20 YEARS AFTER METHYLPREDNISOLONE/CHLORAMBUCIL TREATMENT IN IDIOPATHIC MEMBRANOUS NEPHROPATHY STAGE II–III WITH NEPHROTIC SYNDROME

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Abstract: There is now controlled evidence that a 6-month course with methylprednisolone and chlorambucil may favour remission of the nephrotic syndrome and may significantly improve the 10-year kidney survival in patients with idiopathic membranous nephropathy. We analyzed the outcome of 15 nephrotic patients (proteinuria 7.06 ± 1.07g/d), stage II–III membranous nephropathy, aged 37.93 ± 2.32, 8 males and 7 females, with normal serum creatinine (62.8 ± 2.34 µmol/l), followed > 10 years after the treatment. It consisted of 1g i.v. methylprednisolone for three consecutive days, followed by oral steroids 0.4 mg/kg/d and chlorambucil 0.2 mg/kg/d monthly, alternatively. 10 patients, age and sex matched, who refused any treatment of any reason, represented the control group. Complete remission was defined as protein loss of 0.2 g/d, partial 0.2–2 g/d with normal creatinine and renal dysfunction as increase in plasma creatinine. The follow-up period was between 10 and 20 years. Complete remission after the treatment was noted in 9/15, partial in 4/15, and 2/15 patients did not respond. 10-year survival rate of the whole group was 100%, 15-year – 86.7%, i.e. two patients with persistent nephrotic syndrome developed end-stage renal failure after 12 years. 13/15 patients (complete, partial remission) were followed > 15 years without development of end-stage renal failure. One patient (female, 32) developed idiopathic thrombocytopenia after 8 years. 3 patients (complete remission) were followed > 20 years, they are still without proteinuria. 10-year survival rate of untreated patients was 40%. It is concluded that in nephrotic patients with stage II–III membranous nephropathy steroids/chlorambucil therapy may be effective in favoring remission and in preserving renal function.

Key words: Chlorambucil, membranous nephropathy, nephrotic syndrome, steroids.
Introduction

Idiopathic membranous nephropathy (IMN) is a common cause of the nephrotic syndrome in adults [1, 2]. In favorable cases renal function may remain stable despite persisting proteinuria and even spontaneous remission of nephrotic syndrome can occur. There are patients, however, who are invalided by or even die from complications related to the nephrotic syndrome and some other progress to end-stage renal failure [3, 4, 5]. Because of the spontaneously variable course, it is often difficult to evaluate the effects of a specific treatment on the natural outcome of IMN. The problem is further complicated by the fact that a large variety of therapeutic schedules has been used in this disease [6, 7, 8, 9, 10, 11, 12, 13, 14, 15].

In 1984 Ponticelli et al. published the results of a controlled study where patients with IMN 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 [16, 17]. After a median follow-up of five years, treated patients had more remissions of the nephrotic syndrome and showed lower values of serum creatinine than untreated controls.

The aim of the present study was to evaluate the long-term efficacy of steroid/chlorambucil treatment on the outcome of patients with IMN with similar clinico-pathological features.

Methods

Patients

15 adult patients, aged 37.93 ± 2.32, 8 male and 7 female, with stage II–III membranous nephropathy at biopsy, without mesangial proliferation and tubulointerstitial changes were treated in the way previously described by Ponticelli [16]. All patients were nephrotic, the degree of proteinuria was 7.06 ± 1.07 g/d, with normal serum creatinine (< 110 µmol/l) and normal blood pressure (< 140/90 mmHg). Control group consisted of 10 patients stage II–III, age and sex-matched, with similar clinical features, who refused the treatment of any reason.

Treatment

The treatment consisted of 1g intravenous methylprednisolone given every 24 hours for three consecutive days, followed by oral steroids at a dose of 0.5 mg/kg/daily for 27 days (Cycle A). After the first month steroid treatment was replaced by chlorambucil (0.2 mg/kg/daily) for one month (Cycle B). Cycle A and B were repeated three times, so that the whole treatment lasted 6 months.
Complete remission was defined as protein loss to 0.2 g/d, partial as proteinuria 0.2–2 g/d with normal serum creatinine. Renal dysfunction was defined as increase in plasma creatinine and end-stage renal failure as necessity of renal replacement therapy.

*Follow-up*

Out-patient follow-up was performed, with laboratory investigations monthly for the first year, every three months during the second year and every six months in patients with complete remission. The whole follow-up period was between 10 and 20 years.

*Results*

Table 1 – Таблица 1

<table>
<thead>
<tr>
<th>Survival of the treated patients – responders and not-responders</th>
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Complete remission after the treatment was noted in 9/15 and partial in 4/15 patients. Two of the treated patients with IMN did not respond. 10-year survival rate of the whole group was 100%, 15-year – 86.7%, i.e. two patients who had not respond to the treatment developed end-stage renal failure after 12 years follow-up. 13/15 patients with complete or partial remission were followed longer than 15 years, without development of end-stage renal failure. Three of the cases with complete remission were followed more than 20 years, they are still without significant proteinuria and their renal function is normal. One patient with complete remission, female, 32 years old, developed idiopathic thrombocytopenia after 8 years with appearance of non-nephrotic proteinuria (1.2 g/daily). Both disorders, proteinuria and thrombocytopenia, were successfully treated with steroids (only). Proteinuria appeared again in two patients during the follow-up. They were
male, 27 and 34 years old. Non-nephrotic proteinuria (1.2 g/daily and 2.2 g/daily) appeared after 10 years and disappeared completely after steroid treatment.

Partial remission of the nephrotic syndrome was noted in 2/10 control patients. 10-year survival rate of this group was 40%.

Table 2 – Табела 2

<table>
<thead>
<tr>
<th>Survival of the control group</th>
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<td>Преживување на контролната група</td>
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Discussion

Although some rare patients with IMN can show rapid evolution to uremia, the disease generally runs a slow progressive course, leading to renal failure in unfavorable cases only after 10 or more years [1, 2, 3, 4, 5]. This is the reason why it is difficult to decide to treat or not the patients with IMN. Only few studies reported the natural long-term outcome of IMN. In these studies the actuarial 10-year kidney survival ranged between 50 and 70% [18, 19, 20, 21, 22, 23]. At the end of the follow-up of different lengths different percentage of improvement of the nephrotic syndrome were noted (23–73%), as well as complete disappearance of proteinuria (5–30%). Our control patients presented lower 10-years survival (40%), but they all were nephrotic and it is well known that nephrotic syndrome is one of the predictive factors for poor prognosis in all glomerular diseases.

All our treated patients were also nephrotic, and their outcome was considerably different. Their 10-year survival rate was 86.7%. Moreover, patients given methylprednisolone and chlorambucil had significantly more complete or partial remissions of the nephrotic syndrome than untreated patients. It can be also seen that this way of treatment can prevent relapses taking into consideration that relapsing course of the disease is common in IMN. Relapses of non-nephrotic proteinuria were noted in two previously nephrotic patients with
complete remission. It is interesting that both relapses were noted after 10 years of follow-up.

A main concern with the use of the protocol is the possible development of iatrogenic complications. Some 10% of patients [42] with 10-year follow-up described by Ponticelli et al. [24] had to stop the treatment because of side effects which completely reversed after the discontinuation of the therapy. Three of our patients developed leucopenia during the sixth month (third with chlorambucil) with values of 2000–2800/mm3, and we stopped the therapy two weeks earlier only in one patients (the patient with WBC of 2000). Theoretically chlorambucil may expose to neoplasia, particularly acute leukemia [24]. We did not see any case of leukemia in our series, as well as Ponticelli reported in Italian [24]. One of our patients with complete remission developed acute thrombocytopenia (50,000/mm3) after 8 years, too late to be associated with chlorambucil. The disorder reversed after 8-month steroid treatment.

Analyzing our results it can be concluded than in nephrotic patients with stage II–III the IMN steroid/chlorambucil therapy may be effective in favoring remission and in preserving renal function.

REFERENCES


20 години по терапија
СО МЕТИЛПРЕДНИЗОЛОН/ХЛОРAMBУЦИЛ
КАЈ ИДИОПАТСКА МЕМБРАНОЗНА НЕФРОПАТИЈА
СТАДИУМ II–III СО НЕФРОТСКИ СИНДРОМ

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Денес постојат евидентни податоци дека 6-месечен протокол на терапија со метилпреднизолон и хлорамбуцил може поволно да влијае на појавата на ремисија на нефровниот синдром и може значајно да го подобри 10-годишното преживување на бубрегот кај пациенти со идиопатска мембранозна нефропатија. Ние го анализиравме исходот на болеста кај 15 пациенти со нефровниот синдром (протеинурија 7,06 ± 1,07г/д), стадиум II–III на мембранозна нефропатија, на возраст 37,93 ± 2,32, 8 од мажи и 7 од женски пол, со нормален сеумски креатинин (62,8 ± 2,34), следени > 10 години по терапијата. Таа се состои од 1 гр. iv. метилпреднизолон во тек на 3 дена, следено со орално давање на стероиди од 0,4 мг/кг/д и хлорамбуцил 0,2 мг/кг/д, месечно, альтернативно. Десет пациенти, на идентична возраст и полов структура, кои одбија било каква терапија од било кои причини, ја претставувал контролната група. Комплетната ремисија беше дефинирана како загуба на протеини до 0,2 г/д, парцијална 0,2–2 се нормален креатинин и ренална дисфункција како зголемување на плазмен креатининот. Периодот на следење беше помеѓу 10 и 20 години. Комплетна ремисија по терапијата беше забележана кај 9/15, парцијална кај 4/15, а 2/15 пациенти не одговорија на терапијата. 10-годишната епилептична депресија со преживување на целата група беше 100%, 15-годишната – 86,7%, т.е. двета пациенти со екзистентен нефровен синдром развива терминален фаза на хронична бубренска инсуфициенција по 12 години. 13/15 пациенти со комплетна или парцијална ремисија беа следени > 15 години без развој на терминален уремија. Една пациентка на 32 години по 8 години разви идиопатска тромбоцитопенија. Три пациенти со комплетна ремисија беа следени повеќе од 20 години, тие се уште не беле протеинурија. Десетгодиш-
ната стапка на преживување на нетретираните пациенти беше 40%. Може да се заклучи дека каж нефротските пациенти со стадиум II–III на мембранозна нефропатија терапијата со стероиди/хлорамбусил може да биде ефикасна во индуцирање на ремисијата и презервирање на бубрежната функција.

Ключни зборови: Мембранозна нефропатија, нефротски синдром, стероиди, хлорамбусил.

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