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A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy

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A 10-year follow-up of a randomized study with methylprednisolone and chlorambucil in membranous nephropathy. The natural course of idiopathic membranous nephropathy is variable, with some patients slowly progressing to renal failure while others maintain normal renal function over the entire time. Whether to treat this disease or not is controversial due to the lack of controlled data about the long-term effects of treatment. We updated at 10 years the results of a controlled trial in which 81 patients with idiopathic membranous nephropathy and nephrotic syndrome were randomly assigned to receive symptomatic therapy (39 patients) or a treatment of six months with methylprednisolone and chlorambucil (42 patients). The probability of surviving without developing end-stage renal disease at 10 years was 92% in patients given methylprednisolone and chlorambucil versus 60% in controls ($P = 0.0038$). The slope of the reciprocal of plasma creatinine up to 10 years was significantly better in treated patients than in controls ($P = 0.035$). The probability of having a complete or partial remission of the nephrotic syndrome was significantly higher in treated patients ($P = 0.000$). Patients assigned to therapy spent significantly longer time without nephrotic syndrome than untreated patients ($P = 0.0001$). Four patients had to stop treatment because of reversible side-effects. In the long-term one treated patient developed diabetes and another one became obese. In conclusion, a six-month therapy with methylprednisolone and chlorambucil increases the probability of remission of proteinuria and protects from renal function deterioration even in the long-term. This treatment may avoid dialysis or death within 10 years to about one third of nephrotic patients with membranous nephropathy.

Idiopathic membranous nephropathy is an immune-complex mediated renal disease which is usually associated with the nephrotic syndrome. The course of the disease is variable. Some patients maintain normal kidney function with or without a spontaneous remission of proteinuria, while others progress to end-stage renal failure or die from complications related to the nephrotic syndrome. Unfortunately, the long-term outcome for each patient is difficult to predict at clinical onset, but severe proteinuria [1], elevated serum creatinine [1], or interstitial fibrosis at renal biopsy [2] are frequently associated with a poor prognosis. Whether or not to treat a patient with idiopathic membranous nephropathy is still controversial. Some controlled trials reported beneficial effects of corticosteroids [3] or of cytotoxic drugs [4–6], but other randomized studies failed to show favorable results with these agents [7–9].

In 1984 [10] we published the results of a controlled study where patients with idiopathic membranous nephropathy and nephrotic syndrome were randomized to receive supportive therapy or to be given a six month therapy with methylprednisolone and chlorambucil alternated every other month. After a median follow up of five years, treated patients had more remissions of the nephrotic syndrome and showed a better slope of the reciprocal of plasma creatinine than untreated controls [11]. A decision analysis based on the data at five years confirmed a better quality-adjusted life expectancy for patients randomized to be given combined treatment [12]. A limitation of these studies was the relatively short follow up, while the disease usually runs a slowly progressive course. Therefore, to predict the long-term renal outcome we had to use indirect measures such as the slope of the reciprocal of plasma creatinine, instead of primary end points, such as dialysis or death. On the other hand, some disquieting side effects of chlorambucil may develop in the long-term. Since we continued to follow the patients admitted to this study, we thought interesting to reanalyze the results at 10 years.

Methods

Patients

Between 1976 and 1983, 81 nephrotic adults with idiopathic membranous nephropathy were randomly assigned to be treated with methylprednisolone plus chlorambucil (42 patients) or with symptomatic therapy (39 patients). Criteria for admission and exclusion have been reported elsewhere [10, 11].

Therapy

Treatment consisted of 1 g intravenous methylprednisolone given every 24 hours for three consecutive days, followed by oral prednisone at a dose of 0.5 mg/kg/day in a single morning administration for 27 days (Cycle A). After the first month

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prednisone was stopped and the patient was given chlorambucil, 0.2 mg/kg/day for one month (Cycle B). Cycle A and B were repeated three times so that the whole treatment lasted six months, three with corticosteroids and three with chlorambucil. The clinicians were free to give a new course of methylprednisolone and chlorambucil to patients randomized to treatment only after at least two years from the first treatment.

Response criteria

Complete remission was defined as a reduction of urinary protein excretion to 0.2 g or less per day. Partial remission was defined by a daily urinary protein excretion between 0.21 and 2 g with normal plasma creatinine. Renal dysfunction was defined as an increase in the plasma creatinine concentration of at least 50% over the baseline value.

Statistical analysis

The cumulative probability of clinical event (death/dialysis or complete/partial remission for two separate analyses) was estimated according to Kaplan and Meier [13]; comparisons between strata were made with the generalized Wilcoxon test [14]. The analysis was truncated at 10 years in order to have a sufficient number of events for a reliable estimate of the cumulative probability. An index of efficacy was calculated for each patient as the percentage of the remission time, that is:

$$\frac{\text{months in remission}}{\text{total months of follow up}} \times 100$$

Then the two treatments were compared by the Wilcoxon test.

The reciprocal of the plasma creatinine values for the two treatments were compared by mixed-factorial analysis of variance for repeated measurements [15] with the treatment as a fixed "between patient" factor at two levels and time as a fixed "within patient" factor at twenty-one levels (every 6 months). The Geisser-Greenhouse [16] procedure of the the correction of the degrees of freedom for the statistical significance of the within patient terms was followed.

Patients who did not complete treatment were included in the analysis according to the intention-to-treat principle. For the four patients who died and the 19 who were lost to follow-up, data obtained at the last observation were considered.

Results

As already reported [10, 11], at presentation the treated and the control groups were similar in age, sex, duration of the disease, mean plasma creatinine, mean urinary protein excretion, prevalence of hypertension, as well as for distribution of glomerular stages, and frequency and severity of vascular and tubulointerstitial lesions at renal biopsy. All patients assigned to treatment completed the six months of therapy with the exception of four patients who stopped treatment earlier because of side effects (see later). Ten controls and nine treated patients were lost to follow-up from 12 to 96 months after randomization. The data available at the last observation and the events that occurred including endpoints, were considered for analysis. Two controls, one still nephrotic and the other one with renal function deterioration asked to be treated because of the deterioration of renal function and then were lost to follow-up 22 and 28 months after randomization with unchanged clinical conditions.

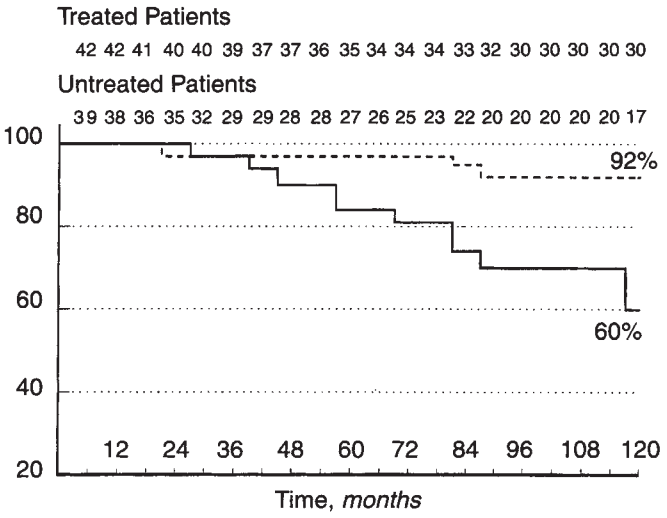

Fig. 1. *Cumulative probability of survival without dialysis in patients who received treatment (- - -) and in untreated controls (——).* The difference is significant ($P = 0.0038$).

Three control patients died. Death was always considered as the end point. A 68-year-old man with persisting nephrotic syndrome and progressive renal insufficiency died of cardiac infarct two years after admission. A 54-year-old woman had viral hepatitis and died of hepato-renal failure 40 months after randomization. A 31-year-old man with persisting nephrotic syndrome and slowly progressive renal insufficiency developed a progressive respiratory insufficiency and suddenly died of cardiorespiratory arrest, 90 months after randomization. One treated patient died of cancer two years after randomization. This 51-year-old man had been a heavy smoker. He was recognized to have a lung cancer 18 months after completing treatment.

Nine control and two treated patients had to be submitted to regular dialysis. The probability of being alive with kidney functioning at 10 years was 0.92 (range 0.83 to 1.00), 95% confidence interval (CI), for treated patients versus 0.60 (0.42 to 0.78), 95% CI for untreated controls (Fig. 1), the difference being statistically significant ($P = 0.0038$).

We evaluated the slopes of the mean reciprocal of plasma creatinine for patients followed for 10 years. We assigned an arbitrary level of plasma creatinine of 10 mg/dl (880 μmol/liter) to patients on maintenance dialysis. After 10 years the mean reciprocal of plasma creatinine as expressed in mg/dl reduced from 1.00 to 0.51 in the control group and from 1.01 to 0.84 in the treated group. The difference between the two slopes was significant ($P = 0.035$). Of interest, the slope of the reciprocal of plasma creatinine significantly dropped in the control group since the 12th month. Instead the slope tended to remain stable in treated patients until the 90th month and then reduced significantly (Fig. 2).

During the follow-up, 15 of 39 controls (38%, 23.4 to 55.4, 95% CI) versus 35 of 42 treated patients (83%, 68.6 to 93.0, 95% CI) had either a complete or a partial remission. The probability of having a remission as a first event at 10 years was significantly higher ($P = 0.0000$) in treated patients than in controls (Fig. 3). At univariate analysis among the considered factors (sex, age, treatment, duration of disease, glomerular stage, vascular lesions,

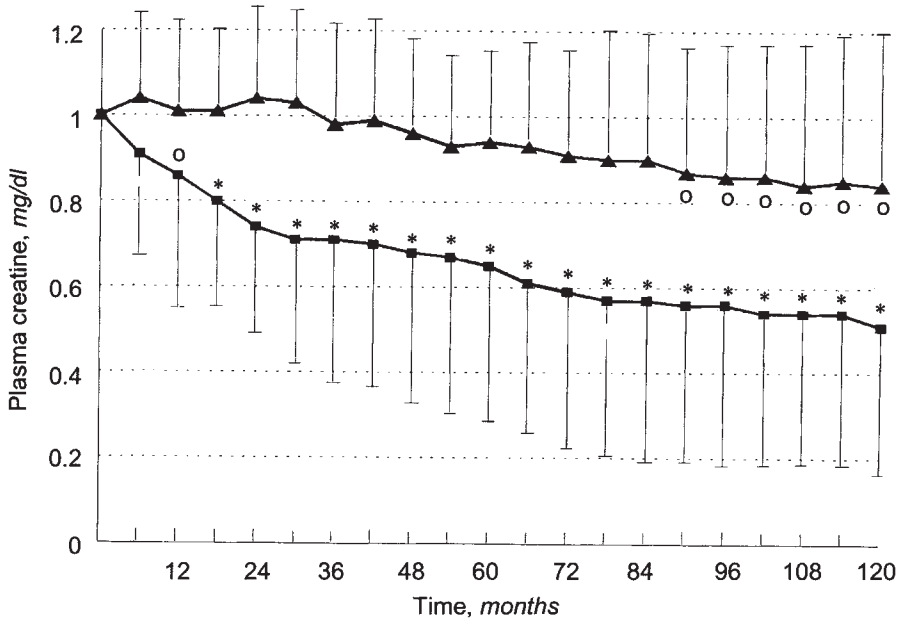

Fig. 2. *Slope of the mean reciprocal of plasma creatinine in 31 treated patients (—▲—) and in 25 untreated controls (—■—) followed for 10 years.* $^{\circ}P < 0.05$ compared to the basal value. $^{*}P < 0.01$ compared to the basal value. The difference between the two slopes is also statistically significant ($P = 0.035$).

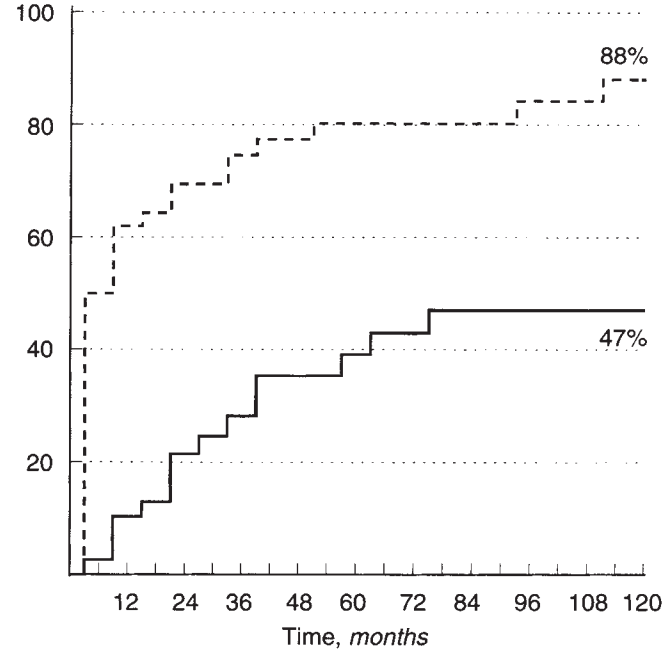

Fig. 3. *Probability of complete or partial remission of the nephrotic syndrome as a first event in the treated group (- - -) and in control group (——).* The difference between the two curves is statistically significant ($P = 0.0000$).

tubulointerstitial lesions, hypertension, plasma creatinine higher or lower than 1 mg/dl, proteinuria higher or lower than 5 g per day) only the treatment was significantly associated with the probability of obtaining a remission ($P = 0.0000$).

In the treated group four patients who attained complete (1 patient) or partial remission (3 patients) were retreated after two to three years because of relapse. All patients showed the same clinical response (1 complete and 3 partial remissions) that lasted for the overall follow-up except for one patient who had a second relapse after partial remission.

Table 1. Clinical status at the last follow-up visit

	Treated patients	Untreated patients
Total	42	39
Complete remission	17 (5)	2
Partial remission	9 (1)	11 (1)
Nephrotic syndrome	9 (3)	6 (6)
Renal dysfunction	4	8 (3)
Dialysis	2	9
Death	1	3

In brackets are the patients lost to follow up and their clinical status at the last visit. For the definitions see **Methods.**

Patients assigned to receive therapy spent significantly longer time without nephrotic syndrome than untreated patients (58% of the total follow-up period, SD ± 46.9 median 57.0%, vs. 22%, ± 37.0 median 0%; $P = 0.0001$). At the last follow-up visit 26 of 42 (61.9%, 45.6 to 76.4, 95% CI) treated patients were in remission either completely (17 patients) or partially (9 patients), while only 13 of 39 untreated controls (33.3%, 19.1 to 50.2, 95% CI) were in remission of the nephrotic syndrome (complete in 2 patients and partial in 11; Table 1).

Side effects

Four patients assigned to methylprednisolone and chlorambucil had to stop therapy between the third and the fifth month because of side-effects (two peptic ulcers, one pneumonitis, one gastric intolerance to chlorambucil). All the four patients completely recovered from side effects with adequate therapeutic measures. During treatment, two other patients had moderate leukopenia, two experienced tremors, two cramps and one anxiety. Two patients had gastric pain during chlorambucil and one developed an increase in serum transaminases. All these side-effects reversed after treatment was completed. In the long-term one patient

developed obesity and another patient developed diabetes mellitus four years after treatment. No other side effects were reported in the long-term follow-up.

Discussion

In this controlled study, the 10-year survival probability with a functioning kidney was 0.60 in patients who never received any specific treatment. These patients spent almost 80% of their time with a nephrotic syndrome, and about 2/3 of untreated patients who survived without dialysis were still nephrotic at the last follow-up visit. The outcome was considerably different in patients who received methylprednisolone and chlorambucil. The 10-year survival probability with functioning kidney was 0.92, significantly better than that observed in the untreated group. The slope of the reciprocal of plasma creatinine remained stable in the treated group up to 90 months, then reduced but the decline was significantly slower than that observed in the untreated controls. Moreover, patients given methylprednisolone and chlorambucil had significantly more complete or partial remissions of the nephrotic syndrome than untreated patients. At univariate analysis the treatment was the only factor significantly associated with remission. Looking at the whole follow-up, patients assigned to methylprednisolone and chlorambucil spent 58% of their time without nephrotic syndrome and 60% of them were non-nephrotic at the last follow-up visit. Thus, this study shows that a course of six months with methylprednisolone and chlorambucil favors the remission of the nephrotic syndrome and can avoid dialysis or death within 10 years to about one third of patients with membranous nephropathy and a nephrotic syndrome.

One might wonder whether these differences are due to the fact that untreated controls had by chance a particularly bad outcome, in spite of the homogeneous distribution at presentation of those clinical and histological factors that may be associated with a poor prognosis. The natural history of membranous nephropathy is difficult to assess since it can vary according to the selection criteria, geography, and genetic characteristics. Some studies reported a 10-year kidney survival of 50% or less in Caucasian patients with nephrotic syndrome [17–19]. Better results have been reported in other series. Donadio, Torres and Velosa [20] reported a 10-year kidney survival of 58%. Cattran et al [21] found that the actuarial probability of maintaining normal creatinine clearance at eight years was 60% in untreated patients. Both these studies included a number of patients with asymptomatic proteinuria. In spite of this, the results were not so different from the 60% 10-year kidney survival observed in our untreated nephrotic controls. Recently Schieppati et al [22] reported a pure kidney survival rate of 0.72 at eight years for 100 patients with membranous nephropathy who never received either corticosteroids or cytotoxic agents. They concluded that such a benign natural course of the disease does not support the use of corticosteroids and immunosuppressive agents. In their retrospective study 37% of patients were non-nephrotic, the median follow-up was 39 months and deaths were excluded from the analysis. Instead in our controlled trial all patients had a nephrotic syndrome, the follow-up was considerably longer, and deaths were considered in the calculation. Even with these penalties the survival rate with kidney functioning of our untreated controls was 0.70 at eight years, meaning that they fared at least as well as the untreated patients reported by Schieppati et al [22]. Thus, in spite of the favorable natural course observed in our untreated controls methylprednisolone and chlorambucil significantly increased the probabilities of surviving without dialysis at 10 years, and significantly improved the chances of attaining remission.

A main concern with the use of our protocol is the possible developement of iatrogenic complications. Some 10% of patients had to stop treatment because of side effects which completely reversed after discontinuation of therapy. Theoretically chlorambucil may expose to neoplasia, particularly acute leukemia. This severe complication appears to be related to high cumulative doses, to a long duration of treatment [23, 24], and to the nature of the disease, being more frequent in patients with cancer [25] or polycytemia vera [26] which is considered to be a pre-leukemic condition. We did not see any case of leukemia in this series. We observed one case of lung cancer which developed in a heavy smoker a few months after randomization. We cannot exclude that membranous nephropathy was secondary to a pre-existing cancer in this patient, since it is well known that membranous nephropathy can be associated with cancer [27], and can often precede the diagnosis of cancer of months or even years [28].

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