.016$) were significantly correlated with the progressive deterioration of renal function in our population. In conclusion, hypertension and evidence of chronicity on renal biopsy, proved to be risk factors for progressive renal impairment in our study population. The achieved global outcome can be considered good.

Key Words: Cyclophosphamide (CYC), Lupus nephritis (LN), Complete response (CR), Partial response (PR), Non response (NR)

Introduction

Systemic Lupus Erythematosus (SLE) is a multisystemic autoimmune disease with renal involvement being one of the most frequent and serious manifestations of the disease. Nephritis in SLE carries significant morbidity and mortality and is an important determinant for survival[1-3]. Among the different World Health Organization (WHO) histological classes of lupus nephritis, diffuse proliferative glomerulonephritis (DPGN) is associated with the worst prognosis in terms of both progression to end stage renal disease (ESRD) and survival[4-6]. Because of the ominous prognosis of DPGN, it is universally agreed that treatment of this histological type of nephritis has to be aggressive.

The clinical experience with cyclophosphamide in SLE now extends well over several decades. The drug has been best studied in lupus nephritis, where there is unequivocal evidence that it modifies the long-term course of the disease[7-9]. Intermittent monthly boluses of intravenous cyclophosphamide have become the standard of treatment for DPGN (WHO class IV) lupus nephritis. In a series of randomized controlled trials conducted at the National Institutes of Health, statistically significant differences between cyclophosphamide and corticosteroids alone have been shown for the prevention of progressive scarring within the kidney,[10] preservation of renal function, induction of renal remission,[11] and reduction in the risk of end-stage renal failure requiring dialysis or renal

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transplantation. These studies provide evidence in favor of intravenous cyclophosphamide for most of the major renal outcomes associated with lupus nephritis. With this in mind we hope to evaluate and analyze our local experience with cyclophosphamide in treatment of lupus nephritis and to search for risk factors for renal and patient survival.

Materials and Methods

Retrospectively we identified all patients diagnosed with biopsy proven lupus nephritis WHO class III and IV from the histopathology register between 1st January, 1995 and 31st December, 2002 and who were subsequently treated with intravenous or oral cyclophosphamide in Hospital Ipoh, Taiping and Teluk Intan. All patients with renal biopsy suggesting WHO class III and IV treated with cyclophosphamide were included in the study.

Demographic data and information regarding disease diagnosis and manifestations were obtained in all patients.

- Age/Gender/Race
- Duration of follow-up
- Baseline/Post treatment and latest creatinine
- Baseline/Post treatment and latest 24H urine protein
- Evidence of Hypertension
- Serological marker – ANA and dsDNA
- Renal biopsy findings – Activity and Chronicity

Criteria for Remission and/or Relapse

Complete remission (CR), partial remission (PR), and non response (NR) of nephritis after immunosuppressive treatment were defined as suggested by Boumpas and Balow, [12-13] with slight modification. Essentially, CR was defined as stabilization or improvement in renal function with reduction of proteinuria to 1 g/day of proteinuria or less. PR was defined as stabilization or improvement in renal function with reduction of proteinuria (if baseline is nephrotic range, >50% decrease in proteinuria but to <3 g/day of proteinuria; if baseline is non nephrotic range, >50% decrease of pretreatment value but >1 g/day of proteinuria). NR was defined as deterioration in renal function after excluding other causes, such as sepsis, nephrotoxic agents, overdiuresis, and renal vein thrombosis. Normally distributed data are presented as mean ± SD. Anova T was used to test for difference between treatment groups. Statistical analysis was performed using SPSS for windows 10.0 (SPSS Inc Chicago, IL).

Results

A total of 41 patients with biopsy-proven WHO class III or IV lupus nephritis were diagnosed, treated and followed-up in Hospital Ipoh, Taiping or Teluk Intan. For the 41 patients who were reviewed, as expected females overwhelmed male by 37 to 4 comprising of 36 cases (87.8%) of class IV and five cases (12.2%) of class III LN. Majority of patients were from Hospital Ipoh with 35 patients, Hospital Taiping, five patients and Hospital Teluk Intan one patient. The mean age at presentation was 31.7 ± 9.8 years and mean serum creatinine at presentation of 87.4 ± 37.2 μmol/L with mean follow-up duration of 84 ± 78 months. A total of 30 patients (73.2%) completed 12 courses of IV cyclophosphamide and one patient (2.4%) completed three months of oral cyclophosphamide.

Of the remaining ten patients (24.4%), two patients (4.9%) died during the treatment, three patients (7.3%) defaulted treatment and five patients (12.2%) are still receiving on-going treatment at the time of completion of the study. Two patients died due to flaring of cerebral lupus during the course of treatment.

Several confounding factors were tested statistically to look for possible correlation with change of renal function. Presence of hypertension ($p<0.003$) and evidence of chronicity on renal biopsy ($p<0.016$) were significantly correlated with the progressive deterioration of renal function in our population. However, a history of cerebral lupus, presence of serological marker dsDNA or ANA and evidence of activity in renal biopsy do not correlate with change of renal function. Presence of chronicity or activity is taken as presence of any one of the marker that suggest chronicity or activity in the renal biopsy.

Discussion

This is a retrospective study to review the efficacy of cyclophosphamide in treatment of lupus nephritis WHO class III and IV in Hospital Ipoh, Taiping and Teluk Intan. The use of cyclophosphamide has been well established as the standard treatment and the outcome has progressively improved in the last three decades with a local study showing encouraging respond and outcome[7]. Our results of 41 patients with mean follow-up of 84 ± 78 months confirmed the effectiveness of cyclophosphamide, with results comparable with most of the published controlled and uncontrolled studies [7-9] regarding the efficacy of IV

pulse cyclophosphamide in severe lupus nephritis. The achieved global outcome can be considered good.

However, expansion of the number of patients over a longer observation period is needed to show more significant outcome. In addition, no toxicity data was collected as the study was conducted retrospectively. In our study, we have demonstrated that the presence of hypertension and evidence of chronicity on renal biopsy are risk factors for progressive renal impairment. These findings were also noted in other similar published data. It is therefore important to initiate aggressive management in these groups of patient with the hope of preventing and delaying the occurrence of renal failure.

Furthermore, we need to advise and educate our patients to ensure compliance to treatment in view of the relatively high rate of defaulter. These could possibly be attributed to the adverse effects of the therapy and lack of understanding of the importance of completing therapy.

Table I: Summary of treatment outcomes for patients who completed the prescribed course of cyclophosphamide

Treatment outcome	No	%
Complete response (CR)	22	71.0%
Partial response (PR)	8	25.8%
No response (NR)	1	3.2%
Total	**31**	**100.0%**

In conclusion, our study has shown an acceptable level of response. The use of cyclophosphamide for treatment regimens in LN class III and IV remains the standard treatment for now.

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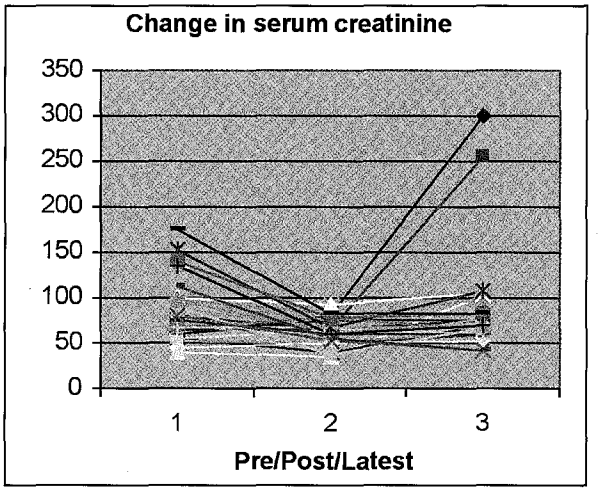

Fig 1: Graph showing serum creatinine pre and post completion of cyclophosphamide therapy followed by the latest available serum creatinine level of 31 patients who completed cyclophosphamide therapy.

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