ORIGINAL ARTICLE

Outcome of 85 Lupus Nephritis Patients Treated with Intravenous Cyclophosphamide: A Single Centre 10 Year Experience

A Y K Chan (MRCP), L S Hooi (MRCP), Department of Medicine and Haemodialysis Unit, Hospital Sultanah Aminah, Johor Bahru

Summary

Retrospective analysis was done on 85 patients (76 female, 9 male) with lupus nephritis who started intravenous cyclophosphamide between 1/1/1989 and 31/12/1998. The initial renal biopsy (World Health Organisation) classification was III (4.7%), IV (89.4%) and V (5.9%). Average serum creatinine at time of biopsy was 0.12±0.12mmol/l. Median duration of nephritis before biopsy was 2 months (range 0 - 133). Median duration of follow-up from time of biopsy to outcome (death or end-stage renal failure) was 3.3 years (range 0.3 - 11.8). Nineteen patients died. The calculated proportion alive at 5 years was 75% and at 10 years 64%. The calculated proportion alive with renal function was 74% and 54% at 5 and 10 years respectively. Fifty-two patients completed cyclophosphamide therapy at the end of the study. There were ten episodes of herpes zoster, the most common infection seen. No malignancy was reported.

Key Words: Outcome, Lupus nephritis, Cyclophosphamide (intravenous)

Introduction

Systemic lupus erythematosus (SLE) with renal involvement has a higher prevalence rate among Asians than other racial groups[1]. WHO class III and IV form the largest proportion of biopsy findings among lupus nephritis patients[2,3]. These two WHO classes if untreated have the worst outcome. Renal survival at five years for WHO class IV ranged from 25 - 40% without treatment[4]. Much of the patient survival that is seen today is not contributed by immunosuppressives alone. The introduction of potent anti-hypertensive drugs, antibiotics and renal replacement therapy has led to improvement in survival.

The objective of this study is to determine the outcome of lupus nephritis patients given intravenous cyclophosphamide in a centre in Malaysia where the disease is rife and dialysis acceptance and prevalence rates low by Western figures[5].

Materials and Methods

The charts of all patients who had received at least one dose of IV cyclophosphamide between 1st January 1989 to 31st December 1998 at the Hospital Sultanah Aminah Johor Bahru (HSAJB) were analysed. Those fulfilling the American Rheumatology Association criteria[6] for SLE and with biopsy proven lupus nephritis WHO class III, IV and V were included in this retrospective review. Nephritis was defined by the presence of proteinuria of 0.5g/day, haematuria (>5 RBC/high power field) or presence of cellular casts in the sediment. The histopathological reports of the renal biopsies were reviewed and classified according to the revised 1995 WHO classification of lupus nephritis[7]. Intravenous cyclophosphamide was given at a dose of 0.5g/m^2 body surface area. Patients initially received monthly cyclophosphamide for three months, then two monthly for three doses and followed by three monthly

doses to complete ten doses over 2 years. The dose of cyclophosphamide was lowered if the total white cell count one week post administration was below 4000/μl. Additional doses were given if patients had active nephritis after the tenth dose. The first patient enrolled received cyclophosphamide on the 15th January 1989 and the last patient enrolled received her first dose on the 10th December 1998. The study was terminated at 30th June 1999.

Statistical analysis

The start date was the date of the first renal biopsy. Death was the primary endpoint. Patients alive at 30th June 1999 were censored. The patient whose outcome was unknown was censored at the date of the last follow up. Renal survival was the secondary end point, which is the time to ESRF defined as needing chronic dialysis or death. Kaplan-Meier survival function was used for the time-to-event analysis, which is appropriate for censored data. Log rank test was used to determine the influence of prognostic factors on the risk for renal failure or death. $P<0.05$ is taken as statistically significant. Medcalc ® for Windows was used to analyse the data.

Results

Patient demographics

Between 1st January 1989 and 31st December 1998 there were 85 patients with lupus nephritis class III, IV or V who were given at least one dose of intravenous cyclophosphamide at the Hospital Sultanah Aminah Johor Bahru. All patients received oral prednisolone. One patient had oral cyclophosphamide and azathioprine, and two patients had azathioprine before intravenous cyclophosphamide.

There were 76 females and 9 males. The female to male ratio was 8.4:1. Patients' race, district of origin, age at onset of SLE and WHO class are summarised in Table I, Figures 1 and 2. There were four paediatric (<12 years) patients and they presented to the adult nephrology unit before the inception of paediatric nephrology practice at the hospital (1995). 13 - 19 years was the modal group at diagnosis of SLE. 58.8% of the patients were from the district of Johor Bahru.

Table I
Patient Characteristics

Variable	Mean ± SD	n
Age (yrs)	25.2 ± 10.2	85
	%	n
Female	89.4	76
Race		
Malay	55.3	47
Chinese	37.6	32
Indian	5.9	5
WHO class		
III	4.7	4
IV	89.4	76
V	5.9	5

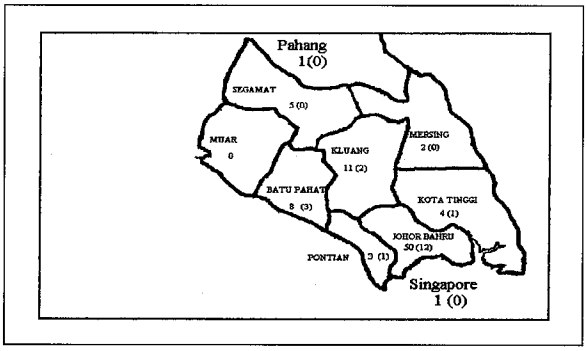

Fig. 1: Origin of 85 patients according to districts in the State of Johor, Malaysia.

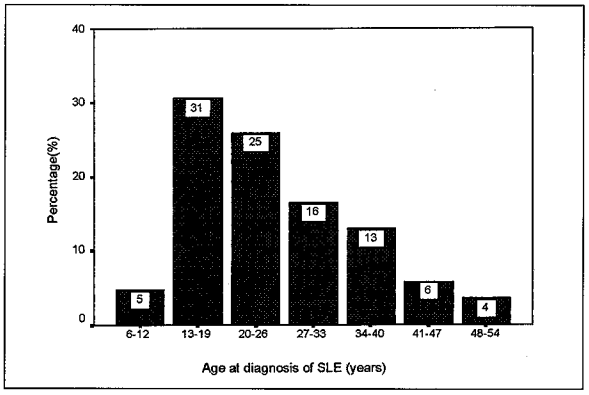

Fig. 2: Age of patients at diagnosis of SLE.

Renal disease and histopathology

Table II summarises the serum creatinine level at biopsy, interval between onset of SLE and nephritis, and duration of nephritis before biopsy in relation to histologic class. 62.4% of the patients had evidence of nephritis within six months of diagnosis of SLE. 10.6% had nephritis diagnosed 5 years or more after the onset of SLE. 65.9% had their first biopsy within 6 months of diagnosis of lupus nephritis.

The mean serum creatinine at time of biopsy was 0.12±0.12mmol/l. Sixteen patients (15 class IV, 1 class V) had serum creatinine of >0.12mmol/l at the time of biopsy. Seven of them required peritoneal dialysis at time of biopsy.

Outcome

Table III summarises the outcome of the 85 patients as at 30th June 1999. Six patients were lost to follow up. With the aid of the National Registration Department's death registry, five of them were found to be dead. Only one patient's outcome could not be determined. Six patients moved to different centres for further follow up. Of these one is dead.

Five patients developed ESRF. Median time to ESRF from renal biopsy was 3.3 years (0.4 - 8.9). Three patients had serum creatinine >0.1 mmol/l at time of biopsy. Two patients are on haemodialysis and one is on continuous ambulatory peritoneal dialysis. Two patients died after reaching ESRF.

Table II
Serum Creatinine at Time of Biopsy, Interval between Diagnosis of SLE to Nephritis, Duration of Lupus Nephritis before Biopsy and Duration of Follow up in Relation to Histologic Class in the First Biopsy in 85 Patients with Lupus Nephritis

WHO Class*	Serum creatinine at biopsy (mmol/l)	Diagnosis of SLE to Nephritis (mths)		Nephritis to Biopsy (mths)		Biopsy to Outcome** (yrs)	
	Mean+SD	Median	Range	Median	Range	Median	Range
III	0.08 ± 0.02	7	0 - 50	5	0.6 - 14.9	6.0	0.8 - 11.8
IV	0.12 ± 0.12	0	0 - 181	1.9	0 - 113	2.9	0.3 - 10.1
V	0.08 ± 0.06	13	0 - 107	16.2	0 - 133	9.5	1.0 - 11.2
Total	0.12 ± 0.12	17.6	0 - 181	2	0 - 133	3.3	0.3 - 11.8

* *Class III : focal proliferative; class IV : diffuse proliferative; class V: membranous*
** *Outcome : death or ESRF*

Table III
Outcome of 85 Lupus Nephritis Patients in Relation to WHO Class in the First Biopsy at 30th June 1999

WHO Class	Male	Alive	%	ESRD	%	Dead	%	Outcome unknown	%
III	0	3	75.0	0	0.0	1	25.0	0	0.0
IV	8	54 (4)	71.1	5*	6.6	16 (3)	21.1	1 (1)	1.3
V	1	5 (1)	100	0	0.0	0	0.0	0	0.0
Total	9	62	72.9	5	5.9	17	20.0	1	1.2

Numbers in parentheses represent male patients
**Two patients died after reaching end stage renal failure*

Table IV
Characteristics of the 19 Patients who Died

Patient	Sex	WHO Class	No. of Doses of Cyclophosphamide Received (n)	Total Dose Received (g)	Cause of Death	Last Dose of Cyclophosphamide to Death (mths)	Time from Biopsy to Death (yrs)
1	M	IV	1*	0.4	Defaulted	3.7	0.5
2	M	IV	4*	2.8	Defaulted	38.8	4.7
3	M	IV	2*	1.4	Defaulted, hepatitis B cirrhosis	71.2	6.3
4	F	IV	2*	1.2	Defaulted	4.0	0.7
5	F	IV	4*	2.7	Cerebral lupus	2.0	1.0
6	F	IV	1*	0.4	Active lupus	0.6	0.3
7	F	IV	1*	0.6	Defaulted	2.0	1.9
8	F	IV	6*	4.4	Pneumonia	2.0	1.1
9	F	IV	3*	2.0	Active lupus with sepsis	5.3	0.7
10	F	IV	5*	2.3	Active lupus	4.4	1.1
11	F	IV	8*	5.2	Acute on chronic renal failure	0.4	8.2
12	F	IV	3*	2.7	ESRF	6.8	0.8
13	F	IV	11	5.9	Defaulted	7.6	2.5
14	F	IV	11	7.2	Defaulted	15.4	3.3
15	F	IV	10	6.9	Cerebral lupus	19.4	3.7
16	F	III	15	10	Active lupus with sepsis	32.3	6.4
17	F	IV	9	5.2	Active lupus with sepsis	10.5	2.7
18	F	IV	10	5.1	Bacterial meningitis	1.2	2.0
19	F	IV	12	7.2	ESRF	9.3	3.3
Mean ± SD				3.9 ± 2.8		12.5 ± 17.7	2.69 ± 2.22

** Did not complete cyclophosphamide therapy*

Table IV details the characteristics of the 19 deaths. Mean time from biopsy to death is 2.69±2.22 years. Seven patients died after defaulting treatment and/or follow up. Nine patients died of active lupus and/or sepsis. The mean interval between death and the preceding dose of cyclophosphamide was 8.6±10.7 months in these 9 patients.

Fifty-two patients completed cyclophosphamide therapy at the end of the study period (Table V). The mean dose of cyclophosphamide received was 7.7±2.1g. Twenty patients are still on treatment. Ten patients did not complete either because they defaulted or died. Nine of them had less than six doses before dropping out. In one patient, treatment was discontinued because of thrombocytopenia.

Table V
Status of Intravenous Cyclophosphamide Therapy at 30th June 1999

Treatment Status	Number
Completed	52
On going	20
Did not complete	
- defaulted or died	10
- reached ESRF	2
- due to complications	1
Total	85

Tables VI and VII look at the relationship between the prognostic factors and outcomes. The differences in outcome between the age at onset and sex were not significant. There was a relationship between serum creatinine >0.12mmol/l at biopsy and ESRF (p=0.004). However if ESRF or death were combined as an outcome this relationship is not significant.

Survival at 5 years was 75% and at 10 years was 64% (Fig. 3). Survival with life supporting renal function at 5 years was 74% and at 10 years was 54%.

Complications of treatment

No malignancy or haemorrhagic cystitis was observed in the 85 patients. Herpes zoster was the leading cause of infection (Table VIII).

Discussion

This is a retrospective analysis on 85 WHO class III, IV and V lupus nephritis patients who were given at least one dose of IV cyclophosphamide between 1989 and 1998.

The female-to-male ratio is typical of lupus elsewhere[8]. Age at onset of SLE where three-quarters were diagnosed between the ages of 13 - 33 years, is also in agreement with other reported series[1]. It is a well-known fact that

Table VI
Prognostic Factors in Relation to Outcome in 84 Patients (One Unknown Outcome)

Prognostic factors		Outcome					
		ESRF or dead	Alive with renal function	p value	ESRF	No ESRF	p value
Serum creatinine at biopsy (mmol/l)	< 0.12	18	51	0.69	2	67	0.004
	> 0.12	4	11		3	12	
Age at diagnosis of SLE (yrs)	< 30	15	42	0.71	3	54	0.65
	> 30	7	20		2	25	
Sex	F	19	57	0.62	5	71	0.47
	M	3	5		0	8	

Table VII
Outcome and Total Dose Received in the 52 Patients who Completed Cyclophosphamide Therapy at 30th June 1999

WHO class	Dose of cyclophosphamide (g)	Outcome			
		Alive	ESRF	Dead	Outcome unknown
III	8.1 ± 1.7	2	0	1	0
IV	7.6 ± 2.1	37	3	5	1
V	7.4 ± 1.7	3	0	0	0
Total	7.7 ± 2.1	42	3	6	1

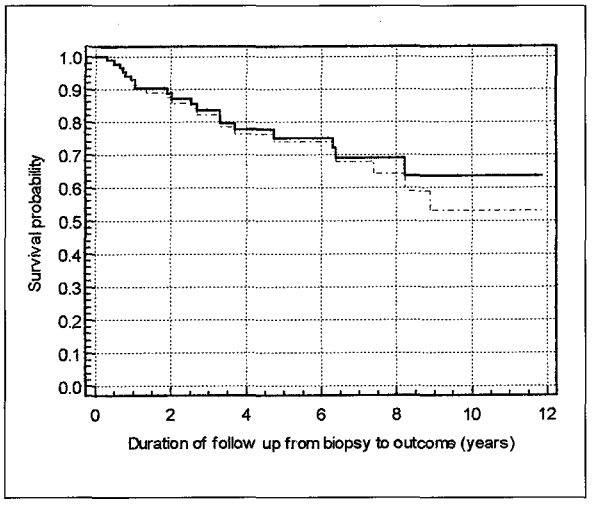

Fig. 3: Kaplan-Meier curve showing probability of survival of 85 patients with lupus nephritis.

——— Patient survival

—·—·—·—·— Alive with renal function

Table VIII
Infections Occurring during Administration of IV Cyclophosphamide

Infections	Number
Herpes zoster	10
Urinary tract infection	9
Pneumonia	5
Tuberculosis	2
Staphylococcal abscess	1
Total	27

nephritis manifests early in the course of SLE[9]. This group of patients replicates this observation. Thus as far as demographics are concerned, this group of patients was representative of a typical lupus population.

The IV cyclophosphamide regimen employed is a modification of that used by the National Institutes of Health[10]. This modified regimen was used because of the need to balance the benefit of cyclophosphamide from its side effects, as the optimal dose and duration of cyclophosphamide in the treatment of lupus nephritis is open to debate[11]. It is now known that the effect of cyclophosphamide can be achieved without inducing leucopenia[12]. The dose of cyclophosphamide was not titrated to lower the white cell count to a nadir of 2000 /ul.

Death occurred early in the course of lupus nephritis in this group of patients. Of the 19 deaths 7 could be directly attributed to defaulting on follow up and/or treatment. Only one of the defaulting patients was from outside the Johor Bahru district. Male patients are more likely to default than female patients (5/9 vs 4/76). A poor understanding of the nature of the disease could have led to non-compliance. Death from sepsis as a result of over immunosuppression is a contentious issue. Only two patients died within two months of the preceding dose of cyclophosphamide. The initial two year period of lupus nephritis therefore represents the most crucial time in the natural history of this disease. Non-compliance, active lupus and sepsis are important causes of adverse outcome.

Adverse factors which have been associated with ESRF are WHO class IV nephritis and serum creatinine >0.12mmol/l at time of biopsy[15]. In this study serum creatinine >0.12mmol/l at time of biopsy was significantly associated with ESRF.

The probability of remaining alive with renal function at 5 and 10 years is 74% and 54% respectively. Attempts to compare survival figures of other studies of different designs and inclusion criteria would be incorrect. Dooley *et al* retrospectively reported on the outcome of 89 patients with class IV lupus nephritis treated with intravenous cyclophosphamide[13]. Renal survival at 5 years was 71%. However patients who died before reaching ESRF were censored in that study. While Mok *et al*'s review included patients with a minimum one year follow up post renal biopsy[14]. In our series the large number of deaths with intact renal function largely contributed to the depressed figures.

No haemorrhagic cystitis was reported, and this observation is consistent with the use of the intravenous route of cyclophosphamide[10]. There were no malignancy observed. Only 28 patients have been followed up for more than 5 years. Close surveillance is required because cyclophosphamide has been linked to

uroepithelial tumours; relative risk 3.7, non-Hodgkin's lymphoma; relative risk 10.9, and squamous cell; carcinoma relative risk 5[16].

Conclusion

This series reports a 75% 5 year survival in lupus nephritis patients on intravenous cyclophosphamide. The main causes of death are non-compliance, active lupus and sepsis. Patient attrition arises early in the course of treatment. The task of treating lupus nephritis patients is in keeping them alive. Educating patients on the nature of the disease may promote adherence to treatment, follow up and lower mortality.

Acknowledgement

We would like to thank the Director General of Health of Malaysia for permission to publish this article.

References

1. Neumann K, Wallace DJ, Azen C *et al.* Lupus in the 1980s: III. Influence of clinical variables, biopsy and treatment on the outcome in 150 patients with lupus nephritis seen at a single center. *Semin Arthritis Rheum* 1995; 25: 47-55.
2. Golbus J, McCune WJ. Lupus nephritis: classification, prognosis, immunopathogenesis, and treatment. *Rheum Dis Clin North Am* 1994; 20: 213-42.
3. Cameron JS. Lupus Nephritis. *J. Am Soc Nephrol* 1999; 10: 413-24.
4. Baldwin DS, Lowenstein J, Rothfield NF, Gallo G, McClusky RT. The clinical course of the proliferative and membranous form of lupus nephropathy. *Ann Int Med* 1970; 73: 929-42.
5. Lim TO, Lim YN (eds). 5th Report of the Malaysian Dialysis and Transplantation Registry, Ministry of Health Malaysia. 1997: 2.
6. 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.
7. Churg J, Bernstein J, Glassock RJ. Lupus nephritis. In: Churg J, Bernstein J, Glassock RJ (eds). Renal diseases - classification and atlas of glomerular diseases. New York : Igaku - Shoin, 1995: 151.
8. 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: 248-253.
9. Derksen R, Hene R, Kater L. The long - term clinical outcome of 56 patients with biopsy - proven lupus nephritis followed at a single center. *Lupus* 1992; 1: 97-103.
10. Austin HA, 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. Dimitrios T, Boumpas MD, Austin HA *et al.* Risk for sustained amenorrhoea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. *Ann Int Med* 1993; 119: 336- 69.
12. Eiser AR, Grishman E, Dreznin S. Intravenous cyclophosphamide in the treatment of type IV lupus nephritis. *Clin Nephrol* 1993; 40: 155-59.
13. Dooley MA, Hogan S, Jennette C, Falk R. Cyclophosphamide therapy for lupus nephritis: poor renal survival in black Americans. *Kidney Int* 1997; 51: 1188-195.
14. Mok CC, Wong RWS, Lau CK. Lupus nephritis in Southern Chinese patients: clinicopathologic findings and long-term outcome. *Am J Kidney Dis* 1999; 34: 315-23.
15. Conlon PJ, Fischer CA, Levesque MC *et al.* Clinical, biochemical and pathological predictors of poor response to intravenous cyclophosphamide in patients with proliferative lupus nephritis. *Clin Nephrol* 1996; 46: 170-75.
16. Kinlen LJ. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am J Med* 1985; 78 Suppl 1A: 44-49.