

INTRAVENOUS PULSE CYCLOPHOSPHAMIDE TREATMENT OF LUPUS NEPHRITIS: A RETROSPECTIVE TEN YEARS STUDY

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Abstract — Nephritis remains an important problem in patients with systemic lupus erythematosus (SLE). We conducted retrospective study to evaluate the efficiency of intravenous pulse cyclophosphamide in lupus nephritis. From 1983 to 1993, we reviewed 133 patients with biopsy proven lupus nephritis, 47 of them excluded because of short period of follow-up or defective laboratory data. Eighty six patients were treated with the following regimens: Sixty patients with intravenous pulse cyclophosphamide; 13 with IV pulse methylprednisolone succinate, 8 with cyclosporine, 4 with azathioprine and one with oral prednisolone. Sixteen patients did not respond to IV cyclophosphamide. We evaluated renal biopsy, pretreatment mean arterial pressure (MAP), BUN, creatinine and proteinuria as prognostic and risk factors of nonresponders. The results of this study showed that diffuse proliferative glomerulonephritis (DPGN) had the poorest outcome and most of nonresponders (11/16), were of DPGN. There was a correlation between initial serum creatinine level and response to IV cyclophosphamide, but there was no correlation between BUN, MAP, degree of proteinuria and response to IV cyclophosphamide. IV pulse cyclophosphamide was more effective than steroid alone in preventing renal failure in lupus nephritis.
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Key words: SLE, nephritis, IV pulse cyclophosphamide

INTRODUCTION

Systemic lupus erythematosus (SLE), is a chronic remitting and relapsing illness characterized by injury to virtually every organ in the body. Renal involvement is one of concern because of its potential for morbidity, mortality and influence on course and therapy of SLE. Renal involvement are extremely variable. Based on clinical findings such as proteinuria, abnormal urinary sediment and renal function, it appears to be involved in 35% to 90% of cases. On light microscopic exam kidney is involved in 60 to 70% of cases, but if immunofluorescence and electron microscopy are included in the examination of biopsies material, almost all patients with SLE shows some renal involvement. The prognosis for lupus nephritis has changed dramatically over the years, consequent to improved management of active disease and supportive therapy for complications such as infection and renal failure. Before 1970, life expectancy was 40% at five years (1), while in recent reports it is

approximately 90% at 10 years. The improved renal prognosis, could be partly attributable to cytotoxic agents. Monthly high dose intravenous cyclophosphamide appeared to be the most effective form of therapy in patient with renal failure. The aims of this study were to evaluate response of lupus nephritis to IV cyclophosphamide and whether proteinuria alleviated by IV pulse cyclophosphamide.

MATERIALS AND METHODS

From 1983 to 1993, a retrospective study conducted on 133 patients with biopsy proven lupus nephritis. Out of 133 patients, 42 were excluded because of short follow-up, defective laboratory data, and 3 were excluded because, there was no signs of SLE. In the remaining 88 patients, SLE diagnosed according to the criterias of American Rheumatic Association. All of them showed signs of systemic involvement or renal abnormalities. Twenty one patients were serologically negative for Anti-DNA Ab, ANA, and L.E. cells, four of them were MGN, 15 were DPGN, and two were FSGN (focal proliferative glomerulonephritis), on biopsies. Eighty six patients were followed montly for six months, and then every 2 or 3 months. Laboratory tests consists of BUN, Creatinine, 24 hours urine for protein, CBC, ESR, Cholestrol and triglyceride. Therapeutic regimen were as follows: 60 patients received pulse cyclophosphamide, 13 pulse methylprednisolone, 8 cyclosporine, 4 azathioprine and one received oral prednisolone. Rising serum creatinine or creatinine more than 3.5 mg/dl were regarded as failure to treatment. Mean arterial pressure (MAP) more than 106 mmHg regarded as hypertension. We evaluated initial MAP, BUN, Creatinine, Proteinuria, and renal biopsy as prognostic and risk factors of nonresponders.

RESULTS

Mean age of patients was 24 ± 10 years (9 to 59 years), and mean duration of follow-up was 56.6 months (12-185 months). Female to male ratio was 7/1. Histological findings were; 3 (3.5%) mesangial glomerulonephritis (GN), 7 (8.1%) Focal proliferative glomerulonephritis (FPGN), 15 (17.4%) Membranous glomerulonephritis (MGN), 61 (71%) diffuse proliferative glomerulonephritis (DPGN). On rebiopsy, 3 patients (two FPGN, one MGN), transformed to DPGN. Out of 60 patients treated with IV cyclophosphamide 3 (5%), were FPGN, 45 (75%) were DPGN, and 12 (20%) were MGN. Sixteen, patients (26.6%) did not respond to IV cyclophosphamide (nonresponders), 11 were DPGN, 3 MGN, and 2 FPGN, on biopsy. Mean arterial pressure more than 106 regarded as hypertension, 51.1% of responders and 60% of nonresponders were hypertensive. Mean MAPs were 103.54 and 106.4 mmHg in responders and nonresponders respectively. There were no correlation between initial MAP and response to IV cyclophosphamide. Mean initial serum creatinine level were 1.16 and 1.88 mg/dl in responders and nonresponders respectively. There was a correlation between initial serum creatinine level and response to IV cyclophosphamide. Mean BUNs were 26.59 and 41.3 mg/dl in responders and nonresponders respectively. There was no correlation between initial BUN and response to treatment. Mean 24 hours urine for protein excretion were 4.59 g and 3.91 g in responders and nonresponders respectively, and there was no correlation between this parameter and response to treatment with IV cyclophosphamide.

DISCUSSION

One of the most important complication associated with poor outcome in SLE patients is renal involvement, which remains as one of the main cause of death and encompass heterogenous groups of clinical manifestations and histological lesions. These vary greatly in their therapeutic and prognostic implications. At presentation most patients with lupus nephritis are clinically asymptomatic, therefore, BP, BUN, Creatinine, urinary sediment, 24 hours urine collection for protein, complements and anti - DNA-Ab should be measured periodically. Renal biopsy is indicated when results would influence therapeutic decisions, however some authors believe that it should be performed in all lupus patients (1).

Histologic characteristic of our patients were as follows;

	our results	other centers
Class 1 minimal disease	0%	0.26%
Class 2 mesangial	3.5%	26%
Class 3 FPGN	8.1%	18%
Class 4 DPGN	71%	38%
Class 5 MGN	17.4%	16%
Class 6 sclerosing	0%	1.8%

There were significant difference between our results and other centers experiences, because most of our patients were referral, and there were a long time between diagnosis of SLE and renal biopsy. The most common type was DPGN, which had the poorest outcome. These patients should be followed carefully. We evaluated initial MAP, BUN, Creatinine, and proteinuria as prognostic factors of lupus nephritis and risks of nonresponders. Hypertension has been studied in numerous reports with different results. Prevalence of hypertension was reported to be 7 to 14% (2), but it is increasing over the years (25 to 49% during 1980 to 1990), (2). This findings could be due to increased survival of patients, precipitation of immune complexes in vessels wall, dyslipidemia and long term steroid therapy (3). Pollak and co - worker described a direct correlation between diastolic blood pressure and renal injury (11). This has been confirmed in other studies (4). 36% of our patients were hypertensive (MAP more than 106 mmHg). 60% of ESRD patients and 48% of cases with nephrotic range proteinuria were hypertensive. There were no correlation between pretreatment MAP and prevalence of renal failure and prevalence of hypertension in proliferative GN and severe lupus nephritis was 44.6%. Hypertension and arteriolar nephrosclerosis and dyslipidemia are complications of severe systemic disease, not direct consequence of immunologic features of SLE (6). Severe renal injury causes hypertension and hypertension causes arteriolar sclerosis and secondary vascular injury (2). To overcome this vicious circle, we should treat the underlying disease. The most appropriate drug to interrupt the process of injury is cyclophosphamide. Nondrug therapeutic intervention including sodium, caloric and fat restriction beside drug therapy, if indicated are also necessary. Steroid therapy for extrarenal manifestation of SLE, if indicated should be used cautiously and with lower dosage, if possible. Serum creatinine level is the major prognostic factors in patients with lupus nephritis. Andrew and co - workers found a direct correlation between mortality, renal failure and initial serum cratinine level, 29 percent versus 6.5 percent (7). In our study, there was a direct relation between initial serum creatinine level and prognosis of lupus nephritis. Fourteen patients had creatinine > 1.8 mg/dl, 9 of them did not respond to intravenous cyclophosphamide. Fifty three percent of nonresponders and 12.2% of

responders had creatinine > 1.8 mg/dl. Out of 14 patients with creatinine > 1.8 mg/dl, two cases were MGN, 2 FPGN and 10 were DPGN. Mean age of patients with creatinine > 1.8 mg/dl was higher than patients with creatinine < 1.8 mg/dl (29.2±3.6 years vs 22.9±2.9 years). Prevalence of nephrotic range proteinuria and hypertension (MAP > 106 mm Hg) in patients with creatinine > 1.8 mg/dl were 61.5% and 50% respectively. Based on the above data, initial serum creatinine level is the most important prognostic factor in lupus nephritis. In cases with creatinine > 1.8 mg/dl, renal biopsy should be performed as soon as possible, and they should be followed carefully. Initial BUN has no correlation with prognosis and response to treatment in lupus nephritis. This factor is a relative parameter of renal function, and is influenced with several other factors, including trauma, fever, infection, gastrointestinal bleeding, tetracycline and steroid intake. We did not find any correlation between BUN, and prognosis of lupus nephritis.

There was no correlation between the degree of proteinuria, response to treatment and prognosis of our patients. The effects of IV cyclophosphamide on proteinuria, 19 (52.8%) responded to treatment, and proteinuria decreased to nonnephrotic range. Comparison of IV pulse cyclophosphamide with pulse methylprednisolone succinate, that has been performed in numerous studies, as D.T. Bounpass co workers reported that while only 52% of patients responded to IV pulse methylprednisolone, 85% of patients responded to IV pulse cyclophosphamide (8). Our results are as follows;

Renal function	IV Prednisolone N=13	IV Cyclophosphamide N=16
Improved	7/13 (54%)	12/16(75%)
Deteriorated	6/13 (46%)	4/16(25%)

IV cyclophosphamide was more effective than steroid in preventing renal failure in our cases.

Complications of cyclophosphamide were, transient leukopenia in about 10% of patients, two developed sepsis, and one haemorrhagic cystitis.

We conclude that, IV cyclophosphamide is the preferred therapeutic regimen for lupus nephritis.

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