Long-term Outcome of Patients with Idiopathic Membranous Nephropathy

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Abstract: Although idiopathic membranous nephropathy (iMN) is a common glomerular disease, its therapy still remains controversial. The aim of our study was to analyse the outcome of patients with iMN diagnosed and treated in our center. We retrospectively studied 82 patients with iMN that were diagnosed between January 1991 and June 2002. The group consisted of 57 males (69.5%) and 25 females (30.5%) with a mean age of 53 years. The mean follow-up was 56 ± 38 months. Remission was achieved in 59.2% of patients treated with chlorambucil, 71.4% treated with cyclophosphamide, 85.7% treated with cyclosporine and in 71.4% of those who were left untreated intentionally. However, the proportion of patients in the different treatment subgroups differed significantly (60% vs. 8.5% vs. 8.5% vs. 23%, respectively). The relapse rate was 31.3%. The second-line treatment was effective in a majority of the patients. At the end of follow-up, almost 70% of the patients were in remission with the parameters of nephrotic syndrome significantly improved and renal function unchanged. The renal survival was 100%. Immunosuppressive therapy is effective in iMN, but spontaneous remissions occur as well. Although relapses are frequent, almost 70% of the patients were in remission at the end of follow-up. The renal survival in our group of iMN patients was very good, probably due to preserved renal function at diagnosis.

Introduction

Worldwide, idiopathic membranous nephropathy (iMN) remains the most common cause of adult-onset nephrotic syndrome (NS) [1]. The disease shows a benign or indolent course in the majority of patients, with a rate of spontaneous complete or partial remission of NS as high as 30% or more [2]. On the other hand, a substantial proportion (around 30%) of the patients progress to end-stage renal failure (ESRF) in 5 to 20 years [2–4]. The incidence rate of iMN results in the disease being the second or third most common primary glomerulopathy to terminate in ESRF [5].

The immunosuppressive treatment of iMN is still a matter of debate. Some authors treat all patients with NS, based on a randomized controlled trial conducted in Italy demonstrating that treatment with a combination of chlorambucil and prednisone improves renal survival [6]. Other authors feel that only patients at high risk of progression should be given therapy. How to identify these patients and whether they really benefit from any immunosuppressive regimen in long term is as yet uncertain [7].

During the period studied, our approach to the disease was rather active. Here we report on the outcome of our patients with iMN.

Patients and methods

We performed a retrospective analysis of all patients with iMN diagnosed in our center between January 1991 and July 2002. In this period we performed a total of

1940 renal biopsies (RB). Membranous nephropathy (MN) was diagnosed in 129 cases, which represents 6.6% of all biopsies. The available data from the Czech Registry of RB between the years 1994–2000 show that 39.3% of indications for RB represents nephrotic syndrome [8]. We could thus roughly estimate that MN is diagnosed in about 17% of patients with nephrotic syndrome. The patients with secondary MN were excluded on clinical and/or laboratory grounds. An underlying cause was identified in 40 of the 129 patients (31.0%, 70% women, 30% men). It was a drug in 18 cases, autoimmunity in 11 cases, neoplasia in 8 cases and hepatitis B in 3 cases. A detailed analysis of these patients was published elsewhere [9]. Seven patients, lost to follow-up immediately after the RB, were also excluded from the study.

The chlorambucil (CHB) regimen consisted of 6 month pulses of chlorambucil at a dose of 0.1 mg/kg/day (day 1–14) with steroids (5 mg/kg of methylprednisolone iv day 1–3, 0.5 mg/kg of prednisone day 4–14), followed by a pause without therapy (day 15–28). The treatment with cyclosporine (Cyclosporin A, CyA) was started at a dose of 5mg/kg/day in two equal doses at 12-hour intervals. Adjustments in dosages were made to achieve a whole-blood 12-hour trough level between 80–120 ng/mL (by high-performance liquid chromatography). All patients received prednisone at a maximum dose of 20 mg, which was gradually tapered to a maintenance dose not exceeding 10mg per day. The effect and adverse effects were assessed at 6 months. In responsive patients was, the minimal time of the CyA administration was one year. Cyclophosphamide (CYC) was administered at an initial dose of 1.5–2mg/kg/day and gradually tapered by approximately 0.5 mg/kg/day every 3 months and discontinued after one year of treatment. Steroids were used concomitantly at a maximum dose of 0.5 mg/kg of prednisone, which was gradually tapered to a maintenance dose not exceeding 10 mg per day. The azathioprine (AZA) – based regimen was identical with that of CYC. Conservative treatment was not standardized; however, most of the patients were using angiotensing-converting enzyme (ACE) inhibitors and cholesterol-lowering therapy. Anticoagulant drugs were not prescribed routinely.

Complete remission (CR) was defined as proteinuria < 1 g/day and an improvement, or at least stabilization, of renal function. Partial remission (PR) was defined as a 50% reduction of initial proteinuria, and less than 3.5 g/day with stable renal function.

The statistical analysis was performed using the following tests – the chi-square test for independence in contingency tables to evaluate categorical data, logistic regression to model categorical data, the McNemar test of symmetry in contingence tables for the cases of repeated observations and the paired t-test for repeated data, the ANOVA method with multiple comparison for continuous data. The Kaplan-Meier life survival analysis was used to assess the relapse-free survival of patients. Data were analyzed on a personal computer using statistical package SPSS v12. P values < 0.05 were considered significant.

Results

Patients' characteristics

Eighty-two patients, all Caucasian, were diagnosed with iMN in our center in the period studied. They represented 63.6% of all biopsy-proven MN cases. The iMN group consisted of 57 males (69.5%) and 25 females (30.5%) with a mean age of 53 years, ranging from 17 to 85. Other clinical and laboratory characteristics at diagnosis are outlined in table 1. The mean duration of symptoms (oedema) before diagnosis was 10 ± 31 months. The mean follow-up was 56 ± 38 months.

First-line treatment

According to first-line treatment, four different subgroups were formed – CHB (60%), CYC (8.5%), CyA (8.5%) and the untreated subgroup (23%). At baseline, the patients in all the subgroups had comparable renal function and proteinuria. The results of the treatment are shown in table 2. We did not find any significant impact on the overall response rate (CR + PR); it did not differ in the four subgroups, nor did it depend on age, sex, initial proteinuria, albumin, creatinine level, histological stage or the length of anamnesis.

Table 1 – Patients' characteristics at diagnosis (N=82)

Creatinine clearance (ml/s/1.73 m^2)	1.3 ± 0.6
Creatinine (mmol/L)	114.7 ± 61.2
Proteinuria (g/day)*	7.5 (0.5-27.7)
Albumin (g/L)	25.7 ± 7.7
Cholesterol (mmol/L)	8.8 ± 2.9
Microhematuria	67.9%
Hypertension	81.7%
Histologic stage I	14 (17.1%)
Histologic stage II	36 (43.9%)
Histologic stage III	29 (35.4%)
Histologic stage not determined	3 (3.7%)

Laboratory data are mean ± SD, *Median (range)

Table 2 – Response to first-line treatment in the respective subgroups

Group	No of pts	CR	PR	NR	?/death	RR
CHB	49	14*	15	19	0/1	59.2%
CYC	7	5	0	2	0	71.4%
CyA	7	3*	3	1	0	85.7%
untreated	19	4	1	2	8/4	26.3%
Total	82	26	19	24	13	54.9%

Abbreviations are: CHB = chlorambucil, CYC = cyclophosphamide, CyA = cyclosporine A,
No of pts = number of patients in each group, CR = complete remission, PR = partial remission, NR = no remission, ? = response unknown, RR = response rate (CR + PR). * one of the patients died

Relapses

Not all patients remained in stable remission. Of the 45 patients who developed either a CR or a PR, 14 relapsed to nephrotic range proteinuria. The estimated mean time to relapse was 85 (95%CI 66; 104) months. The details on the relapse rate in the respective subgroups of patients are given in table 3. The occurrence of relapse did not differ in the four subgroups, nor did it depend on sex, age, initial proteinuria, albuminemia, creatinine or histological stage. The relapses increased with the time of follow-up ($p = 0.03$).

Second-line treatment

A second course of immunosuppressive therapy was offered to patients who did not respond to the first-line treatment ($N = 24$) or who relapsed to nephrotic range of proteinuria ($N = 14$). These 38 patients were treated with CyA (55.2%), CHB (15.8%), CYC (5.3%), AZA (5.3%), or were left untreated (18.4%). Their outcome is described in Table 4. There were no significant differences in the effect of the individual immunosuppressants, whereas the outcome of the untreated subgroup was worse when compared to all the treated patients ($p = 0.04$).

Table 3 – Relapses in the respective subgroups over the follow-up period

	No of R	RR	Time to R / months
CHB	8/29	27.6	15.0
CYC	4/5	80.0	49.5
CyA	2/6	33.3	4.0
untreated	0/5	0.0	
Total	14/45	31.1	17.0

Abbreviations are: CHB = chlorambucil, CYC = cyclophosphamide, CyA = cyclosporine A, No of R = number of relapses in each group, RR = relapse rate

Table 4 – Second-line treatment in the respective subgroups

Group	No of pts	CR	PR	NR	unknown	RR
CHB	6	2	4	0	0	100%
CYC	2	0	1	1	0	50%
CyA	21	11	6	4	0	81%
AZA	2	2	0	0	0	100%
Untreated	7	0	0	2	5	0%
Total	38	15	11	7	5	68.4%

Abbreviations are: CHB = chlorambucil, CYC = cyclophosphamide, CyA = cyclosporine A, No of pts = number of patients in each group, CR = complete remission, PR = partial remission, NR = no remission, RR = response rate (CR + PR)

The status at the end of follow-up

The clinical data of the patients at the end of follow-up are shown in Table 5. The status at the end of follow-up did not depend on age, sex, initial albuminemia, creatinine, or the length of anamnesis. The longer the patients were followed, the higher was the probability of remission at the end of follow-up ($p = 0.045$), the lower the initial proteinuria and the bigger the probability of being in remission at the end of follow-up; the significance was, however, only borderline ($p = 0.097$).

The renal survival was 100%. The laboratory data at the end of follow-up are shown in Table 6. The overall reduction of proteinuria was significant ($p = 0.001$), as was the decrease in cholesterol ($p = 0.001$) and microhematuria ($p = 0.001$) and the increase in albuminemia ($p = 0.001$). The renal function did not significantly change when measured both by serum creatinine and by GFR. When we analysed the changes in these parameters in the four subgroups according to the first-line treatment, the same results were noted in all actively treated subgroups (CHB, CyA and CFA). On the other hand, no significant changes apart from borderline decline in cholesterol ($p = 0.054$) were detected in the untreated subgroup.

Mortality

Seven patients died, at a median age of 69 (54–85) years. One male patient (54 years, untreated) died one month after diagnosis of bleeding from perforation of gastric ulcer and peritonitis. Post-mortem, pulmonary embolism was found. One male patient (85 years, untreated) died 4 months after diagnosis in another hospital

Table 5 – Clinical data at the end of follow-up

Status	No of pts	Proportion
Remission	57	69.5%
Active disease	10	12.2%
Dead	7	8.5%
Lost from FU	8	9.7%
Total	82	100%
Renal Failure	0	0%

Abbreviations are: No of pts = number of patients in each group, FU = follow-up.

Table 6 – Patients' characteristics at at the end of follow-up

Creatinine clearance (ml/s/1.73 m^2)	1.5 ± 0.8
Creatinine (mmol/L)	133.7 ± 97.9
Proteinuria (g/day)*	0.71 (0.04–18.87)
Albumin (g/L)	38.7 ± 7.5
Cholesterol (mmol/L)	5. 7 ± 1.5
Microhematuria	12.3%

Laboratory data are mean ± SD. *Median (range)se.

of complications of femoral fracture. A post-mortem examination was not performed and no additional data on this patient were available. One female patient (74 years) died 3 months after the diagnosis of pulmonary oedema in another hospital (again, no other data available); this was after the third pulse of CHB, and she was still nephrotic. One male patient (62 years) died 3 months in another hospital of sepsis while nephrotic. He had refused suggested treatment. One female patient (69 years) died of pancreatitis 12 months after diagnosis in CR induced by cyclosporine that was already tapered. One male patient (55 years) died of heart failure of unknown etiology 11 months after diagnosis in CR induced by CHB that was no longer administered at the time of death. The last (female) patient (70 years, untreated) died suddenly at home of unknown causes a few days after the diagnosis.

Discussion

Our study describes the prognosis of patients with iMN. Admittedly, this is a retrospective study and has all the drawbacks inherent to such kind of analysis, inclusive of uneven distribution of the patients in the different treatment subgroups. However, it represents a large cohort of patients with a mean follow-up of almost 5 years. The demographic data confirm the men: women ratio in iMN of approximately 2:1 [10].

The choice of the first-line treatment was based on the predominant practice in the respective years. The patients in the early nineties were treated with CYC. Most of the patients were given CHB in a modified "Ponticelli regimen" [6] and some of the patients in the late nineties were administered CyA as the first-line treatment. The untreated group consisted of patients left untreated intentionally and non-compliant patients whose outcome was mostly unknown. The response rates in the treated groups were high (CHB 59.2%, CYC 71.4%, CyA 85.7%). The results of the untreated subgroup are distorted by a high percentage of deceased and lost patients. Out of the 7 untreated individuals who were still alive and whose results were obtainable, a total of 5 developed spontaneous remission and never relapsed (response rate = 71.4%). These patients represented those left untreated intentionally. They had mostly non-nephrotic proteinuria. Nevertheless, the degree of initial proteinuria was not found to influence the achievement of remission. In general, no parameter studied (treatment subgroup, age, sex, proteinuria, albumin, creatinine, histological stage, length of anamnesis) could be acknowledged to increase the probability of remission. The remission achievement was roughly comparable to that reported by other investigators, which is 22–47% in untreated patients to 75% in treated by CyA, 82% by CYC and 88% by CHB [6, 11, 12].

One-third of the patients who achieved remission experienced at least one relapse after first-line treatment, which seems to be similar or slightly better than the findings of others. The relapse rate reported in literature ranges from 28% at

5 years after treatment with CYC [12] to 43% at 1 year or 50% at 2 years after treatment with CyA [12, 14]. In our hands, there was a marked difference between the disease-free interval between the respective treatment groups: the CyA treated patients tended to relapse early, sometimes when the dose of CyA was only tapered or immediately after the withdrawal, creating a CyA-dependent population. Again, the occurrence of relapse could not be predicted based on any variable studied.

The second-line treatment was similarly effective in inducing remission without any of the used immunosuppressant being clearly superior, but again the proportion of the patients was uneven in the respective subgroups. CyA was used in the majority of the patients, as it is often the case in patients resistant to steroids and cytotoxic agents in alternating monthly cycles or if clinical considerations indicate it may be inappropriately toxic. The untreated subgroup represented almost entirely non-compliant individuals whose outcome was not detectable. The two unresponsive patients were not treated because they refused suggested treatment.

At the end of follow-up, almost 70% of the patients were in remission with the parameters of NS (proteinuria, albumin, cholesterol) significantly improved and renal function unchanged. In our hands, the probability of entering in remission increased with the time of follow-up. As spontaneous remission had occurred in our patients, we could speculate that if the patients were given enough time, they would have developed remissions irrespectively of the treatment given. That would be basically consistent with the findings of increasing spontaneous remissions with the time of follow-up observed by many investigators (reviewed in 3). Unfortunately, this retrospective non-randomized study can not answer this question. On the other hand, untreated patients who present with NS have a higher risk for developing complications (e.g. thrombosis, accelerated atherogenesis) than patients who enter into remission. Seven of our patients have died so far. None of them died of causes directly related to the treatment. On the other hand, in three patients the disease itself could be in part responsible for the death (sepsis, pulmonary oedema and pulmonary embolism in nephrotic patients). The renal survival was 100%, which is superior to the results published so far. Admittedly, the length of follow up is still short to assess hard endpoints such as ESRF. Nevertheless, the reported renal survival in untreated patients ranges from 20 to 30% at 7 years [15, 16] to 60% at 10 years [6] and rarely exceeds 90% in treated patients [6, 13, 16]. The reason for preservation of renal function in the course of time lies probably in the early diagnosis and good renal function at baseline. As the renal function did not significantly change toward the end of follow-up, we did not identify any risk factors for progression. For the same reason, we could not show the superiority of one therapeutic approach or another. Since both the duration and severity of proteinuria are known to be surrogate markers for progression, a rapid remission achievement and

maintenance should be an advantage. Moreover, we demonstrated patients dying of complications of NS. The expected reduction of comorbid conditions associated with remission of proteinuria would therefore be another important benefit.

Conclusion

In summary, the treatment with immunosuppressive agents leads to remissions of iMN. Nevertheless, spontaneous remissions occur as well and increase in time. Although relapses are frequent, almost 70% of the patients were in remission at the end of follow-up. The renal survival in our group of iMN patients was very good probably due to preserved renal function at diagnosis. We could not demonstrate any significant beneficial effect of any therapeutic regimen on long-term prognosis of the patients.

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