Outcomes in Patients with Active Lupus Nephritis Requiring Immunosuppressives Who Never Received Cyclophosphamide

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ABSTRACT. ***Objective.*** To assess outcomes in patients with lupus nephritis treated with immunosuppressives compared to those treated with cyclophosphamide in a cohort study and in a matched cohort study.
Methods. Patients with active renal disease treated with immunosuppressive/cytotoxic medications were selected from the University of Toronto Lupus Clinic database. Five outcomes were evaluated: all-cause mortality, renal failure, reversal of active renal disease, relapse of active renal disease, and toxicity.
Results. There were no differences in the outcomes of death, renal failure, reversal or relapse of active renal disease, or toxicity in those using or not using cyclophosphamide.
Conclusion. Antimetabolites should be considered standard of care for patients with lupus nephritis both for induction and for maintenance therapy. (First Release June 15 2007; J Rheumatol 2007; 34:1491–6)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS LUPUS NEPHRITIS OUTCOMES
IMMUNOSUPPRESSIVE AGENTS CYCLOPHOSPHAMIDE

The prognosis of systemic lupus erythematosus (SLE) has improved significantly over the past 3 decades. Although survival has improved progressively, mortality remains high, more than 3 times that of the general population[1]. Renal involvement remains a major cause of increased mortality. Acute lupus nephritis is an associated factor in mortality early in the course of the disease, whereas chronic renal insufficiency plays a role in late mortality[2,3].

Since the landmark studies from the National Institutes of Health (NIH) showing a beneficial effect from the addition of cytotoxic agents in general and cyclophosphamide (CP) in particular, the "standard of care" for lupus nephritis in many centers throughout the world has been steroids and CP[4-12]. Despite the improvement in renal outcome, mortality has not been affected by CP[13], and relapses are common[14]. However, CP has not been approved as therapy for lupus nephritis by any of the drug regulatory agencies. Further, metaanalyses indicate that there is no difference among cytotoxic drugs with respect to the treatment of acute lupus glomerulonephritis[13,15]. A more recent metaanalysis concludes that there was a mortality benefit to treatment with azathioprine (AZA) without improvement of renal outcome, whereas treatment with CP had no mortality benefit but was associated with better renal outcome[16].

In our clinic, steroids plus the antimetabolites (AZA), methotrexate (MTX), and mycophenolate mofetil (MMF) [immunosuppressives (IS)] have been primary therapy for lupus nephritis with only a minority of patients being treated with CP. Renal outcomes and mortality in our patients are at least as good as those published from other large cohorts[1,17]. Therefore our objective was to assess outcomes in patients with lupus nephritis treated with IS compared to patients treated with CP in a cohort study and in a matched cohort study.

MATERIALS AND METHODS

Patient selection. Patients with SLE [≥ 4 American College of Rheumatology (ACR) criteria or 3 ACR criteria plus a typical histological lesion of SLE on renal or skin biopsy] have been followed prospectively at the University of Toronto Lupus Clinic since 1970. At entry and at 2- to 6-monthly intervals patients are evaluated according to a standard protocol, which includes a complete history, examination, and laboratory evaluation[18]. Patients with active renal disease treated with immunosuppressive/cytotoxic medications in the year after diagnosis of active renal disease were selected from the clinic database.

Active renal disease was defined as the presence for 2 consecutive visits of one of: red blood cell casts or hemegranular casts, hematuria or pyuria in the absence of other causes, or proteinuria (> 500 mg/24 h, or ≥ 3+ on dipstick), or an abnormal renal biopsy showing active lupus nephritis.

Outcome measures. Five outcomes were evaluated: (1) all-cause mortality [measured by standardized mortality ratios (SMR)]; (2) renal failure (dialysis/transplant or serum creatinine > 200 μmol/l on 2 or more consecutive visits); (3) reversal of active renal disease [disappearance of the feature(s) of active renal disease]; (4) relapse of active renal disease (recurrence of

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active renal disease by above definition after a period of remission). Patients whose active renal disease was based solely on the renal biopsy were excluded from the analysis of reversal or relapse of renal disease; and (5) toxicity, including infection, amenorrhea, and malignancy.

Analysis. We took a 2-pronged approach to address our objective: (1) a cohort study that included all patients with lupus nephritis who have been on an immunosuppressive/cytotoxic agent in the year after the onset of lupus nephritis; (2) because those patients who received CP may have had more severe renal disease we matched patients who took CP to patients using other immunosuppressive medication by SLE Disease Activity Index 2000 (SLEDAI-2K), basis for diagnosis of active renal disease, and serum creatinine at onset of renal disease.

Descriptive statistics were used to compare CP and IS using t-tests and chi-square tests for the cohort study and McNemar test for the cytotoxic drugs comparison study. Rates of outcomes per 100 person-year were calculated and relative risks (RR) evaluated along with 95% confidence intervals (CI). RR > 1 indicates that IS is at greater risk of the outcome than CP. RR < 1 indicates that CP is at greater risk. Time from onset of renal disease to outcome (censored at 10 yrs) was plotted using Kaplan-Meier curves and compared using log-rank test.

RESULTS

Two hundred eighteen patients fulfilled our entry criteria. There were 188 (86.3%) women; 71% Caucasian, 12% Black, 11% Asian, and 6% other. All LN refers to the first identified episode of lupus nephritis for each patient. Age at LN was 34.4 ± 12.4 with a disease duration of 4.8 ± 5.8 years. Forty patients were treated with CP (18.3%) and 178 with other IS including AZA (85.4%), MTX (9.6%), MMF (6.7%), and others (including cyclosporine 6.8%). No patient in the IS group had ever received cyclosphosphamide. Of the 40 patients treated with CP only 3 had previously received AZA after the start of lupus nephritis and then received CP within the first year of lupus nephritis.

Demographic and disease-related features in these 2 groups are shown in Table 1. Renal biopsies were available for 80 patients in the IS group and for 22 in the CP group. The frequency of proliferative nephritis classes 3 and 4 was 62.6% in the IS group and 63.6% in the CP group, and 18% in each group had membranous nephritis.

Survival information was available on all 218 patients. Causes of death in the 2 groups were: IS: atherosclerosis 10, infection 9, lupus activity 6, cancer 3, unknown 6; CP: infection 4, active lupus 2, cancer 1, unknown 1. Of those who died more than 5 years after diagnosis in the IS group, only 2 of 12 died of active SLE. The one CP patient who died after 5 years of disease died of infection in the context of active lupus.

Four patients (2 from each of IS and CP groups) died shortly after the onset of LN and therefore no other outcome was available for them (causes of death were myocardial infarction and infection in the IS group, and infection and cancer in the CP group). Reversal was evaluated in patients where LN was identified on a basis other than renal biopsy alone, and these patients comprise a sample of 165 for the IS group and 35 for the CP group. Relapse was evaluated only in patients who had achieved reversal.

There were no differences in the outcomes of death, renal failure, reversal of active renal disease, relapse of active renal disease, or toxicity in those using CP and those not using CP (Table 2). Specifically, when proteinuria alone was the definition of the renal relapse there was no difference in relapse rate between the 2 groups: 69 patients had relapse (60 in the IS group and 9 in the CP group). In total, 20 had relapse due to abnormal proteinuria alone, 17/60 (28.3%) in the IS group and 3/9 (33.3%) in the CP group (p = 0.71). Similarly, there was no difference in infection, amenorrhea, or cancer in the 2 groups. Since the sample size decreases as time progresses, we might be interested in the earlier differences between the curves. The Wilcoxon tests in the Kaplan-Meier curves place more emphasis on earlier differences between the survival curves, while the log-rank test looks at the entire curves. The Wilcoxon p values for the curves in Figure 1 are: for survival, p = 0.35, for failure, p = 0.17, for reversal, p = 0.44, and for relapse, p = 0.39. Thus whether early or late, there were no differences between the 2 treatment groups.

In assessing time from onset of renal disease to outcome censoring at 10 years there were no differences in the 2

Table 1. Demographics and disease related features in the study population.

Variable	Immunosuppressives	Cyclophosphamide	p
Number	178	40	
Age at diagnosis	29.0 ± 12.5	32.4 ± 12.9	0.12
Female (%)	151 (84.8)	37 (92.5)	0.20
Race, %			
Caucasian/Black/Asian/others	73/11/10/6	58/18/15/10	0.05 (Caucasian vs others)
Age at onset of renal disease	33.9 ± 12.3	36.3 ± 12.7	0.27
Disease duration at onset	5.0 ± 5.7	3.9 ± 6.3	0.31
Serum creatinine	99.9 ± 66.2	131.9 ± 62.4	0.006
SLEDAI-2K	12.7 ± 8.8	17.4 ± 10.5	0.004
AMS 1 year prior	12.1 ± 8.7	16.9 ± 10.3	0.003
Followup from onset of lupus nephritis to last clinic visit	6.5 ± 7.3	5.5 ± 5.0	0.31

SLEDAI-2K: SLE Disease Activity Index 2000; AMS: adjusted mean SLEDAI-2K.

Table 2. Outcomes in patients with active lupus nephritis.

Variable	Immunosuppressives (IS), n (%)	Cyclophosphamide (CP), n (%)	p
Death	34/178 (19.1)	8/40 (20)	0.90
Progression to renal failure	35/176 (19.9)	10/38 (26.3)	0.38
Reversal of activity*	114/165 (69.1)	26/35 (74.3)	0.54
Relapse of renal activity**	60/114 (52.6)	9/26 (34.6)	0.10
Infection	123/177 (67.6)	30/39 (67.9)	0.44
Amenorrhea	21/125 (16.8)	8/33 (24.2)	0.33
Cancer	6/176 (3.4)	2/40 (5)	0.64

* n = 165 in IS and 35 in CP group excluding 11 IS patients and 3 CP patients whose diagnosis was made on the basis of renal biopsy alone; ** n = 114 in IS and 26 in CP who had reversal of active disease and were subject to relapse.

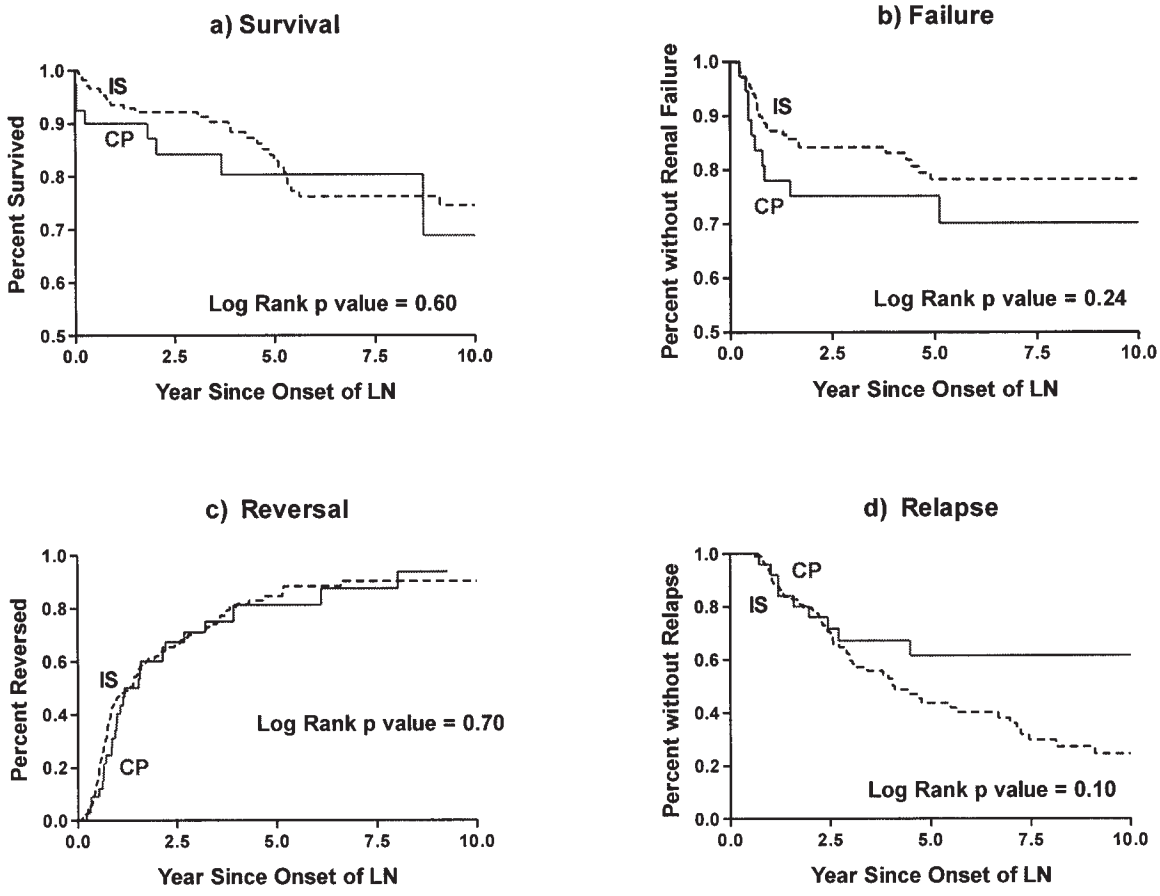

Figure 1. Kaplan-Meier and log-rank tests for outcomes. Assessing time from onset of renal disease to outcome censoring at 10 years, there were no differences in the 2 groups with respect to death, renal failure, reversal of active renal disease, and relapse of active renal disease. IS: immunosuppressive group (broken line), CP: cyclophosphamide group (solid line).

groups with respect to death, renal failure, reversal of active renal disease, and relapse of active renal disease (Figure 1). Further, there was no difference in steroid use in the year after onset of renal disease between those treated with other IS and those treated with CP, in terms of percentage taking steroids (98.3% vs 100%; p = 1.0) and cumulative dose (6.25 ± 6.44 vs 7.05 ± 4.32 g; p = 0.35).

CP-treated patients had more severe disease at diagnosis of active renal disease; therefore we performed a matched cohort-control study of the 34 CP-treated patients with a

minimum of 1 year of followup and 34 IS patients matched by SLEDAI-2K, basis for diagnosis of active renal disease, and serum creatinine at baseline. Demographic and disease-related features in these 2 groups are shown in Table 3.

There were no differences in the outcomes of death, renal failure, reversal of active renal disease, or relapse of active renal disease in those taking and those not taking CP. Similarly, there was no difference in infection, amenorrhea, or cancer in the 2 groups (Table 4). When the analysis was performed again, removing the 3 patients who had received IS prior to CP, the results were unchanged. Similarly, when the analysis was restricted to those patients with class 3 or 4 disease (50 in the IS group, 14 in the CP group) the outcomes were again not significantly different.

There was no difference in steroid use in the year after onset of renal disease between those treated with IS and those treated with CP, in terms of both percentage taking steroids (100% vs 100%; p = 1.0) and cumulative dose (7.80 ± 4.22 vs 7.68 ± 4.08 g; p = 0.90).

Rates of outcomes per 100 patient-years are provided in Table 5 so that our results may be compared with other series in future analyses. As can be seen by the overlapping confidence intervals in each of the outcomes, whether looking at the total cohort analyses or the matched cohort analyses there are no major differences in the rate of outcomes in the 2 groups (Table 5).

DISCUSSION

Since the landmark studies of the NIH in the 1970s and 1980s[4-11], intravenous CP therapy has become the standard of care for lupus nephritis, despite the fact that the original studies are based on very small numbers of patients. Although short-term efficacy was demonstrated, many patients failed to achieve total remission and a significant proportion of patients later relapsed[10,12,14,19]. In addition, significant toxicity has been reported with the use of CP[20,21]. Subsequent studies have shown that equally beneficial results could be obtained with AZA[15,22-24].

Recently there has been increased interest in MMF both as an induction agent and as maintenance therapy after induction with CP. As an induction agent MMF has been proven as effective as CP[25,26]. For patients with proliferative lupus nephritis, short-term therapy with intravenous CP followed by maintenance therapy with MMF or AZA appears to be more efficacious and safer than longterm therapy with intravenous CP[27]. All these studies would suggest a reexamination of CP as the standard of care for lupus nephritis.

In our clinic, since its inception in 1970, AZA has been

Table 3. Demographics and disease related features in the matched population.

Variable	Immunosuppressives	Cyclophosphamide	p
Number	34	34	
Age at diagnosis	28.6 ± 14.9	32 ± 13.4	0.36
Female (%)	32 (94.1)	32 (94.1)	1.00
Race, %			
Caucasian/Black/Asian/others	77/9/6/9	56/21/12/12	0.09 (Caucasian vs others)
Age at onset of renal disease	33.2 ± 14.2	36.0 ± 13.1	0.43
Disease duration at onset	4.6 ± 6.4	4.1 ± 6.6	0.74
Serum creatinine	119.1 ± 69.4	125.1 ± 54.5	0.49
SLEDAI-2K	15.4 ± 8.5	15.3 ± 8.1	0.89
AMS 1 year prior	15.0 ± 8.0	15.1 ± 8.1	0.94
Followup from onset of lupus nephritis to last clinic visit	9.3 ± 8.6	6.5 ± 4.8	0.09

For abbreviations, see Table 1.

Table 4. Outcomes in the matched cohort study.

Variable	Immunosuppressives, n (%)	Cyclophosphamide, n (%)	p
Death	4/34 (11.9)	4/34 (11.9)	1.00
Renal failure	11/34 (32.4)	9/34 (26.5)	0.48
Reversal of active renal disease*	25/31 (80.7)	25/31 (80.7)	1.0
Relapse of active renal disease**	15/25 (60)	9/25 (36)	0.07
Infection	28/34 (82.4)	27/34 (79.4)	0.74
Amenorrhea	4/31 (12.9)	8/30 (26.7)	0.16
Cancer	1/34 (2.9)	1/34 (2.9)	1.00

* n = Patients whose active renal disease was diagnosed on the basis of renal biopsy were excluded; ** n = 25 in each group who were subject to relapse.

Table 5. Rates of outcomes per 100 patient-years.

	Unmatched			Matched		
	IS	CP	RR*	IS	CP	RR*
Death	2.9 (2.1, 4.1)	3.6 (1.8, 7.1)	0.81 (0.38, 1.75) p = 0.60	1.3 (0.5, 3.4)	1.8 (0.7, 4.8)	0.71 (0.18, 2.82) p = 0.62
Failure	3.5 (2.5, 4.9)	5.3 (2.8, 9.8)	0.66 (0.33, 1.34) p = 0.25	4.3 (2.4, 7.8)	4.8 (2.5, 9.2)	0.91 (0.38, 2.19) p = 0.83
Reversal	38.9 (32.4, 46.8)	38.1 (26.0, 56.0)	1.02 (0.67, 1.56) p = 0.92	30.8 (20.8, 45.6)	37.6 (25.4, 55.6)	0.82 (0.47, 1.43) p = 0.49
Relapse	13.5 (10.5, 17.4)	6.9 (3.6, 13.3)	1.96 (0.97, 3.94) p = 0.06	12.7 (7.7, 21.1)	7.0 (3.6, 13.4)	1.83 (0.80, 4.18) p = 0.15
Infection	34.0 (28.5, 40.6)	47.3 (33.1, 67.6)	0.72 (0.48, 1.07) p = 0.10	31.4 (21.7, 45.5)	43.7 (30.0, 63.7)	0.72 (0.42, 1.22) p = 0.22
Amenorrhea	2.4 (1.6, 3.7)	4.7 (2.4, 9.4)	0.52 (0.23, 1.17) p = 0.11	1.6 (0.6, 4.2)	4.8 (2.4, 9.5)	0.33 (0.10, 1.10) p = 0.07
Cancer	0.5 (0.2, 1.2)	0.9 (0.2, 3.6)	0.58 (0.12, 2.87) p = 0.50	0.3 (0, 2.3)	0.5 (0.1, 3.2)	0.70 (0.04, 11.2) p = 0.80

* Relative Risk (RR): IS/CP, the p value is to test if RR = 1. IS: immunosuppressives; CP: cyclophosphamide.

the major IS agent used in conjunction with corticosteroids to treat patients with SLE including lupus nephritis. In the last 15 years some patients with lupus nephritis have also been treated with MTX[23]. The relatively small number of patients treated with CP in our clinic have either been referred to the clinic taking CP or have been refractory or intolerant to AZA or MTX. With this approach our outcomes have been as good as if not better than those reported from other large cohorts[1,17].

In our study, we showed that patients with lupus nephritis treated with IS agents other than CP had outcomes similar to those treated with CP in terms of death, progression to renal failure, reversal of active renal disease, and relapse after a period of quiescence, as well as in the complications of infection, amenorrhea, and cancer. This was not due to differences in treatment with corticosteroids, as the cumulative dose of steroids after the onset of renal disease was similar in both treatment groups. Further, the time from onset of renal disease to the outcomes was similar in both treatment groups. We used 2 approaches to study this problem. First, we compared outcomes in all patients with active renal disease treated with IS/cytotoxic medications in the year after diagnosis of active renal disease, comprising 40 patients who took CP and 178 who took other IS. Because patients who received CP had a higher serum creatinine and more active disease at the onset of renal disease and in the year prior to onset of renal disease, we used a cohort-control design comparing patients treated with CP to those matched on SLEDAI-2K, basis for diagnosis of active renal disease, and serum creatinine at onset of renal disease who took other IS drugs. In both approaches similar results were obtained. Treatment of active lupus nephritis with CP was not superior to treatment with other IS drugs with respect to death, renal failure, and reversal of renal disease, prevention of relapse, and toxicity. This was also shown when rates of these outcomes were determined per 100 years of followup (Table 5).

Although the numbers in our study were small, the overall results are very consistent and support the observations made by others, that patients treated with IS/cytotoxic agents other than CP may have favorable outcomes[15,22]. It should be noted, however, that our study was not a randomized controlled trial and therefore did not provide the opportunity to assess the treatment modalities "head to head," including comparable doses, concurrent therapies, and duration of therapy. A randomized controlled trial comparing AZA plus methylprednisolone with CP plus oral steroids was recently published. Unfortunately the study was underpowered and the concomitant steroid therapy was aymmteric such that the initial report identified no differences between the 2 regimens[28]. A followup study that focused on the renal biopsies showed that only 9 patients reached the primary endpoint. We are told that these occurred significantly more commonly among the AZA-treated patients, but the numbers are not provided. The authors concluded that although CP and AZA are both effective in reducing active lesions in lupus nephritis, progression of chronic lesions was more effectively stopped by CP[29]. This has been done for the newer antimetabolite MMF by Ginzler, *et al*[26] as an induction agent and Contreras, *et al*[27] as maintenance therapy.

Based on our studies and those of others, antimetabolites should be considered standard of care for patients with lupus nephritis both for induction and for maintenance therapy.

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