Long-term prognosis of 160 patients with idiopathic membranous nephropathy and nephrotic syndrome, and efficacy of combination therapy with corticosteroid and cyclosporine

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Background

We reported that combination therapy with corticosteroid and cyclosporine for idiopathic membranous nephropathy with nephrotic syndrome led to the introduction of remission earlier in comparison with other treatments at the 53rd ERA-EDTA meeting. It remains controversial whether cyclosporine is effective for improving the long-term renal prognosis.

Objectives

We examined the long-term renal prognosis of patients with idiopathic membranous nephropathy and differences in the prognosis among treatment methods.

Methods

- Design: retrospective cohort study
- Patients: 281 patients with membranous nephropathy diagnosed based on kidney biopsy findings in our hospital between 1979 and 2016, and 160 patients who underwent immunosuppressive therapy for nephrotic syndrome and were followed-up for at least 1 year, excluding those with secondary membranous nephropathy.
- Parameters investigated: age, gender, blood pressure, excretion of urinary protein, hematuria score at the time of treatment initiation, use of RAS inhibitors, treatment methods, and laboratory data as follows, total protein, serum albumin, urea nitrogen, serum creatinine, eGFR, total cholesterol.
- Outcome: end-stage renal disease (ESRD) or a 50% increase in the creatinine (Cre) level.
- Definitions: "ESRD" was defined as dialysis initiation or renal transplantation. "50% increase in the creatinine level" was defined as 1.5-fold or more creatinine increase compared to the level at the start of treatment and observed three consecutive times at least.
- Statistics: a log-rank test was performed using the Kaplan-Meier method. In addition, Cox's proportional hazard analysis was conducted using factors involved in kidney hypofunction as covariants. P values less than 0.05 were considered statistically significant.

Treatment strategy of patients

P group	Corticosteroids were given in the form of prednisolone starting at 20 to 40 mg/day orally and tapered over a period of 4 weeks or more according to the response to therapy.
CPA group	Cyclophosphamide was administered orally at 50 mg/day and stopped after 8 to 12 weeks. Given prednisolone dose was 15 to 40 mg/day orally.
CyA group	Cyclosporine was administered orally at 100 to 150 mg/day. Given prednisolone dose was 10 to 30 mg/day orally.

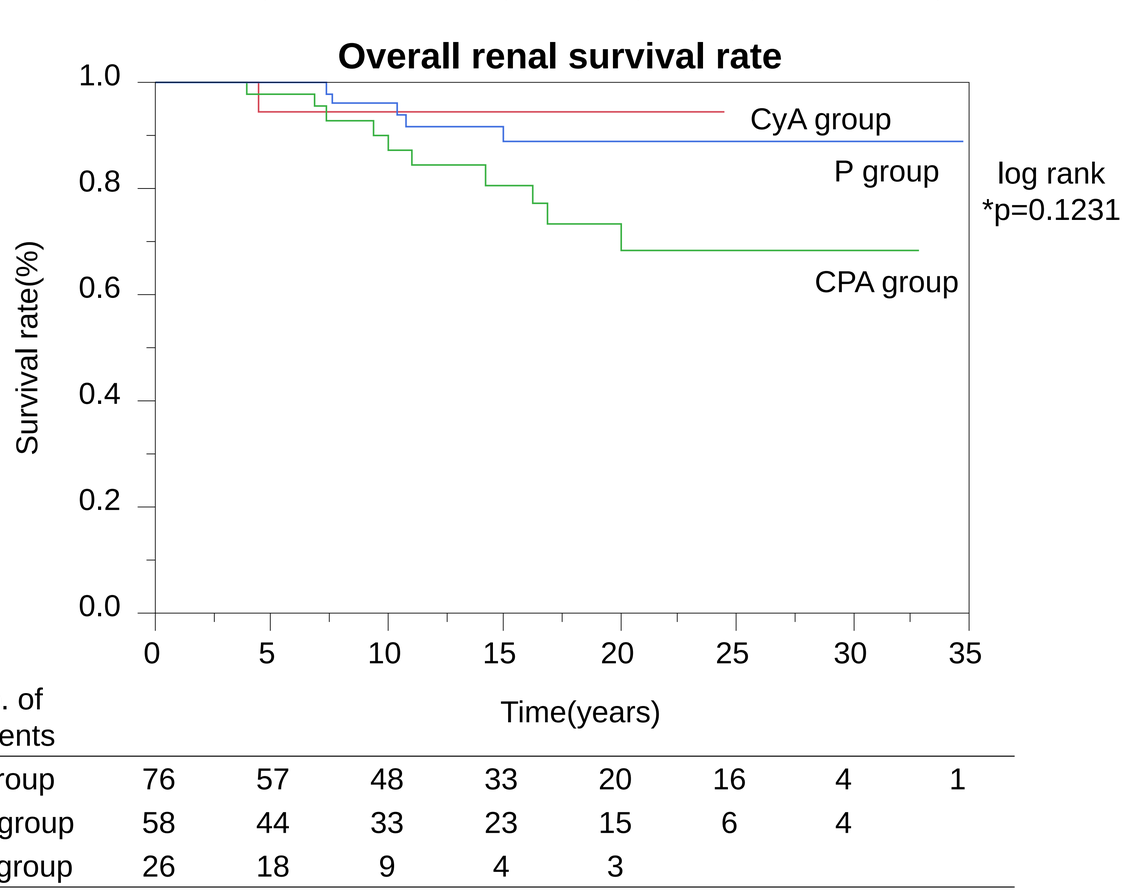
Results

Baseline characteristics

Variables	Treatment groups			
	P group (*n* = 76)	CPA group (*n* = 58)	CyA group (*n* = 26)	p value
Age (years)	52.9 ± 12.6	52.4 ± 9.9	59.7 ± 12.1	0.0209
Gender (M : F)	43 : 33	32 : 26	16 : 10	0.8590
MAP (mmHg)	96.2 ± 13.5	100.6 ± 15.5	94.6 ± 13.1	0.1144
Proteinuria (g/day)	5.7 ± 3.2	4.9 ± 3.2	3.7 ± 2.2	0.0115
Hematuria score*	0.9 ± 1.1	1.0 ± 1.2	1.3 ± 1.1	0.3586
Total protein (g/dL)	5.0 ± 0.7	5.2 ± 0.9	5.3 ± 0.9	0.1886
Serum albumin (g/dL)	2.5 ± 0.6	2.6 ± 0.8	2.7 ± 0.7	0.3590
Urea nitrogen (mg/dL)	14.8 ± 4.6	15.4 ± 5.8	15.5 ± 6.0	0.7543
Serum creatinine (mg/dL)	0.8 ± 0.2	0.9 ± 0.2	0.8 ± 0.2	0.5061
eGFR (ml/min/1.73m^2)	72.6 ± 16.5	70.4 ± 20.0	74.0 ± 17.9	0.6560
Total cholesterol (mg/dL)	327.7 ± 92.6	294.6 ± 92.1	322.1 ± 105.6	0.1389
RAS inhibitors (y : n)	11 : 65	18 : 40	11 : 15	0.0071

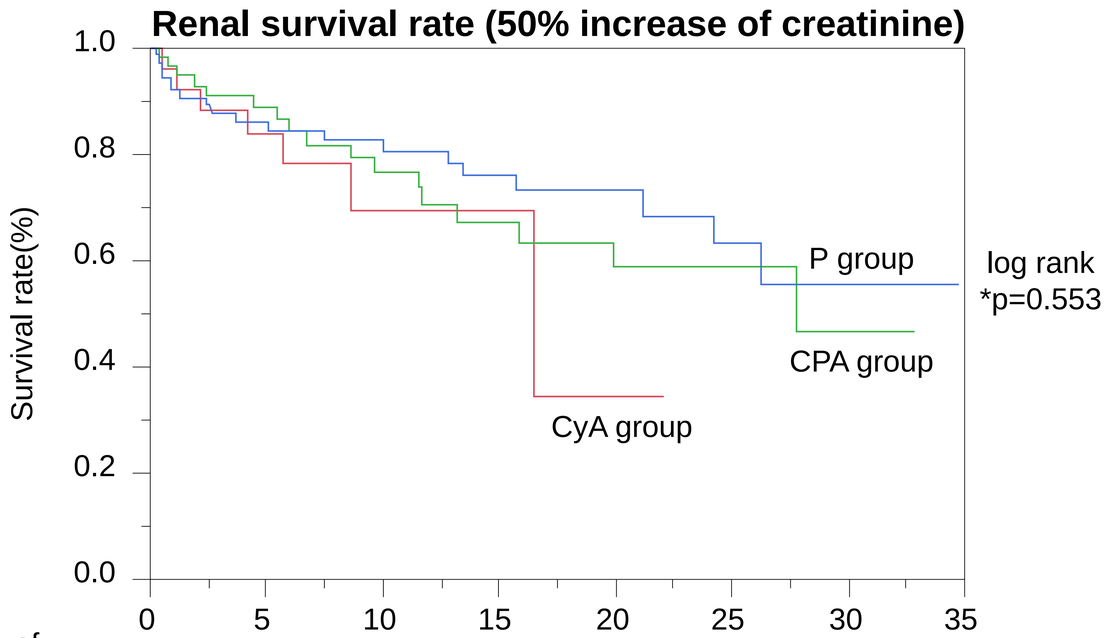
Values are expressed as mean ± SD, or number (percentage).
Abbreviations are: MAP, mean arterial pressure(mmHg), RAS, Renin Angiotensin System
*Hematuria score: U-RBC/HPF <5/HPF=0, 5-9/HPF=1, 10-29/HPF=2, 30-49/HPF=3, >50/HPF=4, macro hematuria=5,

Overall renal survival rate



No. of patients	Time(years)							
P group	76	57	48	33	20	16	4	1
CPA group	58	44	33	23	15	6	4	
CyA group	26	18	9	4	3			

Renal survival rate (50% increase of creatinine)



No. of patients	Time(years)							
P group	76	51	43	30	18	14	3	1
CPA group	58	41	29	20	13	6	4	
CyA group	26	16	8	3	2			

Factors associated with 50% increase of serum creatinine

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age (every 10y)	2.00	1.45-2.78	<0.0001	2.17	1.49-3.22	<0.0001
Gender (F as ref.)	0.65	0.35-1.18	0.1544	0.55	0.29-1.05	0.0713
MAP (every 10mmHg)	1.39	1.15-1.67	0.001	1.39	1.08-1.77	0.0095
Proteinuria (g/day)	1.05	0.96-1.14	0.2824	1.07	0.97-1.17	0.1962
Hematuria score	1.08	0.80-1.40	0.6101			
Total protein (g/dL)	0.72	0.49-1.07	0.1017			
Serum albumin (g/dL)	0.65	0.41-1.03	0.0695			
Urea nitrogen (mg/dL)	1.02	0.96-1.08	0.4752			
Serum creatinine (mg/dL)	1.33	0.30-5.37	0.7015			
eGFR (10ml/min/1.73m^2)	0.87	0.72-1.05	0.1493	1.00	0.82-1.21	0.9769
Total cholesterol (10mg/dl)	1.02	0.98-1.06	0.2657			
CyA group (vs CPA group)	1.48	0.59-3.18	0.3759	1.03	0.35-2.85	0.9511
P group (vs CPA group)	0.77	0.41-1.40	0.3857	0.88	0.43-1.81	0.7169
RAS inhibitors (yes)	2.46	1.27-4.59	0.0087	1.33	0.60-2.88	0.4743

Summary

- When regarding ESRD as an outcome, the renal survival rates after 10 years in the P, CPA, and CyA groups were 96.1, 87.4, and 94.7%, respectively. Those after 20 years were 89.1, 69.1, and 94.7%, respectively.
- When regarding a 50% increase in the Cre level as an outcome, the rates after 10 years were 80.7, 76.8, and 69.5%, respectively.
- There were no significant differences among the 3 groups (log-rank, p=0.553).
- Cox's proportional hazard analysis involving adjustment with the sex, blood pressure, urinary protein level, Alb level, eGFR, and treatment methods showed that the hazard ratios of combination therapy with cyclosporine and monotherapy with corticosteroid were 1.03 (95%CI: 0.35-2.85) and 0.88 (95%CI: 0.43-1.81), respectively, regarding combination therapy with cyclophosphamide as a reference. There were no significant differences among the 3 groups.
- Age and MAP are the factors related to outcome of 50% increase of Cre levels.

Discussion

- In this study, CPA group therapy is different from KDIGO guideline recommendations. The usage of CPA is not cyclical use, mean CPA dosage is 0.88 mg/kg/d, and corticosteroid is in the form of orally prednisolone.
- Cyclosporine is beneficial reducing proteinuria in nephrotic syndrome, but relapse is often occur (1,2,3). In this study, we don't analyze about relapse of proteinuria, and don't evaluate that the change of immunosuppressive agents.
- Nephrotoxicity is a well-known adverse effect of cyclosporine. We couldn't give a consideration to this point.
- Hassan reported that CyA was effective in achieving sustained long-term remission without relapses, when gradually tapered to low maintenance dose given for 5.5 years(4).
- According to Cochrane Database 2014, there was no evidence that calcineurin inhibitors could alter the combined outcome of death or ESRD(5).

Conclusion

These results suggest that the effects of combination therapy with cyclosporine to prevent kidney function deterioration are similar to those of combination therapy with cyclophosphamide in idiopathic membranous nephropathy patients with nephrotic syndrome.

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