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Oral cyclophosphamide versus chlorambucil in the treatment of patients with membranous nephropathy and renal insufficiency

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Summary

We treated patients with idiopathic membranous nephropathy (iMGN) and renal insufficiency, using: (i) ($n=15$) monthly cycles of steroids (1 g methylprednisolone i.v. on three consecutive days, followed by oral prednisone 0.5 mg/kg/day months 1, 3 and 5) and chlorambucil (0.15 mg/kg/day months 2, 4 and 6); or (ii) ($n=17$) oral cyclophosphamide (1.5–2.0 mg/kg/day for 1 year) and steroids in a comparable dose. The groups were comparable in age, renal function and levels of proteinuria. During the 6 months preceding treatment, serum creatinine levels increased from 148 ± 50 to 219 ± 73 µmol/l in the chlorambucil group and from 164 ± 86 to 274 ± 126 µmol/l in the cyclophosphamide group. Median (range) follow-ups were: chlorambucil 38 months (8–71); cyclophosphamide 26 months (5–68) (NS). Renal function improved in both groups, but the improvement was short-lived in the chlorambucil group; 12 months after starting treatment, mean serum creatinine was 6.3 µmol/l lower in the chlorambucil group and 121 µmol/l lower in the cyclophosphamide group ($p<0.01$). Four chlorambucil-treated patients developed ESRD, and five needed a second course of therapy, whereas only one cyclophosphamide-treated patient developed ESRD ($p<0.05$). Remissions of proteinuria occurred more frequently after cyclophosphamide treatment (15/17 vs. 5/15; $p<0.01$). Side-effects necessitated interruption of treatment in six patients on cyclophosphamide and in 11 on chlorambucil ($p<0.05$). In our patients, oral cyclophosphamide was better tolerated than oral chlorambucil. The suggested greater efficacy of the oral cyclophosphamide regimen needs to be ascertained by longer follow-up.

Introduction

In the majority of patients with idiopathic membranous nephropathy (iMGN), the renal disease runs a benign course; about 50% of nephrotic patients with iMGN will spontaneously enter a partial or complete remission. However, up to 40% will develop end-stage renal failure.[1] There is no consensus about the treatment of patients with iMGN.[2] Most clinicians tend to follow the recommendations of Cattran, who recently suggested that treatment with immunosuppressive drugs should be considered only in patients with long-standing proteinuria and/or evidence of deteriorating renal function.[3] Both chlorambucil and cyclosporine were mentioned as treatment options. However, information on the tolerability and efficacy of immunosuppressive treatment in patients with iMGN and renal insufficiency is limited to small, non-randomized studies. Positive effects have been described for chlorambucil,[4,5] oral cyclophosphamide,[6,7] azathioprine,[8,9] and cyclosporine.[10] Formal comparisons of immunosuppressive drug regimens have not been reported. Over the past 10 years, we have used immunosuppressive therapy in patients with iMGN and renal insufficiency.[11,12] We developed treatment schedules with chlorambucil and oral cyclophosphamide, both combined with corticosteroids. At the end of 1996, we analysed the

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long-term outcome of all patients treated with chlorambucil.[13] The results were less favourable than expected. Most remarkable was the high incidence of side-effects, often necessitating interruption or premature withdrawal of chlorambucil treatment. These results prompted us to analyse the results of treatment with oral cyclophosphamide and to compare them with those for chlorambucil treatment.

Methods

From 1986 onwards, we have used immunosuppressive therapy in patients with membranous glomerulopathy. To be eligible for such treatment, patients were required to have biopsy-proven membranous nephropathy, nephrotic syndrome and deteriorating renal function. Patients younger than 18 years or with evidence of secondary types of membranous nephropathy were excluded. In 1986, we treated one patient with chlorambucil and prednisone in a pilot phase. From 1989 onwards, patients were randomized for treatment with either chlorambucil and corticosteroids ($n=9$) or intravenous boluses of cyclophosphamide and methylprednisolone. Intravenous cyclophosphamide proved an ineffective treatment modality.[12] Therefore, we conducted a pilot study in which we treated all eligible patients with oral cyclophosphamide and prednisone ($n=7$). From 1994 till 1996, patients were then asked to participate in a randomized trial in which we compared chlorambucil and corticosteroids with oral cyclophosphamide and corticosteroids. Patients unwilling to participate in this study were treated with the oral cyclophosphamide treatment regimen. Our interim analysis revealed a particularly high frequency of side-effects with chlorambucil treatment.[13] Therefore, we decided in 1996 to halt this randomized study prematurely. Meanwhile, five patients were included in each treatment group and in parallel with the study, another five patients were treated with oral cyclophosphamide. At start of the present analysis the cumulative number of patients that had been treated with chlorambucil and prednisone was 15, whereas 17 patients had received oral cyclophosphamide and prednisone.

Treatment regimens

Patients assigned to chlorambucil treatment were treated according to the scheme originally described by Ponticelli et al.,[14] although we used a lower dose of chlorambucil in view of the more severe side-effects of this drug in patients with renal insufficiency.[4,11] In brief, the patients received three cycles of steroids consisting of intravenous pulses of methylprednisolone, 1 g on three consecutive days, followed by oral prednisone 0.5 mg/kg of body weight per day for 27 days. Each cycle was followed by 1 month of treatment with oral chlorambucil (0.15 mg/kg per day). The total duration of treatment was 6 months. Patients treated with oral cyclophosphamide received this drug in a daily dose of 1.5 to 2 mg/kg body weight for 1 year. In the pilot phase (in which seven patients were treated) concomitant treatment consisted of oral prednisone 60 mg/day or 125 mg every other day for at least 8 weeks (mean cumulative dose 8400 mg, range 4200–13650 mg). The last 10 patients received intravenous pulses of methylprednisolone, 1 g each on 3 consecutive days at the beginning of the first, third and fifth month, and oral prednisone 0.5 mg/kg every other day for 6 months. The latter schedule precisely matches the corticosteroid dose given to chlorambucil-treated patients.

All patients received diuretics and antihypertensive drugs if required. Clinical examinations, biochemical profiles and full blood counts were done every one or two weeks during the first months of treatment, and at regular intervals thereafter. The end-point was defined as deterioration of renal function requiring a second course of immunosuppressive therapy or the development of end-stage renal disease. A second course of immunosuppressive therapy was offered to patients who experienced a rise of serum creatinine of $>50\%$ over the lowest value reached after the first immunosuppressive treatment. Otherwise patients were followed until July 1997.

For calculations of renal survival, the time of renal death was defined as the time of the start of a second course of immunosuppressive treatment or the time of start of renal replacement therapy. We have used the reciprocal of serum creatinine (1000/serum creatinine level) to assess the effects of treatment on the progression of renal insufficiency. Changes in this ratio parallel changes in endogenous creatinine clearance. For the calculations, 1000 μmol/l was used as the serum creatinine level in patients on renal replacement therapy. To correct for inappropriate 24-h urine collections, the amount of urinary protein was adjusted for the amount of urinary creatinine (protein-creatinine index). A complete remission of proteinuria was defined as a reduction of the protein-creatinine index to less then 0.2 g/10 mmol creatinine, and a partial remission as a protein-creatinine index of between 0.2 and 2.0 g/10 mmol creatinine.

Statistics

Changes in biochemical parameters were analysed with repeated measures ANOVA, and post-test according to Newman-Keuls. Comparisons between groups were done by Fisher's test, Mann-Whitney U test, or unpaired t-test where appropriate.

Probabilities of survival were calculated by the Kaplan-Meier method and for comparison of survival curves the log rank test was used. Results are given as means ± SD, or medians and range when appropriate. A p value <0.05 was considered significant.

Results

The baseline characteristics of both treatment groups are summarized in Table 1. All but two patients were male. Both treatment groups were comparable with respect to age, blood pressure, renal function, proteinuria, and the interval between renal biopsy and start of the immunosuppressive treatment. In four patients of the chlorambucil group and in five of the cyclophosphamide group, this interval was more than 2.5 years. All patients had evidence of renal function deterioration. In the 6 months before the start of treatment, serum creatinine levels of patients in the chlorambucil group increased from 148 ± 50 to 219 ± 73 μmol/l; in the cyclophosphamide group, serum creatinine increased from 164 ± 86 to 274 ± 126 μmol/l (chlorambucil vs. cyclophosphamide: p = NS). Six patients in the chlorambucil group had received prednisone therapy in an earlier phase of the disease, whereas in the cyclophosphamide group, eight patients had been treated previously (four with prednisone and four with prednisone and chlorambucil). Seven patients in the chlorambucil group and nine patients in the cyclophosphamide group were treated with an angiotensin-converting enzyme inhibitor. During the course of follow-up, the blood pressures of the patients in the chlorambucil group did not differ significantly from the blood pressures in the cyclophosphamide-treated patients (systolic blood pressure at month 12; 140 ± 11 vs. 135 ± 20 mmHg (NS), at month 24; 136 ± 17 vs. 137 ± 18 mmHg, diastolic blood pressure at month 12; 89 ± 8 vs. 83 ± 8 mmHg, at month 24; 87 ± 17 vs. 85 ± 16 mmHg.

Short-term effects of treatment are given in Table 2. Both treatment regimens reversed the deterioration of renal function, as evidenced by the decrease of serum creatinine. In most patients, improvement of renal function was already apparent after 1 month of therapy. Overall, renal function improved or stabilized in 13/15 patients on chlorambucil, and in all patients on cyclophosphamide. The improvement of renal function was also evident from significant changes in the slope of 1000/serum creatinine. In the chlorambucil group the slope of 1000/Screat changed from –0.38 (95%CI –0.48 to –0.29) in the 6 months before start of treatment to 0.29 (95%CI 0.13 to 0.44) in the 6 months after start of treatment. In the cyclophosphamide group, values were –0.53 (95%CI –0.75 to –0.30) and 0.40 (95%CI 0.21 to 0.58), respectively. However, in the chlorambucil-treated patients the improvement in renal function was short-lasting. In these patients a decline in renal function was already apparent at 12 months after start of treatment, which contrasts with the findings in the cyclophosphamide-treated patients: at 12 months serum creatinine levels had changed by –6.3 μmol/l (95%CI –65 to 52 μmol/l) in the chlorambucil group and by –121 μmol/l (95%CI –166 to –76 μmol/l) in the cyclophosphamide group ($p<0.01$). This difference is also reflected in the slope of 1000/Screat from 6 to 12 months (chlorambucil –0.16, 95%CI –0.24 to –0.08 vs. cyclophosphamide 0.00, 95%CI –0.11 to 0.11, $p<0.05$).

Long-term follow-up

The median duration of follow-up was 26 months (range 5–68) in the cyclophosphamide group and 38 months (range 8–71) in the chlorambucil group (NS). Eleven of the cyclophosphamide-treated patients and 14 of the chlorambucil-treated patients were followed for at least 24 months (NS). Pertinent data for the individual patients of both treatment groups are given in Tables 3 and 4. In the chlorambucil group, four patients progressed to ESRD, whereas in five other patients a second course of therapy was

Table 1 Baseline characteristics

Group	Chlorambucil	Cyclophosphamide
n	15	17
Sex (M/F)	15/0	15/2
Age (years)	51 ± 12	53 ± 14
Time from kidney biopsy to start of treatment (months)	14 (1–120)	11 (1–157)
Blood pressure (mmHg)		
Systolic	145 ± 18	151 ± 29
Diastolic	85 ± 9	89 ± 10
Proteinuria (g/10 mmol creat)	9 ± 2.6	11 ± 5.3
ECC (ml/min)	46 ± 17	43 ± 23

Values are means ± SD or medians (range).

Table 2 Short-term effects of immunosuppressive treatment on renal function and proteinuria

	0 months	3 months	6 months	12 months
Serum creatinine (μmol/l)				
CA	219 ± 73	165 ± 56**	166 ± 54**	216 ± 99
CP	274 ± 126	171 ± 82***	165 ± 80***	174 ± 78***
Serum albumin (g/l)				
CA	22 ± 5.6	26 ± 6.0**	31 ± 6.2***	32 ± 6.8***
CP	22 ± 6.0	29 ± 5.1***	34 ± 5.2***	40 ± 4.7***
Proteinuria (g/10 mmol creatinine)				
CA	9.1 ± 2.6	8.3 ± 5.9	6.5 ± 3.9*	6.8 ± 4.4
CP	11.2 ± 5.3	4.9 ± 2.3***	3.0 ± 2.3***	2.0 ± 3.0**

CA, chlorambucil group; CP, cyclophosphamide group. Values are means ± SD. Treatment was started at 0 months. *$p<0.05$, **$p<0.01$, ***$p<0.001$ vs. 0 months.

given because of deterioration of renal function. Thus far, only one of the cyclophosphamide-treated patients has developed ESRD. The difference in renal survival between the groups is significant ($p<0.05$).

There was a striking difference in the cumulative incidence of the occurrence of a complete or partial remission of proteinuria (Figure 1). Overall, a partial remission of proteinuria was observed in five (33%) patients after chlorambucil treatment and in 15 (92%) patients after cyclophosphamide treatment ($p<0.01$). Of these latter patients, six developed a complete remission, whereas none of the chlorambucil-treated patients did ($p<0.01$). At the end of follow-up, two patients in the chlorambucil group and 11 patients in the cyclophosphamide group were still in remission. The median interval between start of treatment and development of partial remission was 6 months (range 1–24) in the chlorambucil-treated patients and 12 months (range 1–24) in the cyclophosphamide-treated patients. Four patients in the cyclophosphamide group had previously been treated with chlorambucil. Exclusion of these patients did not alter the results, as remissions still occurred more frequently in the cyclophosphamide group (11/13 versus 5/15, $p<0.01$). To further exclude as much as possible any bias because of a difference in the year of treatment start, we have analysed separately the data of patients treated from 1992 onward, and excluded the patients who received cyclophosphamide as retreatment. Results are given in Table 5. This analysis confirmed the superiority of cyclophosphamide treatment.

From Tables 3 and 4, it is evident that side-effects were observed regularly. Side-effects included leukopenia, anaemia, thrombocytopenia, infectious complications and nausea, and occurred more frequently in the chlorambucil group. Overall, only one patient in the chlorambucil group did not experience side-effects, as compared to nine patients in the cyclophosphamide group ($p<0.01$). It is unlikely that the differences in side-effects are related to the use of methylprednisolone. As indicated in Table 4, the incidence of infectious complications was similar in patients treated with or without pulse methylprednisolone.

Treatment had to be reduced, temporarily interrupted, or prematurely stopped in 11/15 chlorambucil-treated patients and in 6/17 cyclophosphamide-treated patients ($p<0.05$).

As a result, patients have used a lower cumulative dosage (9.8 ± 4.1 mg/kg) of chlorambucil than initially scheduled (13.5 mg/kg). For cyclophosphamide, this difference is less clear; the median daily dose amounting to 1.56 mg/kg.

Discussion

In iMGN, immunosuppressive therapy should be reserved for patients at high risk for developing ESRD.[3] Thus far, a steady rise in serum creatinine is the best predictor of future development of ESRD.[15,16] Therefore, it has been recommended that immunosuppressive therapy should be delayed until renal insufficiency becomes apparent. However, little is known on the efficacy of immunosuppressive treatment when it is initiated at this stage of the disease, and comparisons between the various immunosuppressive drugs are lacking. We have compared oral chlorambucil-and oral cyclophosphamide-based regimens, which have been used successfully in previous, smaller studies.[4–7] Our study confirms that immunosuppressive treatment is indeed effective, and able to preserve or even improve renal function when initiated in patients with moderately to severely impaired renal function. Furthermore, our data suggest that oral cyclophosphamide is more effective than chlorambucil, in preserving renal function as well as in inducing remissions of proteinuria.

Admittedly, in the cyclophosphamide-treated patients a longer follow-up is needed to ascertain that renal function will remain stable for a longer

Table 3 Characteristics of patients and effects of treatment in the chlorambucil group

Patient	Sex	Age (years)	Previous therapy#	Follow-up (months)	S. creatinine (μmol/l)			Proteinuria $^{+}$		Side-effects
					Start	Min	End	Start	End	
1	M	43	Y	36	304	248	ESRD	13.8	14.1	*, respiratory tract infection
2	M	34	Y	38	408	211	313**	9.6	8.7	*, leukopenia,
3	M	57	N	40	197	132	512**	7.0	10.2	*, respiratory tract infection,
4	M	66	N	39	287	232	ESRD	6.1	na	*, respiratory tract infection, renal artery stenosis
5	M	47	N	71	143	82	124	9.7	3.4	*, leukopenia
6	M	54	Y	55	176	125	441	8.7	11.3	*, axillary abscess, leuko- and thrombocytopenia
7	M	32	Y	35	231	175	ESRD	6.4	11.6	
8	M	32	Y	38	237	165	ESRD	11.9	3.1	*, mycoplasma pulmonary infection, varicella infection, osteonecrosis, leuko- and thrombocytopenia
9	M	46	N	46	176	109	88	6.7	2.6	nausea, leukopenia
10	M	62	N	25	208	108	113	9.7	1.6	*, leukopenia
11	M	59	N	12	269	146	319**	7.8	9.3	herpes zoster
12	M	67	N	23	165	102	109	6.8	1.7	*, leukopenia
13	M	43	N	8	176	119	229**	12.2	9.8	*, leuko- and thrombocytopenia, anaemia, respiratory tract infection
14	M	59	N	11	183	211	390	13.2	13.7	anaemia necessitating blood transfusions
15	M	57	Y	66	126	135	446**	7.6	11.6	*, leukopenia

S. creatinine, serum creatinine; ESRD, end-stage renal disease; NA, not analysed; $^{+}$Proteinuria is given as g/10 mmol creatinine; *patients in whom chlorambucil dose was reduced, temporarily interrupted or prematurely stopped. # Previous therapy consisted of treatment with short-term high-dose oral prednisone, shortly after the onset of the disease; Min, minimum value of serum creatinine within the first 12 months after start of treatment; **because of deteriorating renal function, five patients received a second course of therapy consisting of oral cyclophosphamide and prednisone (patients 1,3, 11,15) or azathioprine and prednisone (patient 13).

Table 4 Characteristics of patients and effects of treatment in the cyclophosphamide group

Patient	Sex	Age (years)	Previous therapy#	Follow-up (months)	S. creatinine (μmol/l)		Proteinuria^{+}		Side-effects
					Start	End	Start	End	
2	M	37	Y	49	313	215	8.7	0.86	
3	M	61	Y	48	512	274	10.2	0.40	*, respiratory tract infection
11	M	60	Y	23	319	207	9.3	0.13	
15	M	62	Y	68	446	202	11.6	4.1	
16	M	32	Y	49	492	ESRD	19.3	2.4	*, respiratory tract infection
17	M	45	Y	13	162	129	6.6	0.68	respiratory tract infection
18	M	59	N	41	196	88	5.3	5.4	malaise
19	M	60	N	33	323	135	12.9	0.08	
20	M	28	N	27	215	95	11.7	0.18	
21	F	43	N	25	210	169	9.6	0	
22	M	53	N	24	142	126	6.9	0	*, leukopenia, respiratory tract infection
23	M	70	Y	14	386	330	23	1.7	*, leukopenia, anaemia, respiratory tract infection, nausea
24	M	37	Y	8	185	138	5.3	2.0	*, nausea
25	M	70	N	5	195	144	14.1	3.1	
26	M	51	N	12	106	91	4.5	2.3	
27	M	51	N	8	149	82	8.8	1.9	
28	F	72	N	26	305	134	19.4	0.10	*, leukopenia

S. creatinine, serum creatinine; ESRD, end-stage renal disease; $^{+}$proteinuria is given as g/10 mmol creatinine; *patients in whom cyclophosphamide dose was reduced, temporarily interrupted or prematurely stopped. # Previous therapy in the earlier phase of the disease consisted of treatment with prednisone (patients 16,17,23,24) or prednisone and chlorambucil (patients 2,3,11,15). Patients 17 and 20–28 received methylprednisolone pulses.

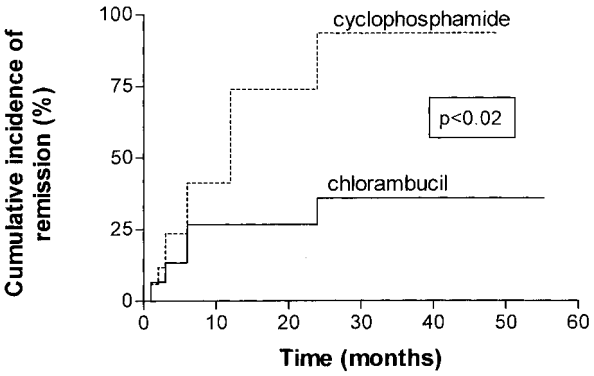

Figure 1. Cumulative incidence of partial remissions of proteinuria (i.e. proteinuria <2 g/10 mmol creatinine) in patients treated with either chlorambucil or cyclophosphamide.

time period. However, we observed a very high rate of remissions of proteinuria in this group, and it is generally accepted that the development of remissions of proteinuria is associated with a good prognosis.[17] Treatment with cyclophosphamide was reasonably well tolerated. In contrast, chlorambucil caused side-effects more frequently, often necessitating interruption of therapy.

Although our study was not fully randomized, it seems unlikely that the observed differences between both drugs are caused by a selection bias. All patients were treated prospectively; the majority of patients as part of a randomized study, or in parallel with one of the randomized studies. Moreover, both groups had similar baseline characteristics, in particular with respect to risk factors such as baseline serum creatinine, rate of renal function deterioration and the amount of proteinuria. Furthermore, the cumulative dose of steroids was comparable in both treatment groups. Subgroup analysis also suggested a higher efficacy of cyclophosphamide treatment, thus confirming and strengthening our overall conclusions.

It is quite possible that the better efficacy of cyclophosphamide is fully explained by the longer duration of cyclophosphamide therapy (12 vs. 6 months) and the lesser need to interrupt treatment. However, it is also possible that cyclophosphamide is a more effective drug than chlorambucil. A review of the available literature supports this latter explanation. Thus far, six other studies have addressed the effects of cyclophosphamide or chlorambucil in patients with iMGN and deteriorating renal function.[4–7,18,19] The results of these non-randomized, small studies and the current study are summarized in Table 6. From this table, it is evident that

Table 5 Analysis of data of patients treated from 1992 onward

	Chlorambucil ($n=8$)	Cyclophosphamide ($n=12$)	p
Follow-up duration (months)	25 ± 14	19 ± 11	
Serum creatinine month 0	170 ± 45	215 ± 83	
Rise of creatinine >50%	5	0	<0.01
Proteinuria month 0	9.3 ± 2.8	10.7 ± 5.9	
Partial remission	3	11	<0.02
Complete remission	0	5	0.055

Table 6 Summary of therapeutic trials

Reference	*n*	Sex (M/F)	S. creatinine (μmol)	Follow-up (months)	Proteinuria				Renal function		
					Cumulative		Final FU				
					CR	PR	CR	PR	IM	S	ESRD
Cyclophosphamide											
6	11	9/2	198(159–371)	33(12–54)	4	5	3	4	7	4	0
7	9	7/2	222(130–300)	83(13–144)	4	4	3	4	4	1	4
18	4	NA	>200	NA	3	1	3	1	3	1	0
This study	17	15/2	274(106–492)	26(5–67)	6	9	6	5	13	3	1
Total	41				17	19	15	14	27	9	5
Chlorambucil											
4	8	7/1	194(122–312)	21(16–42)	1	4	1	3	7	0	1
5	7	6/1	247(190–360)	32(17–59)	1	4	1	3	4	1	2
19	9	6/3	227(115–420)	20(12–24)	0	3	0	3	4	3	2
This study	15	15/0	219(126–408)	37(10–70)	0	5	0	2	4	2	9
Total	39				2	16	2	11	19	6	14

S. creatinine, serum creatinine; CR, complete remission; PR, partial remission; FU, follow-up; Im, improved; S, stabilized; ESRD, end-stage renal disease, for this analysis including patients who died or had evidence of progressive renal failure.

remissions of proteinuria are more frequent during treatment with cyclophosphamide, a complete remission occurring in 16/41 patients after cyclophosphamide and in 2/39 patients on chlorambucil ($p<0.001$). A similar significant difference is observed when counting the number of complete and partial remissions (Table 6). The differences remain present after exclusion of the data of the present study, complete remissions occurring in 11/24 patients on cyclophosphamide and in 2/24 patients on chlorambucil ($p<0.01$). Admittedly, with respect to the effects on renal function, the differences are not significant.

The available literature data do not allow meaningful conclusions on the efficacy of oral cyclophosphamide in comparison with immunosuppressive drugs such as azathioprine and cyclosporine. We are aware of only one study in which patients with iMGN and renal failure were treated with cyclosporine.[10] In this study, only 9 patients were included, and although renal function was preserved, the results are somewhat disappointing since neither improvement of renal function nor sustained remissions of proteinuria were observed. Two groups of investigators have reported on the effects of azathioprine.[8,9] The initial data, on only 10 and 6 patients, respectively, showed an improvement of renal function after start of azathioprine. In the short term, sustained remissions of proteinuria were rare, occurring in only 3/16 patients. However, with longer follow-up, results seem more favourable. Bone and colleagues recently reported 10-year follow-up data for 21 patients treated with azathioprine.[20] In most patients there was a permanent improvement of renal function, and a partial or complete remission of proteinuria occurred in up to two third of patients.[20] These data show that treatment with azathioprine has favourable effects. It should be noted however, that these results were obtained with continued, possibly lifelong treatment with low-dose azathioprine and prednisone. Longer follow-up of our cyclophosphamide-treated patients is needed to see whether limited duration of treatment with this drug has similar effects in the long run.

For chlorambucil therapy, we have adapted the treatment protocol developed by Ponticelli *et al*. for patients with iMGN and normal renal function.[14] In their patients, side-effects were uncommon (occurring in 10% of patients). Although we have used a

lower dosage, we observed a very high incidence of side-effects. Similar observations were made by Mathieson and Warwick.[4,5] This suggests that patients with renal insufficiency are more sensitive to the side-effects of chlorambucil. An even lower dose might have been better tolerated,[19] but the efficacy of such low doses has not been proven. A formal comparison of the efficacy of oral chlorambucil and cyclophosphamide can best be performed in patients with normal renal function.

In conclusion, immunosuppressive treatment preserves renal function and can result in complete remission of proteinuria in patients with iMGN and renal insufficiency. In view of its efficacy and tolerability, we prefer oral cyclophosphamide over chlorambucil for the treatment of these patients.

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