Cyclophosphamide in relapsing remitting multiple sclerosis

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7 patients with relapsing-remitting multiple sclerosis (MS) were subjected to an intensive course of intravenous (I.V.) cyclophosphamide (CY) therapy. All patients received induction therapy with 11 daily doses of 300 mg/m² and then a single dose every six months for three years. After one year of follow-up all patients showed a decrease in relapse rate (0.57.57); in the two subsequent years of follow-up 2 patients showed a mild worsening while the others were clinically stable.

As suggested by others, our results indicate that I.V. CY therapy may influence the clinical course of relapsing-remitting MS.

Key-Words: Multiple sclerosis — immunosuppressive therapy

Introduction

On the assumption that MS is related to abnormal function of immune regulation [13, 18], a number of clinical trials with cyclophosphamide (CY) have been conducted in the attempt to suppress the immune system or to restore immune balance [4, 6, 8, 14-17]. Most of the studies have focused on chronic progressive MS with the aim of stopping the progression of the disease [4, 6, 8, 14-17]. In the last few years relapsing-remitting MS patients have also received immunosuppressive therapy with CY in order to prevent or decrease the number of relapses [5]. Current treatment regimens provide for induction therapy followed by maintenance boluses [19]. These regimens with high doses of I.V. CY showed positive effects on episodes of relapsing remitting MS but carry the risk of immediate side effects like hemorrhagic cystitis, infections, peritonitis. Moreover, it is not clear how often and how long maintenance boluses must be administered to maintain the clinical effect and avoid long term toxicity. These data led us to conduct a pilot trial with a new treatment regimen of I.V. CY in patients with relapsing-remitting MS to test tolerability and effects of future relapses.

Patients and methods

Patients with high disease activity as evaluated by frequency of relapse or with severe sequelae from prior relapses as evaluated by the expanded disability status scale (EDSS) score, were selected. 7 patients (4 males, 3 females) aged between 17 and 39 years, all meeting established criteria for definite MS [12] were enrolled into the study. Each patient was observed for two years before treatment and evaluated at bimonthly visits with standard neurological examination and determination of EDSS score. All patients had a relapsing-remitting form of disease with two or more exacerbations per year in the last two years. At entry, the EDSS score [10], evaluated at least 30 days after the end of last relapse, ranged from 3 to 6.5. All patients received a starting therapy of I.V. CY with daily doses of 300 mg/m² and successively a single dose of 300 mg/m² every six months over a period of three years. Large volumes of fluids (3,000 cc) were given orally and intravenously to prevent bladder toxicity. During the treatment, all patients also received antiemetic drugs if nausea and vomiting developed. Urinalysis and complete blood cells counts were performed every two days during the starting treatment and every week.
following events occurred: 1) microscopic hematuria; 2) urinary infection; 3) white cells less than 1,500/mmc; 4) platelets less than 100,000/mmc.

Standard neurological examination and determination of EDSS score were performed before and after every phase of treatment. In addition clinical evaluation was repeated every two months over a period of three years and whenever the patients reported a worsening of their condition.

Results

Clinical data of patients (age, age at onset, duration of disease, number of annual relapses and EDSS score) are presented in Table I. No patient failed to complete the induction treatment because of severe side effects.

One patient (N. 1) had a urinary infection three days after the end of the induction period and received antibiotic therapy with complete remission of symptoms. All patients presented nausea and vomiting during the treatment, which was well controlled with antiemetic drugs. All patients had alopecia, which returned to normal 60-90 days after the end of induction therapy. The clinical course of disease is shown in Table II. Clinical response was expressed by the EDSS score and the annual number of relapses. After one year of follow-up all patients showed a decrease of relapses (4 vs 18 relapses/year). 3 patients (n. 1, n. 5, n. 7) showed a decrease in EDSS score compared with pretreatment state 3 patients (n. 2, n. 3, n. 4) remained unchanged and one (n. 6) worsened by 0.5 point in EDSS score.

6 patients (n. 1, n. 2, n. 3, n. 4, n. 5, n. 7) were followed in the subsequent two years. Patient n. 6 refused to continue the treatment after two maintenance doses because his condition worsened.

In the second year of follow-up 4 patients (n. 1, n. 2, n. 4, n. 7) were clinically stable in terms of EDSS score or relapse rate; patients n. 5 showed 2 relapses versus 1 relapse in the year before and a 1.0 point worsening in EDSS score; patient n. 3 worsened only in relapse rate (1 vs 0 relapse/year).

In the third year 4 patients (n. 2, n. 3, n. 4 and n. 5) remained clinically unchanged; patients (n. 2, n. 3, n. 4 and n. 7) remained clinically unchanged; patient n. 1 showed a worsening of 0.5 point in EDSS score and in relapse rate (3 vs 1 relapse/year); patient n. 5 worsened in relapse rate (3 vs 2 relapse/year). None of the 15 relapses observed during the study occurred within three months after therapy administrations.

Discussion

Cyclophosphamide had been reported to be effective in the treatment of MS [2, 4-7, 9, 15]. Haus-