ORIGINAL ARTICLE

Comparison of Treatment Regimes for Lupus Nephritis

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Summary

The best therapeutic choice in the treatment of lupus nephritis remains open to debate. In addition, there have been little data on the treatment of lupus nephritis in Asian patients. The objective of this study was to look at the response rate and complications of treatment given for lupus nephritis in a group of South East Asian patients with systemic lupus erythematosus (SLE). This was a retrospective, cross-sectional study of 103 patients with lupus nephritis. Detailed analysis was done on 58 patients with Class IV disease. The median time to remission was 12.1 months for azathioprine (AZA), 15.01 months for oral cyclophosphamide (CPM) and 15.25 months for intravenous (IV) CPM. The percentage of patients achieving remission after the first course of treatment was 42.9% with AZA, 83.3% with oral CPM and 90.9% with IV CPM. Overall, 41/58 (70.7%) of patients went into remission following the first course of treatment. Seventeen (41.5%) subsequently relapsed, requiring a second course of treatment. Fifty-two (50.5%) of all patients had drug-related complications from their treatment. The most frequent complication for the group was amenorrhoea (23.3% of all patients, 40% of those who had CPM previously), which was significantly more frequent in patients given CPM. In conclusion, more patients achieve remission when treated with CPM compared with AZA alone but this is associated with a higher complication rate, especially amenorrhoea.

Key Words: Azathioprine, Complications, Cyclophosphamide, Outcome, Renal, Systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multisystem involvement. Renal disease is a common manifestation and is responsible for considerable morbidity and mortality. Lupus nephritis varies in severity and is an important predictor of poor outcome in SLE patients[1]. The treatment of lupus nephritis has improved substantially over the past 20 years and the proportion of patients going into end-stage renal failure much less. This can be attributed to a number of factors, including earlier diagnosis of lupus nephritis, judicious use of

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corticosteroids and cytotoxic agents such as azathioprine (AZA) and cyclophosphamide (CPM), better treatment of concurrent infections, hyperlipidaemia and hypertension. However, the best therapeutic regime remains open to debate. Most of the current treatment regimes for lupus nephritis centre around the use corticosteroids and/or cytotoxic agents or a combination of these drugs[1]. Although these drugs are effective, they are associated with significant toxicity and morbidity.

In Asian patients, lupus nephritis will be present in approximately 75% of patients with SLE during the course of the disease[2,3], a higher figure than that reported in Caucasian populations[1]. There have only been a few studies that have looked at the response to treatment of lupus nephritis[4,5,6] and the complications of treatment[6] in Asian patients. The objective of this study was to look at the response rate and complications of treatment given for lupus nephritis in a group of predominantly Chinese, South East Asian SLE patients.

Materials and Methods

This was a retrospective, cross-sectional survey of SLE patients with documented lupus nephritis attending the SLE Clinic at our centre between June to August 2000. All patients fulfilled the American College of Rheumatology (ACR) criteria for the diagnosis of SLE[7]. Information on their age, sex, date of diagnosis of SLE, organ system involvement of SLE, current status of their lupus nephritis, renal biopsy results, current SLE disease activity, previous and current treatment of their lupus nephritis and their associated complications was obtained from their hospital records. The renal biopsies were classified according to the 1995 revised World Health Organisation classification of lupus nephritis[8]. For this study, the duration to remission of their lupus nephritis was calculated from the date of the start of cytotoxic therapy to the date of their first clinic visit where the urinalysis did not show active nephritis. Remission in lupus nephritis was considered to be present when there was protein 2+ or less, the absence of cellular casts and less than 5 white blood cells or red blood cells per high powered field on urine dipstick and microscopy[7]. We studied the treatment given following the first renal biopsy only. Patients who required a second renal biopsy was classified as having failed to respond to therapy.

Normally distributed data are presented as mean $\pm$ SD. Non-normally distributed data are presented as median values. The Kruskal-Wallis test was used to test for differences between the treatment groups and duration of treatment and duration to remission. The Chi-Square test was used to test for any associations between the treatment groups in the percentage achieving remission and between the groups who did or did not have amenorrhoea. Statistical analysis was performed using SPSS for Windows 9.0 (SPSS Inc., Chicago, IL). The study was approved by the hospital's Ethics Committee.

Results

A total of 106 patients were identified, of whom 103 were studied. In the remaining 3 patients, the relevant hospital case records could not be traced and thus they were excluded from the study. The baseline characteristics of the study population are shown in Table I. Forty-seven (45.6%) had renal disease at presentation. In those who did not have renal disease on presentation, the mean ($\pm$ 1 SD) duration of disease before the onset of renal disease was 4.34 $\pm$ 4.61 years. Of this study population, 96 (93.2%) had a renal biopsy. The World Health Organisation classification of the first renal biopsy was as follows: Class I 6 (5.8%), Class II 10 (9.7%), Class III 4 (3.9%), Class IV 58 (56.3%) and Class V 18 (17.5%). The remaining 7 patients clinically had lupus nephritis but did not

Table I: Patient Characteristics at Presentation

Sex: Female	97 (94.2%)
Male	6 (5.8%)
Race: Chinese	82 (79.6%)
Malay	18 (17.5%)
Indian	3 (2.9%)
Age at diagnosis of SLE	25.09 ± 10.56 years
Age at time of study	34.99 ± 12.41 years
Duration of SLE at time of study	10.02 ± 6.31 years
Age at renal involvement	27.37 ± 11.24 years
Duration of SLE at renal involvement	2.34 ± 4.06 years
Serum creatinine at presentation	85.24 ± 46.17 μmol/l
Serum creatinine during the study (10 years later)	82.05 ± 34.05 μmol/l
24 hour urine protein excretion at presentation of renal disease	1.81 ± 2.18 g/24 hours
SLEDAI score during the study	11 ± 8

Values are given as mean ± 1 standard deviation, unless otherwise stated

Table II: Treatment Regimes in the Study Population

Treatment	All (%)	Class I	Class II	Class III	Class IV	Class V	No biopsy
AZA only	31 (30.1)	1 (16.7%)	8 (80%)	1 (25%)	14 (24.1%)	5 (27.8%)	2 (28.6%)
Oral CPM	26 (25.2)	3 (50%)	2 (20%)	3 (75%)	12 (20.7%)	6 (33.3%)	0
IV CPM	13 (12.6)	0	0	0	11 (19.0%)	1 (5.6%)	1 (14.3%)
Oral CPM and AZA	8 (7.8)	0	0	0	8 (13.8%)	0	0
IV CPM and AZA	4 (3.9)	0	0	0	4 (6.9%)	0	0
IV CPM and oral CPM	4 (3.9)	1 (16.7%)	0	0	3 (5.2%)	0	0
Prednisolone only	17 (16.5)	1 (16.7%)	0	0	6 (10.3%)	6 (33.3%)	4 (57.1%)

AZA = azathioprine
CPM = cyclophosphamide
IV = intravenous

Table III: Treatment Response in Class IV Lupus Nephritis

Agent(s)	Median Duration of Treatment (months)[a]	Median Duration to Remission (months)[b]	Percentage Achieving Remission[c]
AZA only	11.54	12.12	42.86
Oral CPM only	9.04	15.01	83.33
IV CPM only	17.13	15.25	90.91
Oral CPM and AZA	16.59	13.45	75.0
IV CPM and AZA	31.38	14.04	75.0
Oral and IV CPM	26.07	16.57	100

AZA = azathioprine
CPM = cyclophosphamide
IV = intravenous

a : p = 0.082 (Kruskal-Wallis test)
b : p = 0.971 (Kruskal-Wallis test)
c : p = 0.001 (Pearson Chi-Square test)

Table IV: Complications of Treatment for All Patients

Complication	Oral CPMa	IV CPM	AZA	Pred	Others	Total (%) n = 103
Amenorrhoea	17	5	1	1	0	24 (23.3)
Herpes zoster	1	0	2	4	0	7 (6.8)
Haemorrhagic cystitis	1	0	0	0	0	1 (1.0)
Leucopenia	4	0	4	0	0	8 (7.8)
Thrombocyto-penia	0	1	1	0	0	2 (1.9)
Fungal infection	0	1	0	4	0	5 (4.9)
Cataracts	0	0	0	9	0	9 (8.7)
Osteoporosis	0	0	0	4	0	4 (3.9)
Pancytopenia	0	1	3	0	0	4 (3.9)
Others	0	1	1	5	2	9 (8.7)

a = includes the patients on both oral and IV CPM
AZA = azathioprine
CPM = cyclophosphamide
Pred = prednisolone
IV = intravenous

have a renal biopsy because of persistent thrombocytopenia. They were thus excluded from further analysis. The number of patients being treated with each particular agent are shown in Table II. All patients were given prednisolone.

Due to the difference in response to treatment of the various classes of lupus nephritis, we present the results of treatment efficacy for patients with Class IV disease, the majority of the study population. The median duration of follow-up was 9 years. The treatment regimes were AZA alone, oral CPM alone, intravenous (IV) CPM, oral CPM followed by AZA, IV CPM followed by AZA and oral CPM followed by IV CPM. The latter was given when an initial course of oral CPM failed to induce remission. The median duration to remission and the percentage going into remission for each agent is shown in Table III. Forty-one (70.7%) of the patients went into remission with the first agent given. There was no difference between the agents in duration to remission. However, AZA alone was significantly less likely to achieve remission with 8/14 (57.1%) patients not in remission after the first course of treatment. Of those that went into remission, 17/41 (41.5%) patients subsequently relapsed, requiring a second course of treatment. These consisted of 4 (23.5%) patients on AZA alone, 9 (52.9%) patients on IV CPM and 4 (23.5%) patients on oral CPM. Of these, 7/17 (41.2%) went into remission with further treatment. On average, AZA was given at a dose of 2mg/kg/day. The mean total cumulative oral CPM and IV CPM dose per patient after the first treatment regime was 24.73 $\pm$ 19.30 g and 10.53 $\pm$ 3.08 g respectively. IV CPM was most commonly given as monthly IV pulses for the first 6 months, followed by 4 further pulses at 3 monthly intervals to complete 10 pulses.

Fifty-two of the 103 patients (50.5%) had 73 recorded drug-related complications from their treatment. However, within this group, 31 patients had 1 complication only, 18 patients had 2 complications each and 3 patients had 3 complications each. The complications associated with each particular treatment are shown in Table IV.

Amenorrhoea was the most common complication, occurring in 24 (23.3%) of the patients. It was significantly more likely in those patients who had been on CPM (Chi-Square test with Yates' correction, $p = 0.00005$), occurring in 40% of those who had been on CPM previously. There was no difference in the dose of IV CPM given between those who became amenorrhoeic and those who did not, 11.24 ± 4.74g and 11.81 ± 2.83g respectively (Chi-Square test $p = 0.25$). However, for those on oral CPM, the average dose given to those who became amenorrhoeic was significantly higher than that given to those who did not become amenorrhoeic, 31.99 ± 23.72g and 25.30 ± 20.39g respectively (Chi-Square test $p = 0.046$).

Discussion

There is no doubt that the introduction of cytotoxic drugs, in addition to prednisolone, to the treatment of patients with lupus nephritis has improved their overall survival[9,10,11]. The 2 major cytotoxic drugs that have been studied in lupus nephritis are AZA and CPM. Clinical trials from the National Institute of Health (NIH) group have shown the superior efficacy of CPM compared to prednisolone alone for the treatment of lupus nephritis[10,11,12]. In addition, IV CPM monthly boluses has been shown to be less toxic than oral CPM with the same efficacy [10]. However, it is not clear from previous studies whether there is any difference in efficacy between AZA and CPM. Cameron[13] compared patients with proliferative lupus nephritis treated with either AZA or CPM and found no difference in either renal or patient survival. However, Steinberg[14] showed that AZA was similar to prednisolone alone, both of which were worse than CPM in the prevention of end stage renal failure (ESRF) in patients with lupus nephritis. A recent meta-analysis showed no difference in either total mortality or ESRF between the patients given AZA or CPM[15]. In addition, a recent retrospective study showed a 10 year survival of 87% in patients with proliferative lupus nephritis treated with AZA which compared favourably with results obtained with CPM[16]. Our results cannot be directly compared to the other studies as it was retrospective and does not include the patients that went into ESRF or defaulted further follow-up. Also, as it was retrospective, the treatment regimes were not absolutely standardised. Notwithstanding that, it is interesting that our study showed that a smaller proportion of patients with Class IV disease were in remission after their first course of AZA (42.86%) compared to CPM (83.33% and 90.91% for oral and IV CPM respectively), suggesting a greater efficacy of CPM.

The proportion of patients going into ESRF varies; a figure as high as 21.2% was found in a series which included patients from the 1950s[17]. However, more recent authors have found the proportion to be lower, 6.1% in a study from the United States[11] and 15% in a study from Europe[16]. From the Asian region, one study from Malaysia found that only 6.6% of their patients with Class IV disease went into ESRF after 10 years of follow-up but this study was complicated by the fact that 21% of their patients died from other causes[6]. A study from Hong Kong showed that 81.2% of their patients still had normal renal function after 10 years[4] and one study from China showed that 11.6% of their lupus nephritis patients went into ESRF[5]. Therefore, we feel that the proportion of patients going into ESRF would be small, and as such, they would not substantially alter the practical conclusions of this study, which are, in those patients who are treated for Class IV lupus nephritis, a larger proportion of those given CPM achieve remission compared to the group given AZA alone.

This study also found that the median times to remission for all the regimes is similar, ranging from 12 to 16 months. There have been little data in the literature on the time to remission in lupus nephritis, although it has been said that the response to IV CPM should be seen by 4 to 6

months[1]. For IV CPM, the time to remission has been shown to vary from as short as a median time to remission of 10 months [18] to a mean of 21.2 months[19]. We were unable to find any such data for AZA. Our results confirm the clinical impression that treatment for lupus nephritis needs to be continued between 18 to 24 months before assessing the response to treatment.

The relapse rate following treatment of lupus nephritis varies. Studies have found that the rates of relapse have ranged from 25% at 5 years and 46% at 10 years[20], 36% early after therapy withdrawal [21] to 50% at 79 months after IV CPM[18]. Our study result of 41.5% relapse after the first course of therapy would be consistent with this. One option to reduce a high relapse rate would be to consider prolonged treatment regimes as there was only a 13.6% relapse rate in a group of patients treated for a minimum of 5 years before withdrawal of treatment was considered but this was associated with a higher incidence of major complications[22].

One reason why there is concern regarding the use of CPM is due to the higher frequency of side effects compared to AZA. Premature ovarian failure is a major complication following the use of CPM, especially oral CPM, in SLE patients, as many of these patients will be premenopausal women. The incidence of amenorrhoea following CPM therapy ranges from 26% to 71% [10,23,24,25]. It is related to the total cumulative dose of CPM given. Thus, it is more common in patients given oral CPM compared to IV CPM [10] and more common in patients on long course IV CPM compared to short course CPM [23]. Our incidence of 41.4% patients becoming amenorrhoeic after CPM is in keeping with previous studies, as is the fact that more patients on oral CPM become amenorrhoiec after treatment compared to IV CPM due to the higher cumulative dose of CPM when on the oral regime. It is known that the incidence of amenorrhoea increases with age [23,24,25] and although this group of patients were young with a mean age of 25.3 years, the proportion that had premature menopause was still alarmingly high. The cumulative dose of CPM that leads to ovarian failure is not definitely known, but previous papers have suggested a mean dose of 28.3g [25], over 36g [24] or an approximate minimum total dose of 200-300 mg/kg [26]. This is not dissimilar to our finding of a mean dose of 32g in those who became amenorrhoeic on oral CPM. We would therefore suggest that it would be prudent to try to keep the total cumulative dose of CPM to below 20g per patient to minimize the risk of premature ovarian failure.

The treatment of lupus nephritis is associated with significant morbidity with 50.5% of our patients having a significant drug-related side effect from their therapy. This is similar to a rate of 49% found in a long-term follow-up of lupus nephritis patients[22]. With regard to the other complications, herpes zoster was the most common infection (6.8% patients), in keeping with other studies [6,10] and cataracts secondary to corticosteroid therapy (8.7% patients). The latter is a well recognised complication of corticosteroid therapy [27]. Therefore, as this is a young group of patients, they would need to be monitored for future problems, although there is a suggestion from the literature that significant cataracts requiring surgery are rare [22,27]. This would be consistent with this group of patients whose cataracts were all detected on routine ophthalmological assessment and not because they had any symptoms. Haemorrhagic cystitis has been reported to occur in 17% of patients with lupus treated with long-term oral CPM [10]. This is a much higher figure than the 1 case (1%) of haemorrhagic cystitis seen in this study in a patient on oral CPM.

In conclusion, for Class IV lupus nephritis, CPM would be the agent of choice in inducing remission. However, it is associated with a higher complication rate, especially amenorrhoea, compared to AZA alone.

References

1. Wallace DJ, Hahn BH, Klippel JH. Lupus nephritis, in 'Dubois' Systemic Lupus Erythematosus', 5th Ed., eds Wallace DJ, Hahn BH, Philadelphia: William and Wilkins, 1997; 1053-65.
2. Wang F, Wang CL, Tan CT, Manivasagar M. Systemic lupus erythematosus in Malaysia: a study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. Lupus 1997; 6: 248-53.
3. Thumboo J, Fong KY, Chng HH et al. The effects of ethnicity on disease patterns in 472 Orientals with systemic lupus erythematosus. J Rheumatol 1998; 25: 1299-304.
4. Mok CC, Wong RWS, Lau CS. Lupus nephritis in southern Chinese patients: clinicopathologic findings and long-term outcome. Am J Kidney Dis 1999; 34: 315-23.
5. Shen K, Yu Y, Tang Z, Liu Z, Li L. The prognosis of biopsy-proven lupus nephritis in Chinese patients: long term follow-up of 86 cases. Chin Med J (Engl) 1997; 110: 502-507.
6. Chan AYK, Hooi LS. Outcome of 85 lupus nephritis patients treated with intravenous cyclophosphamide: a single centre 10 year experience. Med J Malaysia 2000; 55: 14-20.
7. Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25: 1271-77.
8. Churg J, Bernstein J, Glassock RJ: Lupus Nephritis, in 'Renal Diseases. Classification and Atlas of Glomerular Diseases', eds Churg J, Bernstein J, Glassock RJ, New York, Igaku-Shoin, 1995; pg 151.
9. Felson DT, Anderson J. Evidence for the superiority of immunosuppressive drugs and prednisolone over prednisolone alone in lupus nephritis. N Engl J Med 1984; 311: 1528-33.
10. Austin HA III, Klippel JH, Balow JE et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986; 314: 614-19.
11. Gourley MF, Austin HA III, Scott D et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996; 125: 549-57.
12. Boumpas DT, Austin HA III, Vaughan EM et al. Controlled trial of pulse methylprednisolone versus two regimes of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992; 340: 741-45.
13. Cameron JS. What is the role of long-term cytotoxic agents in the treatment of lupus nephritis? J Nephrol 1993; 6: 172-76.
14. Steinberg AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes cyclophosphamide versus those treated with prednisone only. Arthritis Rheum 1991; 34: 945-50.
15. Bansal VK, Beto JA. Treatment of lupus nephritis: a meta-analysis of clinical trials. Am J Kidney Dis 1997; 29: 193-99.
16. Nossent HC, Koldingsnes W. Long-term efficacy of azathioprine treatment for proliferative lupus nephritis. Rheumatology (Oxford) 2000; 39: 969-74.
17. Berden JHM. Lupus nephritis. Kidney Int 1997; 52: 538-58.
18. Ioannidis JPA, Boki KA, Katsorida ME et al. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophosphamide. Kidney Int 2000; 57: 258-64.
19. Pando JA, Gourley MF, Boumpas DT, Austin HA III, Balow JE, Klippel JH. Rates of renal remission and relapse in patients with lupus nephritis treated with bolus cyclophosphamide. Arthritis Rheum 1994; 39 (Suppl): S179.
20. Ciruelo E, de la Cruz J, Lopez I, Gomez-Reino JJ. Cumulative rate of relapse of lupus nephritis after successful treatment with cyclophosphamide. Arthritis Rheum 1996; 39: 2028-34.
21. Pablos JL, Gutierrez-Millet V, Gomez-Reino JJ. Remission of lupus nephritis with cyclophosphamide and late relapses following therapy withdrawal. Scand J Rheumatol 1994; 23: 142-44.
22. Bono L, Cameron JS, Hicks JA. The very long-term prognosis and complications of lupus nephritis and its treatment. Q J Med 1999; 92: 211-18.
23. Boumpas DT, Austin HA III, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk for sustained amenorrhea in patients with systemic lupus

erythematosus receiving intermittent pulse cyclophosphamide therapy. Ann Intern Med 1993; 119: 366-69.

24. Wang CL, Wang F, Bosco JJ. Ovarian failure in oral cyclophosphamide treatment for systemic lupus erythematosus. Lupus 1995; 4: 11-14.

25. Mok CC, Lau CS, Wong RW. Risk factors for ovarian failure in patients with systemic lupus erythematosus receiving cyclophosphamide therapy. Arthritis Rheum 1998; 41: 831-37.

26. Rikvees SA, Crawford JD. The relationship of gonadal activity and chemotherapy-induced gonadal damage. JAMA 1988; 259: 2123-25.

27. Quismorio FP. Systemic corticosteroid therapy in systemic lupus erythematosus, in 'Dubois' Systemic Lupus Erythematosus', 5th Ed., eds Wallace DJ, Hahn BH, Philadelphia: William and Wilkins, 1997; 1141-62.