SHORT COMMUNICATION

Mitoxantrone therapy in rapidly worsening multiple sclerosis

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Abstract

Background: **This study evaluates mitoxantrone (MX) therapy in patients with relapsing remitting and secondary progressive multiple sclerosis (MS).**
Objectives: **Evaluation of the disability progression and side effects of MX.**
Methods: **There were studied 33 patients (10 males, 23 females), average age 48.5±9.9 SD) with relapsing remitting and secondary progressive MS. The disability was evaluated using Expanded Disability Status Scale (EDSS). Time period from the onset to secondary progressive course of the disease was 9.3 years. Patients, whose disability progression increased by one or more EDSS point per one year, and not responding to other therapy, were treated with mitoxantrone. Patients were treated once monthly with intravenous administration of mitoxantrone 12 mg/m², not exceeding the maximum cumulative dose of 14 mg/m² and Solu-Medrol 1000 mg. Six pulses were done in each patient. EDSS score was measured at the beginning of the treatment and after twelwe month. Disability progression was evaluated. Nonparametric Wilcoxon matched pair test was used for statistical analysis.** ***(Tab. 1, Fig. 3, Ref. 5.)***
Key words: multiple sclerosis, immunotherapy, mitoxantrone, EDSS.

This study evaluates mitoxantrone (MX) therapy in patients with worsening secondary progressive multiple sclerosis (MS). Recently, MX has been approved for the treatment of patients with relapsing remitting or secondary progressive MS. MX has a statistically significant impact on the reduction of relapse rate and delay in disability progression in these patients. However, cardiac side-effects and myelosuppressive activity limit its use.

Objectives: Evaluation of the disability progression and side-effects of MX.

Methods

33 patients were studied (10 males and 23 females, mean age 48.5±9.9 SD) with definite relapsing remitting and secondary progressive MS (Tab. 1). The disability was evaluated using Expanded Disability Status Scale (EDSS). Time period from the onset to secondary progressive course of the disease was 9.3±9.8 years. Patients in secondary progressive phase whose disability progression rate increased by one or more EDSS point per one year, and not responding to other therapy, were treated with mitoxantrone. Patients were treated once monthly with intravenous administration of mitoxantrone 12 mg/m², not exceeding the maximum cumulative dose of 140 mg/m² and methylprednisone 1000 mg. Six pulses were administered to each patient, three patients were treated twice. EDSS score was measured at the beginning of the treatment and after twelwe month. Disability progression was evaluated.

Computation for the statistical analysis was performed using the computer software package STATISTICA (version 6.0). All statistical analyses were two-sided and performed level. Baseline demographic, clinical characteristics and adverse events frequency were summarized using descriptive statistics (n, mean, SD, median, minimum and maximum) or frequency tables. Comparison of Expanded Disability Status Scale (EDSS) at the baseline and one year after treatment was performed using the nonparametric Wilcoxon matched paired test, as the hypothesis of normal data distribution was rejected (Kolmogorov–Smirniv test).

Results

We did not find statistically significant difference between baseline EDSS score 5.64±1.01 (mean±SD) and EDSS score

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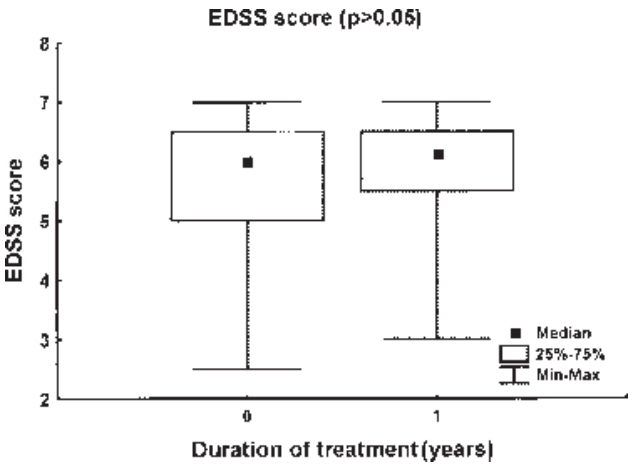

Fig. 1. Baseline EDSS score and EDSS score after one year.

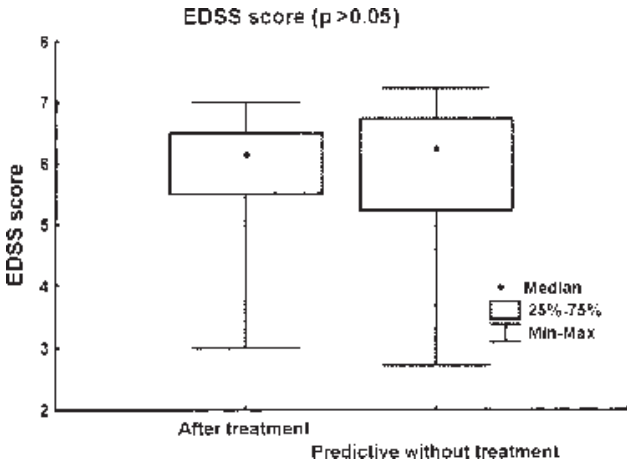

Fig. 2. EDSS score after one year of treatment and predictive EDSS score without treatment.

after one year of treatment 5.83±1.16 (mean±SD) ($p>0.05$) (Fig. 1).

In our study group, the progression of disability was mild, however the difference between our results and natural course of the disease was not statistically significant ($p>0.05$) (Fig. 2).

We observed drug-related mostly mild and transient, adverse events. Fifteen patients exhibited side effects such as nausea and vomiting, few days after administration of a drug. Seven patients showed mild, transient increase in liver enzymes and twelwe patients showed mild, transient anemia and leukopenia, not requiring treatment interruption. Eight patients developed transient partial hair loss, two patients developed thrombophlebitis, in one case amenorrhoea and rash was present. Two patients stopped the treatment because of serious side-effects – pneumonia and thrombophlebitis. In one patient liver carcinoma developed one year after the therapy. In our study group cardiotoxicity was not observed (Fig. 3).

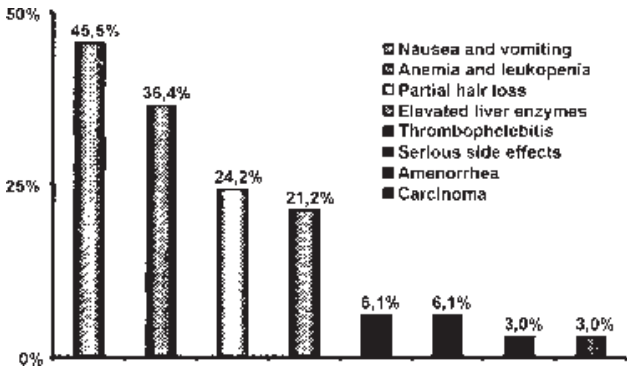

Fig. 3. The total sum of individual percentual types of therapeutical side effects is more than 100 %, in respect to several complications in each patient (n=15).

Discussion

MS is a chronic, recurrent inflammatory disorders of the CNS. Four different clinical courses of MS have been identified – relapsing remitting, secondary progressive, primary progressive and progressive relapsing MS. A number of factor are associated with long term outcome in patients with multiple sclerosis. It is discouraging to discover that after 25 years the number of individuals not developing secondary progressive disease is very small and approximates to 1/20. The most important factors, associated with long term outcome, include the development of a progressive deficit and, most importantly, the time period from the onset to progressive deficit. The therapeutic aim of the disease-modifying treatment in MS is to prevent or postpone long-term disability. Four disease modifying therapies are approved for patients with relapsing-remitting multiple sclerosis. MX treatment provides a new therapeutic modality for patients with rapidly worsening, relapsing remitting and secondary progressive multiple sclerosis. MX, which is usually categorized as an immunosuppressive drug, is now considered to be a specific immunomodulator, inducing macrophage mediated suppression of B-cells, modulating T-helper and T-cytotoxic lymphocyte function. Autoimmune mechanism of MS is the basa for the immunosuppressive therapeutic approaches to MS. Clinical trials have shown that MX had a statistically significant impact on the reduction of relapse rate and delay in disability progression in these patients (1, 2). Its lifetime cumulative dose should not exceed 140 mg/m^2. It is associated with dose related cardiotoxicity, myelosuppressive activity and various side effects (3, 4). Its use is contraindicated in patients with a baseline left ventricular ejection fraction less than 50 %. MX 12 mg/m^2, administered also in this study, is generally well tolerated. Cardiotoxicity was not observed in our patients, although the decrease in the left ventricular ejection fraction and drug-related congestive heart failure are reported in literature (3). We observed mostly mild and transient side effects such as anemia, leukopenia, elevation of liver enzymes, and partial hair loss. However, two patients stopped the treatment due

to serious side effects, and one patient developed liver carcinoma. The progression of the disease, reported in literature, is estimated to 0.23 EDSS point per year (5). EDSS change (last value minus baseline) in our study group was 0.19 EDSS point. The progression of the disease was mild, however, the difference was not statistically significant.

Mitoxantrone delayed the disability progression and was generally well tolerated. The therapy was associated with mostly mild and transient side-effects. Cardiotoxicity was not found in our group of patients.

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