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Effective Treatment of Chronically Progressive Multiple Sclerosis with Low-Dose Cyclophosphamide with Minor Side-Effects

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Summary. Twenty-one multiple sclerosis (MS) patients with a chronically progressive course were treated with a low dose of cyclophosphamide (CY). The control group consisted of 21 MS patients with a chronically progressive course who received the standard treatment (ACTH or cortisone). The control group consisted of patients who preferred the standard therapy because of its beneficial effects. In contrast, the patients of the CY group wanted to try a new therapy because the standard therapy was not effective. Thus before starting the study the progression of the disease was faster in the CY group than in the standard therapy group. As regards age, sex and degree of disability, the two groups were comparable. For 20 of the 21 patients in the CY group the degree of disability (Kurtzke scale) remained stable over 1 year; for 2 of the 20 stable patients there was even an improvement. In the standard therapy group, 7 out of 21 patients were stable over 1 year, while 14 showed progressive disability. A quantitative neurological score at the beginning and 1 year after the therapy showed a nearly identical difference between the CY group and the control group. The changes of the patients' abilities in daily-life activities (which were observed and recorded by the nurses) were similar to the Kurtzke scale data obtained by the physicians. The beneficial effect of CY in chronically progressive MS was thus highly significant ($P<0.001$). The side-effects of low-dose CY were fewer than those of ACTH.

Key words: Multiple sclerosis – Therapy – Immunosuppression – Cyclophosphamide

Introduction

Both ACTH and cortisone are effective in the treatment of multiple sclerosis (MS), but the effect is short lasting, and continuous therapy has more adverse than beneficial effects. The hope that azathioprine might be helpful in MS could not be verified by clinical trials. Cyclosporine A also proved not to be helpful. On the other hand, intensive immunosuppression with CY has been shown to stabilize patients with chronically progressive MS [2–5]; the side effects, however, were severe, e.g. alopecia in 100% of the patients. As we have shown earlier [8] low-dose cyclophosphamide (CY) therapy in MS patients, which lowers the lymphocyte count to half the initial value, is possible with minor side-effects. We have also pointed out that because of the possibly malignant late effects of CY great care has to be taken to cure the cystopyelitis which is present in most MS patients, and in training the neurogenic urinary bladder to normal function before therapy; furthermore, the total CY dose per life should not be higher than 50 g, which allows about 25 single therapeutic steps at intervals of about 9 months [10]. The methods of symptomatic treatment of MS patients (which to date has been the basic treatment), especially regarding the maintenance of a healthy urinary bladder, have been described previously [6, 9].

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Patients and Methods

The MS patients were recruited for this study in such a way as to make a positive result error as unlikely as possible. Therefore, we excluded all patients with a relapsing course. Only patients with a chronically progressive course were included. Furthermore, patients who were satisfied with the effects of ACTH or cortisone were again treated with this standard treatment. Only patients who were dissatisfied with the standard treatment were offered CY. For all patients the diagnosis of MS was clinically definite according to the criteria of McDonald and Halliday [11]. Each group consisted of 21 cases. There was no significant difference between the two groups as regards sex (13 females and 8 males in each group), age and the degree of disability at the start of the investigation (see Fig. 1); however, there was a significant difference regarding the progression index. The progression of the disease had been significantly faster in the experimental group than in the control group ($P<0.05$) (see Fig. 1).

CY (8 mg/kg) was given intravenously at intervals of 4 days until the lymphocyte count was reduced to half the initial value (however, not below 1.000/μl). The total dose averaged 1.9 g

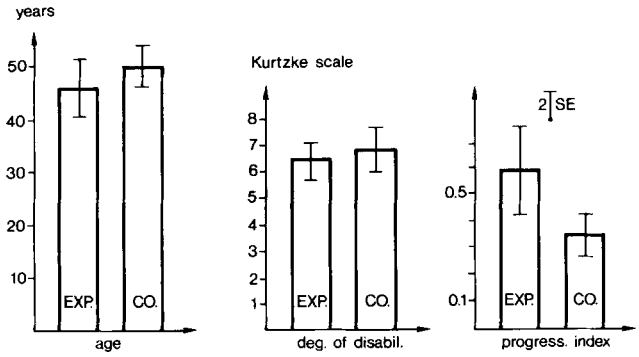

Fig. 1. Age, degree of disability (Kurtzke Scale) and progression index in experimental (CY) and control group patients at the start of the study. Note the significantly more rapid progression of the disease in the experimental group prior to the start of the cyclophosphamide treatment

CY per patient. In order to avoid haemorrhagic cystitis, mesna (20% of the CY dose) was given before the CY infusion as well as 4 and 8 h after. Furthermore at least 31 fluids (mineral water, tea, etc.) were given during the day of the CY infusion. To counteract nausea (which is the main side-effect of CY) domperidone and alizapride were given the day of the CY infusion and the day after. Unlike the patients in the control group, who received a high-dose cortisone or ACTH treatment over 4 weeks, the patients in the CY group did not receive any cortisone or ACTH. Because of the mutagenic and teratogenic risk due to CY, the patients were advised to practise contraception for a period of 1 year. The patients of both groups, the experimental group receiving CY and the control group receiving the standard ACTH or prednisolone treatment, were also treated with physiotherapy and received antispastic drugs if necessary and other symptomatic treatment for 4 weeks.

The clinical course was evaluated in three ways: (1) by the Kurtzke disability scale; (2) with a quantitative neurological score ranging from 1 (minimal symptoms) to 100 (maximal neurological deficit in all systems); (3) according to the abilities of the patient in daily-life activities, such as walking without help, walking with a cane, walking with crutches, or walking with a cart support, sitting in a wheelchair, sitting up in bed, turning in bed, eating, drinking by themself etc. These abilities in the activities of daily life were independently evaluated by the nurses, while the first two criteria were evaluated by the consensus of two physicians. All patients were re-investigated 1 year after treatment in the clinic.

Results

As shown in Fig. 2, 20 out of 21 patients were stabilized over 1 year following the CY treatment according to the Kurtzke disability scale; according to the quantitative neurological score, 19 out of 21 in the CY group were stabilized. There were even some improvements: 2 out of 21 according to the Kurtzke scale and 6 out of 21 according to the neurological score had improved in the CY group after 1 year. In contrast, there were no improvements in the control group, and 14 out of 21 were worse after 1 year according the Kurtzke scale (15 according to the neurological score). The observations of the nurses regarding changes in the abilities of daily-life activities were similar to the data obtained by the two physicians (Fig. 2). The differences are highly significant ($P < 0.001$, chi-square test).

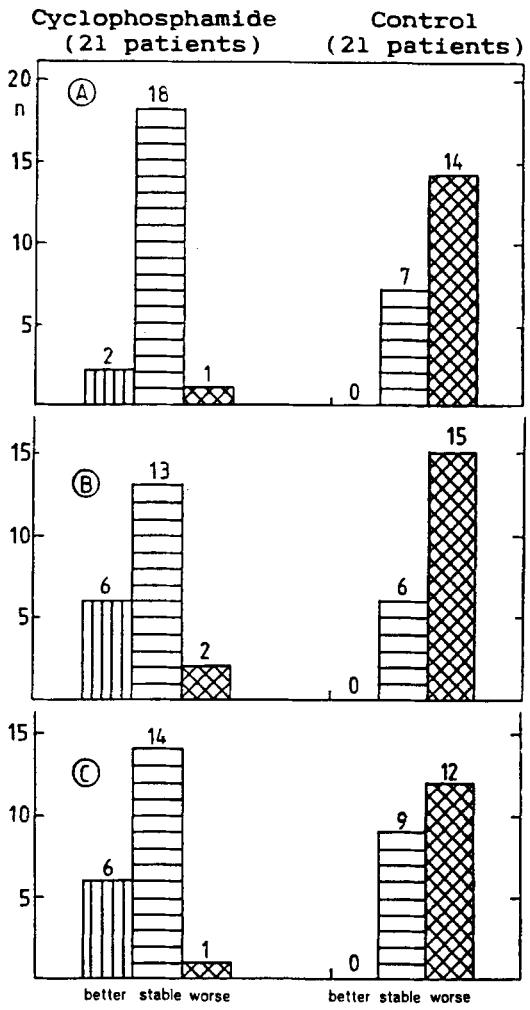

Fig. 2. **A** Changes in Kurtzke Disability Status Scale after 1 year in the CY group and in the control group; n = number of patients. **B** Changes in quantitative neurological examination after 1 year. **C** Changes of the abilities in daily-life activities after 1 year

The usual side-effects of cortisone or ACTH treatment were seen, including oedema. In this group there were no cases with psychosis, thromboembolism or gastric ulcer because we administered preventive doses of antacids, H_2-blocking drugs and low-dose heparin; however, in former years when we did not routinely take these precautions, there were side-effects such as gastric ulcer, exogenous psychosis and even one fatal case of massive lung embolism. In the CY group the main side effect was loss of appetite for 1 day in 4 patients, 1 of whom also had vomiting. Two patients complained of faintness for the day they received the antiemetic drugs. There was no loss of hair in the CY group.

Discussion

So far we have treated 109 MS patients with CY. The majority of them, however, had a relapsing course, which makes a quantitative evaluation difficult over such a short time (1 year). The general impression, however, was favourable in this group treated with low-dose CY as compared with the standard cortisone or ACTH treatment. The stabilizing effect of cortisone does not last as long as that of CY. For a more reliable evaluation we concentrated on MS patients with a chronically progressive course and designed the study in such a way as to make an erroneously favourable result in the CY group unlikely: the patients of the CY group were dissatisfied with the results of previous cortisone or ACTH treatment; from an objective point of view, the patients in the CY group had on the average a significantly faster progression of the disease. Despite this disadvantage, however, the outcome of the CY treatment in this group was significantly more favourable than in the control group (which had a more benign course before the start of this study).

From these results it is clear (at least to us) that CY effectively suppresses the autoimmune reaction in the central nervous system of MS patients even in doses with acceptable side-effects. Since about 2 g CY per treatment per patient is needed and adult patients on the average tolerate about 50 g CY per life [1, 10], patients can be treated about 25 times. Since some patients start to deteriorate after 1 year, we advise spacing treatments at intervals of 9 months.

We now combine CY treatment with a short high-dose methylprednisolone therapy. This has the advantage of the rapid but short-lasting effect of cortisone combined with the long-lasting beneficial effect of CY. Moreover, we now reduce the CY dose to 6 mg/kg for the single intravenous infusion if a patient responds to the 8 mg/kg dose with severe nausea or vomiting.

We cannot, however, recommend CY for home treatment without special precautions regarding already existing inflammatory diseases, especially cystopyelitis. Since many MS patients have a neurogenic disturbance of the urinary bladder and, consequently, cystitis, it is necessary first to cure retention, to train the urinary bladder and to cure the cystitis [6, 7, 9]. Since it is difficult to do this without adequately taking care of the spasticity, we give baclofen and move the paralysed legs by physiotherapy and with the motomed [7, 9] (available from Reck Med. Technik, Betzenweiler, FRG). The availability of efficient immunosuppression in MS patients with CY makes effective symptomatic treatment of these patients [6, 7, 9] even more important. For this purpose, a degree of training and of supervision of the nurses is necessary which is not yet available in many hospitals. For instance, the bladder function should be assessed by ultrasonic measurements of the residual urine; urological operations on the urinary tract as still used in many hospitals should be avoided, since they preclude subsequent application of effective immunosuppression.

We do not regard CY to be the definite solution for the problems of MS patients. However, the success achieved with this drug shows the possibility of effectively stopping the inflammatory autoimmune process. This gives us hope of finding effective drugs with fewer side-effects.

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