PART XX

GENERAL NEPHROLOGY

Chairmen
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CONTROLLED TRIAL OF MONTHLY ALTERNATED COURSES OF STEROID AND CHLORAMBUCIL FOR IDIOPATHIC MEMBRANOUS NEPHROPATHY

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Summary

Forty-nine patients with membranous nephropathy (MN) and nephrotic syndrome (NS) were randomly allocated to supportive or specific therapy. The latter consisted of steroids or chlorambucil given in alternate months for a cumulative period of six months. Three patients in the experimental group were dropped from the study because of therapy related side-effects. At the end of follow-up there were significantly more patients in complete or partial remission in the experimental group than in the controls. The mean serum creatinine did not change in treated patients, but it significantly increased in controls.

Introduction

Membranous nephropathy (MN) is the most frequent cause of nephrotic syndrome (NS) in adults. Its clinical course is variable. Spontaneous remission may occur in some patients, but approximately half of the patients progress to renal failure within 15 years [1]. The possibility of modifying the natural course of nephropathy with specific therapy is still debated, but some encouraging results have been obtained with steroids [2, 3] and alkylating agents [4, 5].

In this controlled multicentre trial we studied the effects of a new therapeutic regimen based on the administration of steroids and chlorambucil given in alternate months for a total period of six months.

Patients and methods

Adult patients with NS (proteinuria > 3.5g per day) and a picture of MN in a renal biopsy were considered for the study. Attempts were made to exclude patients with systemic lupus erythematosus, diabetes mellitus, drug reaction,
neoplasia, hepatitis or other infectious diseases. Patients with plasma creatinine > 1.7mg/100ml and those who had had previous steroid or cytotoxic agent treatment were excluded. After informed consent was obtained the patients were randomly allocated to receive specific therapy or to supportive treatment only. Only patients who were followed for at least one year after the start of treatment were included in the evaluation of the results.

Specific therapy

One gram of methylprednisolone was given intravenously over 20–30 minutes for three consecutive days. Then 0.5mg/kg oral prednisone was administered daily for 27 days (cycle A). At the end of the first month, prednisone was stopped and 0.2mg/kg/day chlorambucil was given for one month with dose reduction if leucocytes fell below 5,000 per cubic millimetre (cycle B). After one month of chlorambucil, the drug was stopped and a new cycle A was begun for 30 days, followed by a cycle B and then by a cycle A and a cycle B.

Definitions

Complete remission: proteinuria < 0.2g per day with normal renal function. Partial remission: proteinuria 0.2–2g per day, with normal renal function. Unchanged: proteinuria > 2g per day and stable renal function. Worsened: plasma creatinine increased at least 50 per cent over basal value.

Statistical analysis

The difference between the numbers of remissions in the two groups was analysed by Fisher's exact test. Analysis of covariance was used to assess differences in serum creatinine between the two groups.

Results

Forty-nine patients with idiopathic MN and NS were admitted to the study. Twenty-five patients were allocated to supportive therapy only and 24 to specific therapy.

Drop out

Three patients in the experimental group were dropped from the study. One patient developed severe hyperglycaemia after having received the first three i.v. pulses of prednisolone. His plasma creatinine and proteinuria are still unchanged two years later. Another patient developed peptic ulcer during the second cycle A, when his plasma creatinine was normal. He stopped therapy. Two years later his plasma creatinine is 3.3mg/100ml. The third patient had gastric intolerance to chlorambucil and stopped therapy in the second month. One year later his plasma creatinine and proteinuria are unchanged. One control patient was excluded.
from the study. This patient, who had had progressive renal insufficiency, developed hepatitis after two years, when her plasma creatinine was 4.4mg/100ml. She died from liver failure 40 months after having been enrolled in the study.

Figure 1
Outcome (Figure 1)

Among the 21 treated patients who were followed for at least one year, 10 had complete remissions. In these patients proteinuria generally disappeared before the therapeutic period was completed, but in three patients complete remission occurred 5–8 months after the end of therapy. Remission persisted in all but one patient who had a relapse of non-nephrotic proteinuria four years after having achieved remission. At the end of the follow-up (mean 28 ± 14 months) nine patients are in complete remission, eight in partial remission, and four are unchanged.

Among the 24 controls, at the end of the follow-up (mean 32 ± 18 months), three patients are in complete remission, four in partial remission, 13 are unchanged and four worsened. There were significantly more patients with remissions, complete or partial, in the treated group (17 of 21) than in the control (7 of 24), (p < 0.01).

Changes in plasma creatinine (Table I)

The group of treated patients did not have any modification of the mean plasma creatinine during the follow-up, while controls showed a progressive increase. At the twelfth month the difference in the mean plasma creatinine between the two groups was statistically significant. During the subsequent period the differences persisted, but the reduced number of patients did not allow statistical evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>6 months</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated group</td>
<td>1.06 ± 0.24</td>
<td>0.99 ± 0.20</td>
<td>1.04 ± 0.22</td>
<td>0.99 ± 0.17</td>
<td>1.00 ± 0.22</td>
</tr>
<tr>
<td>(Number of patients)</td>
<td>(21)</td>
<td>(21)</td>
<td>(21)</td>
<td>(15)</td>
<td>(5)</td>
</tr>
<tr>
<td>Control group</td>
<td>1.10 ± 0.31</td>
<td>1.17 ± 0.37</td>
<td>1.27 ± 0.40</td>
<td>1.26 ± 0.42</td>
<td>1.39 ± 0.67</td>
</tr>
<tr>
<td>(Number of patients)</td>
<td>(24)</td>
<td>(24)</td>
<td>(24)</td>
<td>(16)</td>
<td>(10)</td>
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<tr>
<td>Covariance analysis</td>
<td>ns</td>
<td>p &lt; 0.02</td>
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</table>

Side effects

Tremor (two cases), anxiety (one case) and cramps (two cases) were complained of during steroid administration but disappeared in all cases after stopping steroids. One patient developed obesity and a cushingoid appearance. Another patient complained of gastric pain during chlorambucil administration. In no cases did these side-effects require withdrawal of the therapy.

Discussion

Patients receiving specific therapy had significantly more remissions than controls. Complete remission was sustained and only one of the 10 patients who became
free of proteinuria after treatment had a relapse four years later. No patient who achieved partial remission showed impairment of renal function or reappearance of NS during follow-up. None of the treated patients showed any elevation of plasma creatinine, while four of 24 controls had increases of at least 50 per cent. Moreover the mean plasma creatinine did not change in the experimental group, while that of the control group showed a significant trend towards an increase.

Previous controlled and uncontrolled studies have shown that both steroids [2, 3] and alkylating agents [4, 5] can be beneficial in MN. We decided to alternate the two different agents hoping to reduce the side-effects and to obtain synergistic therapeutic effects. During the steroid cycle, three i.v. megadoses of prednisolone were given, followed by moderate oral doses of prednisone. In our previous experience this kind of steroid administration was not accompanied by severe side effects and gave favourable results in other immunological nephropathies [6, 7]. Chlorambucil was chosen as the alkylating agent because nitrogen mustard produces less alopecia, infertility and cystitis than cyclophosphamide [8]. Malignancy following cytotoxic chemotherapy has been increasingly reported and in this regard alkylating agents are considered to be high-risk drugs [9]. However, the time of exposure seems to be critical. The duration of chemotherapy in patients with non malignant disease who later developed neoplasia was generally for some years [9]. Thus, although the possibility of de novo malignancies in patients given short-term chemotherapy cannot be completely ruled out, it is probably very rare.

In conclusion, although the fate of the MN patient should be assessed only after several years, these preliminary results indicate that our therapeutic schedule can obtain complete or partial remission in most patients with MN and can preserve renal function for at least a short time.

References

3 Coggsins CH. N Engl J Med 1979; 301: 1301
4 Suki WN, Chavez A. Am J Nephrol 1981; 1: 11

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Open Discussion

GABRIEL (London) Could I ask you Dr Ponticelli to be precise as to how you selected those patients who were treated compared with those who were not because you are after all treating the condition in which half the patients remit spontaneously.

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PONTICELLI It was a random choice. Patients with membranous nephropathy and nephrotic syndrome were admitted to the study and then they were randomly allocated treatment or not through a sealed envelope system using a single randomisation list in our centre. So there were not any differences between these patients at the beginning of the study.

DAVISON (Chairman) Dr Gabriel was asking if it was a totally random selection. Was the selection totally random? You have two groups of patients, some of whom are being and some whom are not being treated. Are you sure that the allocation of a patient into a particular group was completely random and there was no influence from the clinician looking after the patient?

PONTICELLI The selection was completely random and there was no influence from the clinician.

DAVISON Does that answer the question?

GABRIEL No, not unless you tell me who selected the patients for treatment or non treatment.

SWAINSON (Christchurch, New Zealand) Could you tell us was the selection also random for the biopsy appearances particularly EM, were all these patients at similar phases of the disease, and perhaps you could let us know whether you think there is any way you can predict whether the patients would respond or not?

PONTICELLI We only considered light microscopy and there was a good stratification between the two populations. We found that most patients in stage I or II responded to therapy. Only one of six patients in stage III or IV responded to therapy with complete remission but relapsed four years later. As far as other possible prognostic factors are concerned we must confirm previous reports which suggested that females do better than males. There were three women in the treatment group and all the three women had complete remission of proteinuria. There were five women in the control group, one achieved complete remission, two partial remission and two remained unchanged. A second prognostic factor is the duration of nephropathy before therapy. Patients who had a long duration of membranous nephropathy responded poorly to therapy. Among five patients in whom nephropathy lasted for more than two years before randomisation, three remained unchanged after therapy and two had only partial remission. So I think that these three points could be of prognostic importance.

MARSH (London) Were the patients in the two different groups matched with regard to the duration of the disease before the start of the trial?

PONTICELLI No, we only retrospectively analysed the stratification. By chance there was no difference as far as age, sex, histological stage of the disease
were concerned. The mean age of treated patients was 42 years and the mean age in controls was 45. The difference was not significant. However the interval between the onset of membranous nephropathy and the beginning of therapy was 12 months in treated groups, versus eight months in the control group. The difference was weakly significant. This last one was the only significant difference between the two groups.

OHNA (Tokyo) Is there some difference of effectiveness between Stage I, II and III?

PONTICELLI Yes there was. In the treated group there were fifteen patients with the stage I or II and we achieved nine complete remissions in them. There were six patients with stage III or IV and only one achieved complete remission.