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A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis

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Abstract

A double-blind clinical trial of mitoxantrone versus methylprednisolone was performed in 49 patients with relapsing, secondary multiple sclerosis. Patients were randomized to receive 13 infusions of mitoxantrone 12 mg/m² (n = 28), or 13 infusions of 1 g of methylprednisolone (n = 21), over 32 months. Twenty-four patients completed the trial. There were no statistical differences between the two groups of patients at study entry. A significant improvement in the Expanded Disability Scale Score (EDSS) was observed in the mitoxantrone group after one year of treatment (p < 0.0022). The total number of relapses, the mean number of relapses/patient/year, and the total number of gadolinium-enhanced lesions on bi-annual MRI scans were significantly decreased in the mitoxantrone group throughout the study period. Nausea, vomiting, and alopecia were more frequent in the mitoxantrone-treated patients. Mitoxantrone has a role in the treatment of MS patients with frequent exacerbations and rapid disease progression.

Introduction

Immunosuppressive agents have been widely used in the treatment of multiple sclerosis (MS), based on the assumption that autoimmune mechanisms are involved in the pathogenesis of this disease. Controlled trials with azathioprine, cyclosporin, cyclophosphamide, and methotrexate, have only shown a modest, if any, beneficial effect on the course of the disease (British and Dutch Multiple Sclerosis Azathioprine Trial Group, 1988 ; Kappos *et al*., 1988 ; Goodkin *et al*., 1991 ; The Multiple Sclerosis Study Group, 1990 ; The Canadian cooperative trial of Cyclophosphamide and plasma exchange in progressive multiple sclerosis, 1991 ; Weiner *et al*., 1993 ; Goodkin *et al*., 1995).

Some pilot studies have suggested that mitoxantrone (MTX) might be beneficial in relapsing secondary progressive MS (Gonsette and Demonty, 1989 ; Mauch *et al*.1991, 1992).This drug belongs to a family of intercalating cytotoxic agents called anthracenediones, that inhibit DNA and RNA synthesis and do not generate free radicals (Pouillart *et al*., 1987). In addition, MTX exerts a potent immunomodulating effect in suppressing humoral immunity (Fidler *et al., 1*986a), reducing T cell numbers and helper activity, and enhancing suppressor function (Fidler *et al*., 1986b).

MTX is also effective in suppressing the development of acute autoimmune encephalomyelitis (EAE) and prevents, or delays, relapses in chronic EAE (Ridge *et al*., 1985 ; Levine *et al*., 1986 ; Lublin *et al*., 1987).

Two prospective, randomized, double-blind, placebo-controlled trials have recently shown that MTX is effective in decreasing disease activity in terms of relapse rate, progression of disability, and magnetic resonance imaging (MRI) parameters, in patients with severe MS (Millefiorini *et al., 1*997 ; Hartung *et al*., 1998). In addition, Edan *et al*. (1997) have shown that in a selected group of MS patients with very active disease, MTX combined with methylprednisolone (MP) was effective in improving both clinical and MRI indices of disease activity over a period of 6 months, whereas MP alone had no effect. These results suggest that MTX may be used in the framework of an escalating immunotherapy for MS patients with rapidly progressive disease (Cursiefen *et al*.,2000).

Here, we report the results of a double-blind, randomized clinical trial of MTX versus MP in relapsing, secondary progressive MS. Corticosteroids are commonly used to reduce the duration and the severity of MS relapses, but data are insufficient to provide evidence that corticosteroids modify the overall course of the disease, particularly at doses used in this trial (Troiano *et al*., 1987 ; Filippini *et al*., 2001).

Methods

Selection of patients

Inclusion criteria were a definite clinical diagnosis of MS (Poser *et al*., 1983), and a relapsing,

secondary progressive form of the disease. Patients had to be aged between 18 and 50, with an Expanded Disability Scale Score (EDSS) of 3 to 6. To be included, patients must have recovered, at least partially, from their last disease relapse at least one month before study entry, and display worsening of their EDSS of 1 point during the last 12 months. Women of child bearing age and wives of male patients were required to use effective birth control until two years after the end of the study. Isotopic cardiac ventriculography and routine blood analysis had to be normal at screening.

Exclusion criteria were : remittent forms of the disease, primary progressive disease, and secondary progressive disease without relapses. Patients who had suffered a major illness (other than MS), or used immunosuppressive drugs (other than corticosteroids), during the three years prior to the study were also excluded.

Treatment

Induction treatment

MP (1g dissolved in 100 ml isotonic saline solution) was given intravenously once a month for three months, over one hour between 8 and 10 a.m. For blinding, a solution of 5 mg methylene blue in saline was then given within an hour of the MP infusion.

For the MTX group, three vials of alizapride, an anti-emetic drug, were given in 100 ml saline solution, followed by MTX, 12 mg/m^2, over one hour, once a month for three months.

Maintenance treatment

Both treatments (MP and methylene blue versus alizapride and MTX) were given once every three months, ten times until month 32. The complete treatment thus consisted of 13 infusions.

Before each administration, blood was taken for hematology screening and the complete dose of MTX was given only if the absolute numbers of neutrophils and platelets were higher than 1500 and 100,000/µl, respectively. The dose of MTX was reduced by 50% for neutrophil counts between 1000 and 1500, and/or platelets counts between 75,000 and 100,000/µl. For lower counts, no active dose was given, but, to maintain the blinding, methylene blue in saline was still administered.

Equilibrium gated cardiac ventriculography with calculation of the ejection fraction was performed at day 0 and every 6 months thereafter. To avoid acute cardiac toxicity, treatment was stopped if the cardiac ejection fraction decreased below 50%.

Treatment of relapses

If the patient suffered a relapse during the study period, the use of either intravenous or oral corticosteroids was allowed but had to be reported. The EDSS was determined by the blinded neurologist (F.L.) and had to show an increase for relapse treatment to be commenced.

Assessment and follow up

Clinical assessments (including EDSS and recording of relapses) were carried out at entry and every three months by the same blinded neurologist (F.L.) before intravenous catheterization for drug injection. In addition to hematological parameters, blood was tested for immunoglobulin (Ig) electrophoresis and routine clinical chemistry before each injection. Hematology was also checked ten days after each infusion.

The MRI imaging protocol consisted of 5 mm thick slices obtained through the brain with proton density and T2 weighted spin echo images before contrast, and a T1 weighted sequence after injection of gadolinium DTPA (0.1 mmol/kg). The assessment of activity on the gadolinium enhanced images was performed by a blinded neuroradiologist (G.D.) on scans obtained at entry and at months 5, 11, 17, 23, 29, and 36.

End-points of the trial

The primary end-point was to assess the effect of MTX on the EDSS at month 36, four months after the last treatment. Aggravation was defined when the EDSS increased by 0.5 point if EDSS was ≥ 5.5 at entry, and by 1 point if EDSS was < 5.5 at entry. Secondary end-points were the number of relapses during the three year study period and the number of gadolinium-enhanced active lesions on MRI scans throughout the study. A third goal was the assessment of side-effects in both groups of patients.

Statistical analysis

Comparisons of proportions were made by $\chi 2$ test or by Fisher exact test. To calculate the evolution of the proportion of patients with EDSS ≥ 5, the repeated measures analysis for categorical data was used. The Wilcoxon test was used to compare the total number of relapses and the total number of gadolinium-enhanced lesions between the two groups of patients. The evolution of lymphocyte counts and of IgM levels were tested using the analysis of variance for repeated measures ; logarithmic transformation was made when necessary. The calculations were made with SAS software, version 6.11.

Results

After approval from the Ethics Committees in two centers, 49 patients (26 from Cliniques

Table 1

Characteristics of patients at day 0

Variables	Methylprednisolone	Mitoxantrone	P
N	21	28	
Age (years)	39.2 ± 7.8	38.3 ± 6.9	NS
male	6	8	NS
female	15	20	
Age at MS onset (years)	28.4 ± 6.5	30.2 ± 7.2	NS
Duration of the MS (years)	10.1 ± 5.9	9.1 ± 5.4	NS
EDSS			
3	2	2	
3.5	1	0	
4	3	5	
4.5	2	1	
5	1	5	
5.5	3	7	
6	9	8	
Number of exacerbations in the 12 months preceding study entry	2.2 ± 1.2 (total = 43)	2.3 ± 1.0 (total = 61)	NS
Number of gadolinium-enhanced active plaques on MRI scan	2.9 ± 4.1 Median = 1 (total = 62)	2.5 ± 4.8 Median = 0 (total = 70)	NS

Table 2

Proportion (%) of patients with EDSS score ≥ 5

	Duration of treatment	Month 0	Month 11	Month 23	Month 36
Methylprednisolone	1 year (N = 19)	63.2	78.9 *		
	2 years (N = 18)	66.6	77.7	72.2**	
	3 years (N = 14)	71.4	78.6	78.6	71.4***
Mitoxantrone	1 year (N = 24)	70.8	41.7 *		
	2 years (N = 13	61.5	46.2	38.5 **	
	3 years (N = 10)	60	40	30	30***

* at 1 year : $p = 0.0022$
** at 2 years : $p = 0.045$
*** at 3 years : NS

Universitaires Saint-Luc, Brussels ; 23 from the National Multiple Sclerosis Center Melsbroek) were enrolled between June 1992 and December 1994. Using a table of random numbers, 28 patients were randomized to receive MTX and 21 received MP.

There was no difference among the patient groups in age, gender ratio, age at onset of disease, duration of disease, EDSS, number of exacerbations in the 12 months preceding study entry, and total number of gadolinium-enhanced lesions on initial MRI scans (Table 1).

In the MTX group (N = 28), 24 patients completed the first year of treatment (six injections), 13 completed the second year of treatment (10 injections), and 10 completed the trial until month 36 (13 injections). Only one patient needed to have the dose of MTX reduced by 50% (on two occasions) because of persisting neutropenia. In the MP group (N = 21), 19 completed the first year, 18 completed the second year, and 14 completed the full trial period.

The proportion of patients with an EDSS ≥5 decreased in the MTX group during the first year, but remained stable or increased in the MP group (p = 0.0022). This score of 5 was considered pivotal because similar numbers of patients displayed scores greater and lower than 5 at study entry.

In the second year, similar results were observed with the proportion of patients with an EDSS ≥ 5 decreasing in the MTX group, and remaining stable or increasing in the MP group (p = 0.0450). During the third year, the proportion of patients with an EDSS ≥ 5 did not decrease further in the MTX group, but remained lower than in the MP group (Table 2).

During the first year, disease progression was noted in seven patients in the MP group and in two in the MTX group (p = 0.03). However, no significant difference in the progression of the disease

Table 3

Mean number of relapses/patient/year

	Duration of treatment	Year 1	Year 2	Year 3
Methylprednisolone	1 year (N = 19)	0.7*		
	2 years (N = 18)	0.7	1.1**	
	3 years (N = 14)	0.6	1.3	1.1***
Mitoxantrone	1 year (N = 24)	0.4*		
	2 years (N = 13)	0.2	0.3**	
	3 years (N = 10)	0.1	0.4	0.2***

* NS
** at 2 years : $p = 0.016$
*** at 3 years : $p = 0.029$

Table 4

Total number of gadolinium-enhanced active plaques on MRI

	Duration of treatment	Month 0	Month 11	Month 23	Month 36
Methylprednisolone	1 year (N = 19)	61	146*		
	2 years (N = 18)	59	146	59**	
	3 years (N = 14)	43	77	26	20***
Mitoxantrone	1 year (N = 24)	70	15*		
	2 years (N = 13)	33	8	10**	
	3 years (N = 10)	32	8	10	6***

* at 1 year : $p = 0.002$
** at 2 years : $p = 0.002$
*** at 3 years : $p = 0.03$

Table 5

Evolution of mean blood lymphocyte counts (/µL) before drug infusion

	Duration of treatment	Month 0	Month 11	Month 23	Month 36
Methylprednisolone	1 year (N = 19)	1581 ± 601	1676 ± 678		
	2 years (N = 18)	1612 ± 606	1713 ± 677	1579 ± 457	
	3 years (N = 14)	1601 ± 677	1673 ± 756	1684 ± 597	1457 ± 319
Mitoxantrone	1 year (N = 24)	1581 ± 545	1200 ± 316		
	2 years (N = 13)	1493 ± 650	1175 ± 312	1169 ± 288	
	3 years (N = 10)	1520 ± 714	1214 ± 331	1216 ± 305	1127 ± 380

All comparisons are non significant (p = 0.067 at month 36)

was seen among the two groups of patients followed over two or three years. Overall, 35% of patients receiving MTX clinically improved compared to 22% of patients who received MP ; this difference, however, was not significant. The proportion of patients with disease progression was identical (21%) in both groups.

There were 15 relapses during the three years of treatment in the MTX group and 49 in the MP group. Considering only patients who completed the trial (N = 14 in the MP group, N = 10 in the MTX group), there were seven relapses in MTX patients and 42 in MP patients (p = 0.01). The mean number of relapses/patient/year was significantly lower in the MTX group after two and three years of treatment (p = 0.016 and 0.029, respectively, Table 3).

MTX-treated patients had fewer gadolinium-enhanced lesions on MRI scan than patients given MP (Table 4). This difference was already present after the first year of treatment (p = 0.002), and persisted during the second year (p = 0.002). Considering only patients who completed the trial, there were 24 gadolinium-enhanced plaques in the MTX group, and 123 in the MP group (p = 0.03).

A non significant decrease in the mean number of lymphocytes was seen in the MTX group in comparison with the MP group. This trend persisted throughout the study (p = 0.067, Table 5).

The mean IgM level decreased significantly in the MTX group (p = 0.0001) during the study period and reached about 50% of the initial value (Table 6). In contrast, no significant differences

Table 6

Evolution of mean blood IgM levels (mg/dL) before drug infusion

	Duration of treatment	Month 0	Month 11	Month 23	Month 36
Methylprednisolone	1 year (N = 19)	211 ± 104	219 ± 109*		
	2 years (N = 18)	217 ± 105	222 ± 111	206 ± 107**	
	3 years (N = 14)	210 ± 115	208 ± 102	205 ± 111	155 ± 61***
Mitoxantrone	1 year (N = 24)	203 ± 106	142 ± 85*		
	2 years (N = 13)	187 ± 101	126 ± 85	116 ± 78**	
	3 years (N = 10)	195 ± 110	127 ± 92	118 ± 85	87 ± 46***

*at 1 year, drug comparison $p = 0.078$; interaction time and drugs $p = 0.0001$
**at 2 years, drug comparison $p = 0.034$; interaction time and drugs $p = 0.0001$
***at 3 years, drug comparison $p = 0.09$; interaction time and drugs $p = 0.0001$

Table 7

Most commonly reported adverse events

	Methylprednisolone N = 21 (%)	Mitoxantrone N = 28 (%)	p
Nausea and vomiting	7 (33.3)	24 (85.7)	0.001
Alopecia	5 (23.8)	15 (53.6)	0.036
Infections	10 (47.6)	16 (57.1)	NS
Tiredness	5 (23.8)	7 (25)	NS
Phlebitis	1 (4.8)	4 (14.3)	NS

were observed in IgG and IgA levels among both groups (not shown).

Nausea, vomiting, and alopecia were more frequently reported in the MTX group than in the MP group (Table 7). Alopecia was always described as minor in the MP group but was sometimes moderate in the MTX group. The incidence of infections and phlebitis was not significantly different among groups even when these side effects were related to the number of months of treatment. Phlebitis was generally limited to the injection site, but one MTX patient experienced extensive brachial phlebitis complicated by pulmonary embolism (see below). The mean myocardial ejection fraction was not significantly different in the two groups when compared at 6 month intervals (data not shown).

Twenty-five patients did not complete the trial : 18 (out of 28) in the MTX group and seven (out of 21) in the MP group ($p = 0.032$). The EDSS and the number of relapses of these patients did not differ at entry from those of patients who completed the trial.

The reasons for discontinuation were varied :

In the MP group, two patients withdrew after the third month for psychological reasons (depression), one patient displayed an anaphylactoid reaction during the 11th infusion, two patients left the study because of a subjective feeling of lack of efficacy after months 20 and 26, one patient stopped without specific reason after month 23, and one wished to participate in another study after month 29. At the time of discontinuation in these seven patients, the EDSS had improved in two, was stable in two, and had worsened in three.

In the MTX group, four patients withdrew for medical reasons : one developed a successfully treated breast cancer diagnosed after month 23, the myocardial ejection fraction fell below 50% (46 and 47%) in two after months 11 and 17 without clinical signs or symptoms, and one developed extensive brachial phlebitis with pulmonary embolism after month 14. This patient recovered completely. The other reasons for discontinuation were excessive side effects, mainly gastro-intestinal (four patients after months 11, 11, 11, and 26), a subjective feeling of lack of efficacy (four patients after months 11, 14, 20, and 26), and various reasons unrelated to the treatment in four cases (after month 20 because of a foreseen pregnancy, after month 2 because of financial problems, after month 8 for unrelated minor surgery, after month 2 because of refusal to receive a blinded treatment). Two patients left the study without giving specific reasons and were lost to follow-up after months 3 and 17, respectively. At the time of study discontinuation in these 18 patients, the EDSS had improved in seven, was stable in six, and had worsened in five.

Discussion

Treatment with MTX, as performed in this study, undoubtedly modified the relapsing-progressive course of the disease. This primary objective of the trial was obtained after one year of treatment (six infusions), as shown by a decreased proportion of patients with an EDSS > 5. Due to a high drop-

out rate, this treatment effect, still present at month 23, was no longer significant by year three. The secondary end-points, however, were reached throughout the study. The total number of relapses and the mean number of relapses/patient/year were significantly lower in the MTX group, as was the total number of gadolinium-enhanced lesions.

These data confirm the results of previous trials showing that MTX is effective in stabilizing or improving the course of severe relapsing, or progressive, MS (Edan *et al*., 1997 ; Millefiorini *et al*., 1997 ; Hartung *et al*., 1998). In the study of Edan *et al*. (1997), 42 patients, selected as having very active disease on clinical and MRI criteria, were randomized to receive either MTX (20 mg IV monthly) and MP (1 g IV monthly), or MP alone for 6 months. MRI data showed a significant month by month decrease in the number of enhancing lesions in the MTX group, with no changes in the steroid only group. There was also a significant reduction in the number of relapses ($p < 0.01$) and an increase in the number of patients free of exacerbation ($p < 0.05$), in the MTX group. The study by Millefiorini *et al*. (1997) enrolled 51 relapsing-remitting MS patients ; 27 of them received an IV infusion of MTX every month for one year at a dose of 8 mg/m^2. A statistically significant difference in the mean number of exacerbations was observed between the MTX group and the placebo group both during the first year, and in the year after treatment. Although there was no statistically significant effect on EDSS progression over two years, the proportion of patients with confirmed progression, as measured by a one point increase on the EDSS, was significantly reduced at the second year evaluation in the MTX group. In an abstract by Hartung *et al*. (1998), 65% of patients with secondary progressive MS were stabilized after two years of treatment with MTX.

Treatment was well tolerated in both groups. Only one patient needed to have the dose of MTX reduced because of persisting neutropenia. The mean blood lymphocyte count decreased slightly in the MTX group. In contrast, there was a pronounced decrease in the serum IgM level, already at year one. The side-effects of nausea/vomiting and alopecia occurred more frequently in the MTX group than the MP group, and two MTX patients presented with an ejection fraction below 50% such that the treatment was stopped. However, as a whole, the MTX group did not display significant changes in this parameter when compared with the MP group.

The most life-threatening event was an extensive brachial phlebitis with pulmonary embolism, although the patient recovered fully from this episode. MTX has not been described as carcinogenic, and the occurrence of one case of breast cancer should not be considered as related to the therapy.

Several limitations must be taken into consideration when the results of this study are interpreted. First, no intention-to-treat analysis was conducted. Second, the high level of the number of drop-outs after one year decreases the statistical power of the study during the second and the third year. This study illustrates the difficulty but also the necessity in maintaining compliance in a double-blind trial of relatively long duration. For these reasons, we recommend a multicentric recruitment with at least, two years treatment duration.

Dropouts for nausea /vomiting should be able to be avoided with the use of potent anti-emetics such as ondansetron and tropisetron. However, other reasons for withdrawal are less easily managed. The subjective feeling of lack of efficacy may have been the result of an unrealistic hope of improvement. MP may exacerbate mood swings, as shown in the two patients who withdrew after only three infusions.

In conclusion, MTX has a role in the treatment of patients with MS who experience frequent exacerbations and show rapid disease progression. On the basis of our results, MTX could be used for two years, as an induction phase, before longer term therapy with less toxic, immunomodulatory drugs. Extended courses of MTX raise concerns about possible cumulative cardiac toxicity.

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