Eur Arch Psychiatry Clin Neurosci (1992) 242:96–102

European Archives of Psychiatry and Clinical Neuroscience

Treatment of Multiple Sclerosis with Mitoxantrone

E. Mauch, H. H. Kornhuber, H. Krapf, U. Fetzer, and H. Laufen

Department of Neurology, Ulm University, W-7959 Dietenbronn/Schwendi 1, Federal Republic of Germany

Received October 13, 1991

Summary. Ten multiple sclerosis patients, all with a rapid deteriorating disease profile, were treated with 12 mg/m^2 of the cytostatic agent mitoxantrone, administered every 3 months. This dosage is only 25% of what a patient with a solid tumour would normally receive during the same time period. In all treated patients the deterioration was stopped following the initial dosage; in four out of ten patients there was even an immediate improvement of the neurological status. Eight out of nine patients showed an improvement after 1 year as compared with their enrolment status; the other one remained stabile. In correlation with the clinical improvement, the mean P100 latencies of visual evoked potentials showed a reduction after 1 year. However, the changes identified through magnetic resonance imaging were even clearer than those seen clinically. At admission, this group of patients presented with a total of 169 gadolinium (Gd)-enhancing lesions. Only 10 lesions were enhancing in nine patients 12 months after the initiation of treatment. It appears that mitoxantrone accelerates the disappearance of Gd-enhancing lesions and prevents the development of new ones. Minimal side effects such as mild nausea and a slight faintness were evident in six patients and then for only 1–2 days.

Key words: Multiple Sclerosis – Therapy – Immunosuppression – Mitoxantrone – Pilot Study

Introduction

Mitoxantrone is a synthetically produced anthraquinone that blocks DNA synthesis by inducing DNA interstrand crosslinking. It also hinders RNA synthesis by binding with messenger RNA.

In the animal model of multiple sclerosis (MS), experimental allergic encephalomyelitis (EAE), mitoxantrone was highly effective in suppressing development of acute EAE and it delayed the development of relapsing EAE [13, 19]. Similar observations were also seen in animal models of rheumatoid arthritis, which is also classified as an autoimmune disease [20]. According to extensive experience in oncology in Germany, where the substance has been used since 1985, the tolerance and long-term toxicity of mitoxantrone in tumour patients is more favourable than that of applied cytostatic agents used to date [8, 12]. A carcinogenic effect of mitoxantrone has not been reported (D. Schmähl, Center for Cancer Research, Heidelberg, personal communication). As mitoxantrone is mainly excreted by hepato-biliary pathways, its use is more favourable in patients with renal insufficiency or chronic cystopyelitis.

In this pilot study, we investigated the effectiveness and tolerance of mitoxantrone in the treatment of MS.

Correspondence to: E. Mauch

Patients and Methods

Ten patients with MS were enrolled in a phase-II pilot study, without a control group, and received four treatments of the cytostatic agent mitoxantrone over a 12-month period. All patients were diagnosed as having "clinically definite" multiple sclerosis according to the criteria of Poser et al. [18]. The trial protocol was approved by the ethics committee of Ulm University and the study was conducted in accordance with the requirements of the declaration of Helsinki. After the trial design had been discussed with all patients, we obtained written informed consent from all patients or their family members.

Patients with a pronounced rapid deterioration profile were selected. According to our inclusion criteria, our patients had to show evidence of deterioration of at least 1.0 on the Kurtzke Dis-

Table 1. Clinical characteristics of patients at onset of study

Patient	Age (years)	Sex	Duration of MS
1	40	F	16
2	27	M	5
3	20	M	6
4	19	F	1
5	37	F	16
6	51	F	14
7	28	F	1
8	27	F	1.5
9	26	M	4
10	32	F	11
Mean	30.7		7.6
SEM	3.1		2.4

ability Status Scale (DSS) within the preceding 12 months. Kurtzke DSS ranges from 0 (normal neurological examination) to 10 (death due to MS). Because of these inclusion criteria, our patient group exhibited a mean reduction of 2.2 on the Kurtzke scale (SEM = 0.6) during the year before the start of the investigation and a mean progression index of 2.0. Progression index is defined by the degree of disability according to the Kurtzke scale divided by the duration of the disease measured in years. In the patients we selected, the progression index was very high. The MS patients normally admitted to our clinic represent a progression index between 0.4 and 0.8.

Three males and seven females with a mean age of 31 (range 19–51) years were enrolled and treated. At the start of our investigation the mean degree of disability in our patients, measured by the Kurtzke DSS, was 6.0 (SEM = 0.6) and the patients had a mean disease duration of 7.6 (SEM = 2.4) years. The clinical characteristics of our patient group are shown in Table 1. Six patients exhibited a remitting and relapsing disease profile and four a remitting and relapsing profile followed by a chronic progressive pattern. Of the six patients with a relapsing and remitting course only three entered into the study during an acute relapse.

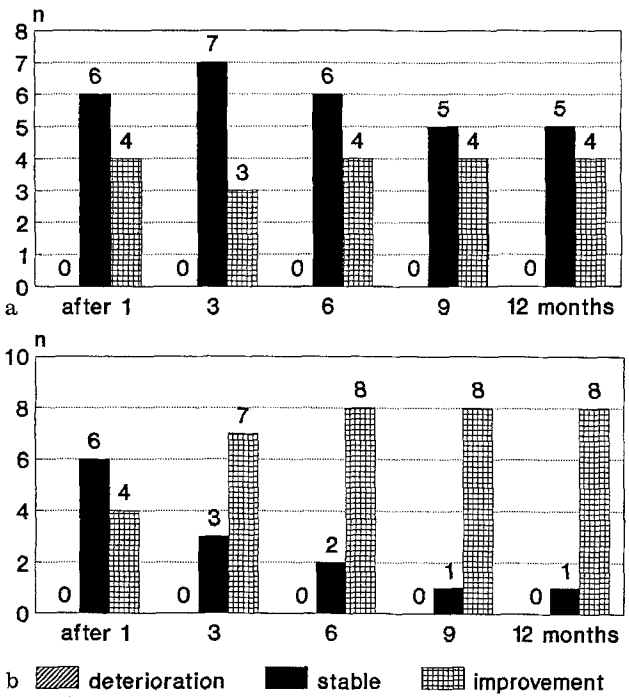


Fig. 1a and b. Documented changes during treatment with mitoxantrone: **a** Kurtzke-Scale; **b** Standard Neurological Examination

Mitoxantrone was administered at 3-month intervals as a single running intravenous infusion of 12 mg/m^2 body surface dissolved in 500 ml of isotonic saline solution. The patients also received domperidon 3 × 2 ml for 3 days beginning with the mitoxantrone infusion and additionally alizaprid if nausea occurred. Concomitant to the first dosage of mitoxantrone, eight patients received high-dose corticosteroid (1 g prednisolon) administered intravenously over 5 days. Two patients did not receive cortisone owing to a previous history of intolerance. Low-dose heparin treatment was given to prevent thrombosis during the cortisone injections and an H2-blocker and antacid to prevent gastric ulcers.

After the first treatment of mitoxantrone, prednisolone was administered as described above only in cases where clinical deterioration was observed. Patient 4 suffered two acute episodes following the first and second treatments and therefore also received high-dose cortisone therapy after mitoxantrone during the second treatment, and then additionally, for a short time from the family doctor, low dose orally preceding the third and fourth treatment. Patient 6 received one high dose of prednisolone after the fourth mitoxantrone therapy. In the case of patient 1, the family doctor administered ongoing low-dose prednisolone between the mitoxantrone treatments. With these three exceptions, prednisolone therapy was never repeated after the first treatment.

The clinical course of the patients was evaluated according to the Kurtzke DSS and a Standard Neurological Examination (SNE) ranging from 0 (no symptoms) to 100 (maximal neurological deficit in all systems). Improvement or deterioration were defined as objective changes in the Kurtzke DSS of 1.0 or more and of 6.0 or more in SNE. Furthermore, we measured the latencies of the major positive deflection (termed "P100") of the visual evoked potentials (VEP) in the course of therapy. For recording of pattern-reversal VEPs, patients were seated 1.8 m from a television screen, which projected the standard alternating checkerboard pattern. Checker size was 20 × 20 mm, the reversal rate 1/s. A commercially available clinical averager (Nicolet Pathfinder) was used. Each trial averaged 2 × 200 reversals for each eye. The response was recorded from Oz referred to Cz. In our laboratory, prolongation of P100 is assumed when the latency of the major positive deflection is longer than 110 ms. When a reliable peak could not be identified or replicated in at least two traces, it was considered absent.

Each patient was investigated six times by magnetic resonance imaging (MRI) with gadolinium (Gd) during the 1-year study. The

Table 2. Changes in clinical parameters at the start of the investigation and after 1 year

Patient	Kurtzke DSS at the start of investigation	Kurtzke DSS after one year	SNE at the start of investigation	SNE after 1 year
1	6	6	32	21
2	8	8	44	35
3	4	Drop out	22	Drop out
4	3	1	15	4
5	6	6	18	16
6	7	7	22	16
7	5	2	22	4
8	9	6	41	14
9	5	3	20	5
10	7	7	50	45
Mean	6.0	5.1	28.6	17.8
SEM	0.6	0.8	3.9	4.9

SNE = Standard neurological examination

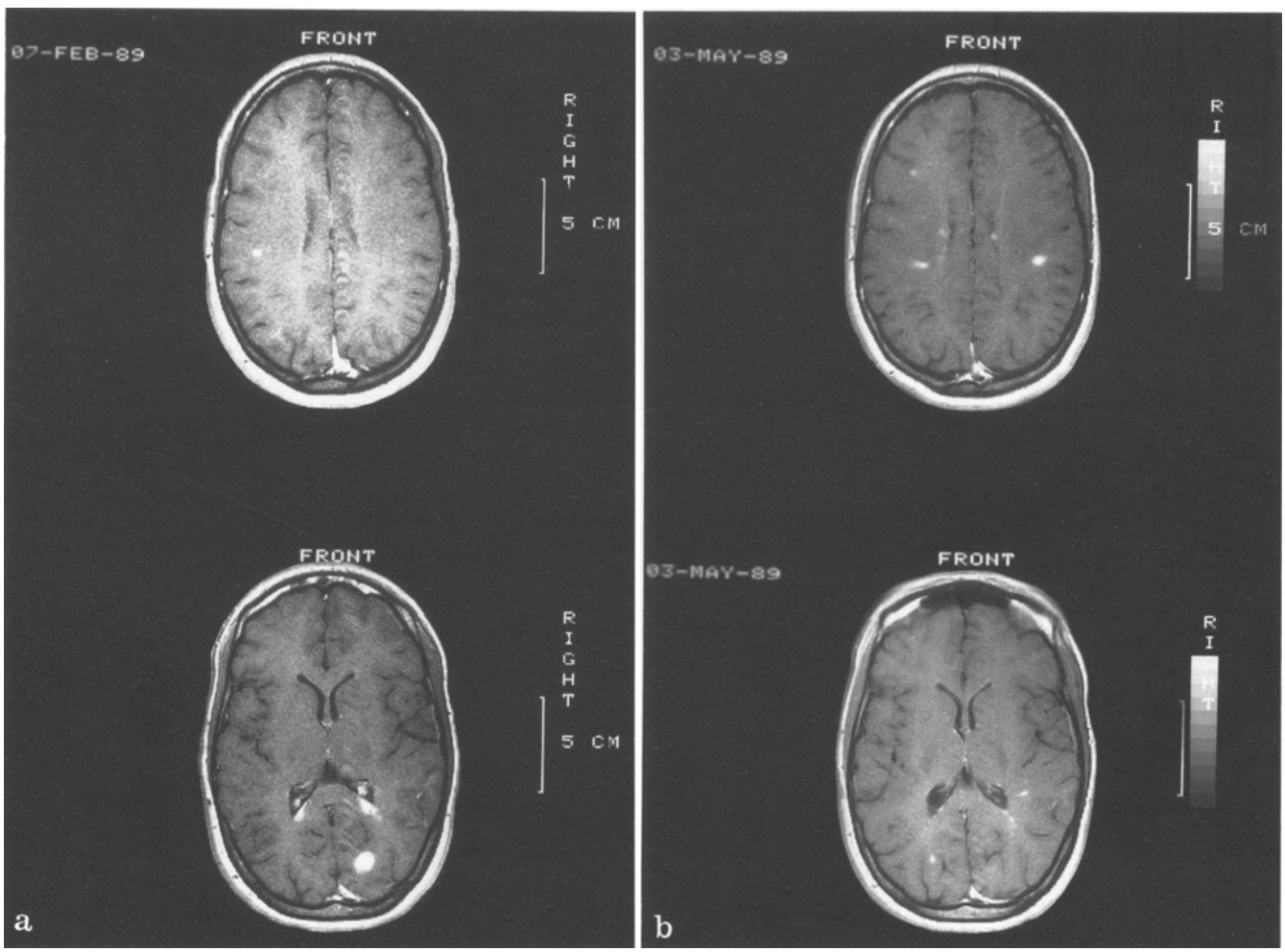
first MRI was performed at the beginning of the study, MRI controls followed after 1, 3, 6, 9 and 12 months, just before the next dose of mitoxantrone. All MRI was performed on a 1-Tesla superconducting imager (Magnetom, Siemens) in axial orientation. Above and below the tentorium we used 5-mm slices without interslice gap. The patients were investigated with spin echo technique with a repetition time (TR) of 2,500 ms and echo delay times (TE) of 30 and 90 ms. After the administration of 0.2 mmol/kg Gd-DTPA (gadolinium-diethylinetriaminepenta-acetic acid; Schering AG), a T1-weighted sequence was performed (TR 500–800 ms, TE 17–30 ms). Patient 4 became pregnant about 8 weeks after the last mitoxantrone infusion. Because of possible risks, we did not use Gd at the final MRI examination in this patient. Despite objective improvement in both the clinical evaluation and the MRI, Patient 3 did not continue treatment after 6 months (two mitoxantrone treatments).

Results

Using the disability grade according to the Kurtzke Scale, five patients remained stable and four improved following a 12-month period, i.e. four mitoxantrone treatments. Looking at the SNE, which is a more sensitive scale in demonstrating clinical changes, eight patients exhibited improvement and one remained stable. Figure 1 presents the clinical follow-up seen during 1 year. When we compared the mean scores of the two scales before mitoxantrone treatment and after 1 year of treatment, we found a reduction from 6.0 (SEM = 0.6) to 5.1 (SEM = 0.8) in the Kurtzke Scale and from 28.6 (SEM = 3.9) to 17.8 (SEM = 4.9) in the SNE. The difference in the SNE showed statistical significance ($P < 0.01$; Wilcoxon-Pratt test). The changes in these clinical parameters are shown in Table 2. The frequency of relapses during the course of our study was reduced to 0.2 (SEM = 0.2) in contrast to 1.7 (SEM = 0.5) in the year before the start of our investigation.

With the exception of patient 7, the P100 latencies of VEPs were delayed bilaterally in all patients. After 1 year, there was a distinct improvement of the latencies in the left eye in patients 4 and 9; in the right eye in patient 1, 5 and 9. Our findings correlate with the clinical improvement in these patients. The mean latency of P100 before the start of mitoxantrone therapy was 146 ms (SEM = 9.5) in the left eye and 148 ms (SEM = 12.3) in the right eye. After 1 year, the mean latency of P100 in the left eye was reduced to 128 ms (SEM = 5.3) and to 124 ms (SEM = 4.9) in the right eye. At enrolment, none of our MS patients suffered from acute optic neuritis.

At the time of admission to the study, this patient group presented with a total number of 169 Gd-enhancing lesions, identified through MRI. In five patients, seven or more enhancing lesions were found. In three



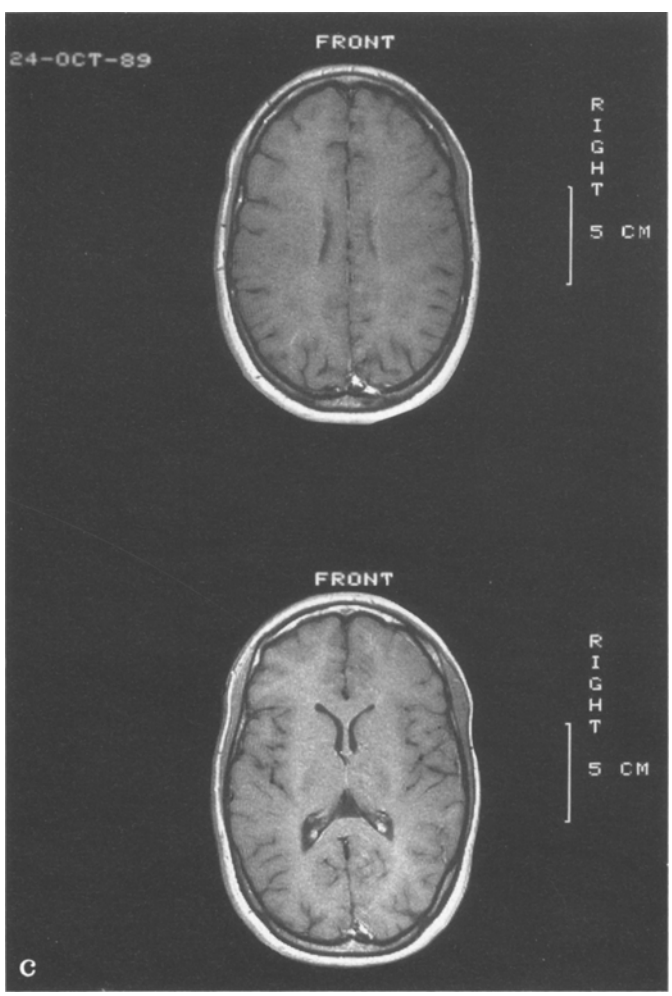
patients no more than two lesions were identified. In two patients only a slight periventricular enhancement was seen. After 12 months, that is four treatments with mitoxantrone, enhancing lesions could be identified only in patient 8 (seven small new lesions). In patient 4, where we did not use Gd because of pregnancy, we detected three new lesions which we suppose would also be Gd enhancing.

Forty enhancing lesions were identified at the end of the first quarter; however, 17 of these were from patient 4, who suffered a relapse 2 weeks preceding the second mitoxantrone treatment. Figure 2 shows the MRI follow-up with post-contrast T1-weighted images in this patient. The first scan (Fig. 2a) was done before treatment and shows a small enhancing lesion on the left parietal lobe and a larger lesion on the right occipital lobe. In Fig. 2b, we see a scan taken during an acute relapse which occurred 3 months after the beginning of treatment and shows multiple enhancing lesions in both hemispheres. In a control scan after 9 months (Fig. 2c) no local Gd enhancement can be detected. The regression of active lesions is not limited only to patients with an acute episode. For example, patient 2 presented with a chronic progressive disease course and had 76 enhancing lesions at baseline which diminished to 0 at 12 months. Figure 3 shows the total number of enhancing lesions over the period of 1 year. The reduction of Gd-enhancing lesions after 1 year shows statistical significance ($P < 0.05$; Wilcoxon-Pratt test). Table 3 additionally demonstrates the changes in VEP and MRI during the 1-year follow-up.

At the time of enrolment, eight of ten patients had received additional medication for symptomatic treatment of multiple sclerosis, mostly antispasmodic and urological drugs, beta-blockers or antidepressants. After 1 year, additional medication was necessary in only four patients.

The side effects of the treatment observed were minimal. Six patients experienced mild, temporary nausea and a slight faintness. These symptoms lasted for only 1–2 days. Patients 2 and 4 experienced occasional vomiting following the infusion. In four patients, no side effects were observed.

Mitoxantrone treatment leads to a significant decrease of leukocyte and lymphocyte count within 6–15 days after the start of therapy. About 2 weeks after the start of treatment leukocytes show a highly significant maximum decrease to a mean value of 3.700/mm^3. Lymphocyte count reaches the nadir of 1.400/mm^3 after only 1 week. Thereafter the white blood count begins to recover with a tendency towards normal values within 21 days. There was no relevant change in the thrombocyte and erythrocyte count nor in the haemoglobin concentration during the mitoxantrone treatment.



Discussion

According to the SNE, which is the most sensitive of the clinical scales applied, a continuous improvement was seen. Eight out of nine patients showed clinical improvement following 12 months of treatment. The score difference of this scale before mitoxantrone therapy and after 1 year shows statistical significance. Gonsette and Demonty [6], who first treated multiple sclerosis with mitoxantrone, were able to stabilize 18 patients with active disease within a follow-up of between 6 months and about 1 year. In comparison with our regime, they used a much higher dosage until lymphopenia was equal to or lower than $1.0 \times 10/\mu l$ or until CD4 cells' and B cells' absolute values were lower than the 1st percentile of a normal population.

Recently a Canadian multicenter study with 168 patients was published describing the immunosuppressive therapy of progressive MS with cyclophosphamide [2]. In an observer-blind controlled three-arm study, cyclophosphamide in two dosage regimes and plasma exchange was tested against placebo. As in our study the patients

Fig. 2a–c. Gadolinium-MRI follow-up in patient 4: **a** first scan before treatment, showing a small enhancing lesion on the left parietal lobe and a larger lesion on the right occipital lobe; **b** third scan taken during an acute relapse, 3 months after the beginning of treatment, showing multiple enhancing lesions in both hemispheres; **c** control-scan after 9 months without local Gadolinium enhancement

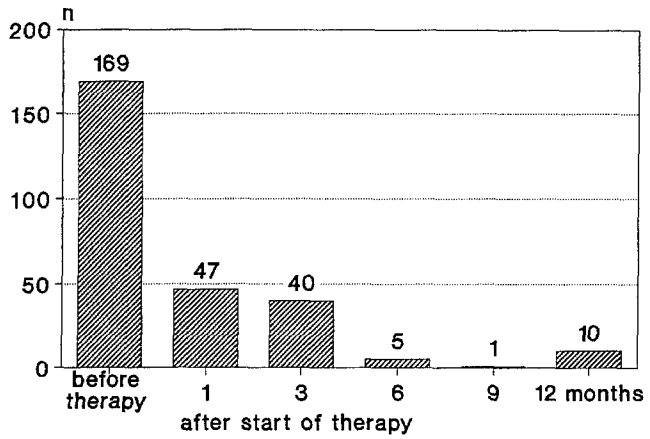


Fig. 3. Number of enhancing lesions identified during mitoxantrone treatment

had to show evidence of deterioration of at least 1.0 on the Expanded Disability Status Scale (EDSS) within the preceding 12 months. The 56 placebo-treated patients of this investigation did not differ significantly from our patients with regard to age, sex and degree of disability at study entry. Only the duration of MS was somewhat longer, 10 years in their patients in comparison with a mean disease duration of 7.4 years for our patient group. During the Canadian study, 39% of the placebo-treated patients had received at least one cortisone dose because of clinical deterioration. After 1 year, only 2% of the Canadian patients had improved according to the Kurtzke scale, 73% were stabilised and 25% had deteriorated during the 1-year follow-up. The mean increase in Kurtzke EDSS was 0.4 over this period.

In contrast to these results, four of our ten patients had improved after 12 months according to the Kurtzke scale and there was a mean decrease of nearly 1.0 in our patients after 1 year. In addition to possible prednisolone effects, the high stabilisation rate of the placebo-treated patients in the Canadian study is probably caused by the insensitivity of the Kurtzke EDSS, especially between 6.0 and 7.0. (6.5 = ambulatory with constant bilateral assistance; 7.0 = essentially restricted to wheelchair).

With the exception of one patient, the P100 latencies of VEP were prolonged bilaterally in all patients. This could be a further indication of the unfavourable course of the disease in our patient group. In fact, in an unselected epidemiological sample of 1055 patients in North-East Scotland, a bilateral prolongation of P100 latency predicted a poor prognosis [16]. The reduction of latencies correlates with clinical improvement in our patients. Moreover, it was possible to reduce the additional medication for symptomatic treatment during the course of the study.

Using the MRI findings, mitoxantrone treatment has led to a substantial reduction in the number of enhancing lesions over a 12-month period. Patient 4 experienced two relapses during treatment with mitoxantrone, in both cases 2 weeks prior to the next planned dose. This finding could be an indication that, in this case, a treatment interval of 3 months was too long. The new lesions that appeared in this patient, three after the first relapse and 17 after the second, also remitted quickly.

There are good reasons to refute the hypothesis that the reduction in the number of enhancing lesions during the 1-year study could be attributed to the short prednisolone therapy administered with the first mitoxantrone treatment or even as a result of spontaneous remission.

The first argument is from patient No. 2 who had not had a relapse in the past and who did not receive any concomitant cortisone treatment. In this patient, the enhancing lesions diminished to 0 after identifying a total of 76 at baseline. It is now widely recognized that short-term (5 days) corticosteroid treatment alone is only effective for treating acute episodes. Moreover, the clinical improvement in these patients usually lasts only a short time. Fog [5] had already reported in 1970 that corticosteroid shortens the bout but does not change the disease progression at all. The statement of Fog is re-

Table 3. Changes in paraclinical parameters at the start of the investigation and after 1 year

Patient	Gd-enh. les. at the start of investigation	Gd-enh. les. after 1 year	VEP left/right at the start of investigation	VEP left/right after one year
1	2	0	139.0/131.0	134.0/123.5
2	76	0	NR/NR	NR/NR
3	7	Drop out	198.5/192.5	Drop out
4	9	3	160.5/NR	125.0/123.0
5	1	0	126.0/187.5	121.0/119.5
6	0	0	132.5/115.0	130.0/115.0
7	1	0	109.5/110.0	104.0/106.5
8	60	7	153.0/151.5	150.0/147.0
9	13	0	152.5/149.0	132.0/132.5
10	0	0	NR/NR	NR/NR
Mean	16.9	1.1	146.4/148.1	128.0/123.9
SEM	8.7	0.8	9.5/ 12.3	5.3/ 4.9

Gd-enh. les. = Gadolinium-enhancing lesions; VEP = visual evoked potentials; NR = not reproduceable

lated to a low-dose therapy but Polman et al. [17] published their experience in which a monthly treatment with 500 mg methylprednisolone IV in ten MS patients had no effect on the clinical course. Their patient group had deteriorated by 0.9 on the Kurtzke scale during the year before study entry and by 0.9 during the 9-month follow-up.

Kesselring et al. [11] reported on treating 50 patients, with 0.5 g prednisolone intravenously for 5 days, where MS was either "definite" or "probable". MRI was carried out both preceding and 15 days following treatment. The analysis showed new lesions in 9 patients; in each of 7 patients one plaque had resolved. No lesions which were present at baseline had disappeared. The authors conclude that "corticosteroids do not appear to rapidly alter the process underlying plaque formation".

Most of the MRI lesions in MS are clinically asymptomatic and new lesions are 5–10 times more frequent than clinical relapses [15]. Therefore, MRI demonstrates the ongoing progression of the disease in clinically stable phases and allows more sensitive and objective monitoring of therapy. Gd-enhancement occurs in almost all new lesions in relapsing-remitting or secondary progressive MS and indicates the presence of inflammation. The initial transient enhancing phase of new lesions generally lasts 4–6 weeks [1, 9, 10, 15].

Enhancement also occurs in some older lesions, which show no other change in appearance on T2-weighted unenhanced MRI. In a serial study by Bastianello et al. [1] 6 of 16 new enhancing lesions were older plaques which did not increase in size. In our study this percentage was lower (8 of 48) similar to the results of Miller et al. [14] (4 of 16). Therefore, if only new lesions were analysed. MRI controls without Gd will underestimate the real disease activity in MS.

Only a few studies have as yet been published, where Gd-enhancing lesions were followed over a longer period of time. The Concerted Action Guidelines of the Commission of the European Communities (CEC) [15] require MRI monitoring for more than 6 months to evaluate treatment effectiveness. Miller et al. [14] were able to identify at baseline a total of 54 enhancing lesions by using MRI and Gd in seven out of nine MS patients in an acute bout. After 4 weeks, 26 lesions were enhancing. Six months later, eight patients exhibited 10 new enhancing lesions, identified by MRI with Gd. The enhancing lesions identified at 6 months represented 18% of the number seen at baseline. The patient group we treated showed 3% of the original lesions after 6 months (two treatments with mitoxantrone). In contrast to our patients, those of Miller et al. [14] were, without exception, in acute relapse. Unfortunately, the authors do not mention the treatment they administered, the degree of severity or the duration of the disease. It seems that their patients were not selected for severity.

Harris et al. [9] investigated six patients with an early mild relapsing-remitting MS (mean duration of disease 17.2 months; mean EDSS 1.9) using monthly Gd-enhanced MRI scans for 8–11 months. None of the six patients were in an acute relapse at the beginning and during the study only two exacerbations – with no permanent worsening of the EDSS – occurred. In spite of these clinical data, at the start 29 Gd-enhancing lesions were detected and during the study in 54 control scans 113 new Gd-enhancing lesions occurred. Four of the six patients had one or more enhancing lesion permanently present on each of the monthly MRI examinations. In the study of Harris et al. [9] only 6 of 60 MRI scans demonstrated no Gd enhancement. In the study of Grossman et al. [7] of 13 MS patients, MRI after 16–24 months showed Gd enhancement in 8 of 13 cases; the total number of the new enhancing lesions was 31.

In our study after start of treatment no Gd enhancement was found ($P < 0.001$; Chi-square test) in 29 of 48 MRI controls. In the other 19 control scans only 48 new lesions appeared. These results record that during mitoxantrone treatment our patients were clinically stable and MRI showed a significant reduction of the Gd-enhancing lesions.

The favourable effect of mitoxantrone in MS therapy may be accounted for by its potent suppressive influence on the humoral immune system though a direct reduction in B-cell number augmented by macrophage-mediated inhibition of B-cell proliferation [3]. In vitro mitoxantrone also shows a macrophage-mediated suppression of T helper cell induction and an enhancement of suppressor function [4].

The side effects observed in this study attributed to mitoxantrone were negligible. In four patients, none were reported or observed. Owing to the potential for long-term cardiotoxicity, no patients with known cardiac risk factors were enrolled in this study. To date the cardiotoxic potential of mitoxantrone has been given much attention in clinical investigations. Gruener et al. [8] and Lenzhofer [12] report an analysis of more than 4450 patients with a variety of malignancies treated with mitoxantrone in clinical studies worldwide. A congestive cardiomyopathy was found in only 3 of these patients who had no further risk factors of cardiotoxicity such as prior treatment with anthracyclines, radiation of the chest or known cardiac or circulation diseases. The authors conclude that the cardiotoxic potential seems to be distinctly lower for mitoxantrone than for other anthracyclines. As a precaution, the package insert for mitoxantrone recommends that, even for patients without risk factors, routine cardiac function tests be carried out once a cumulative dosage of 140 mg/m^2 is reached. However, it should be noted that this recommendation is based on the intensive treatment combinations used in oncology.

This study included routine ECG controls and to date no pathological changes have been observed. Additionally, no local irritation at the site of injection was seen, no stomatitis and no hairloss. Patients with reproductive potential have been advised to use effective contraception or abstinence during and for 3 months following treatment with mitoxantrone.

These results from a selected patient series seem to indicate that mitoxantrone is an effective and very tolerable substance for treating MS. Therefore, mitoxantrone should be considered to be a treatment for a comparative phase-III study.

Acknowledgements. The authors thank Janet Clark for her assistance with this study and for translating the manuscript.

References

1. Bastianello S, Pozzilli C, Bernardi S, Bozzao L, Fantozzi LM, Buttinelli C, Fieschi C (1990) Serial study of gadolinium-DTPA MRI enhancement in multiple sclerosis. Neurology 40: 591–595
2. Canadian Cooperative Multiple Sclerosis Study Group (1991) The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. Lancet 337: 441–446
3. Fidler JM, DeJoy SQ, Gibbons JJ (1986) Selective immunomodulation by the antineoplastic agent mitoxantrone. I. Suppression of B lymphocyte function. J Immunol 137:727–732
4. Fidler JM, DeJoy SQ, Smith FR, Gibbons JJ (1986) Selective immonomodulation by the antineoplastic agent mitoxantrone. II. Nonspecific adherent suppressor cells derived from mitoxantrone-treated mice. J Immunol 136:2747–2754
5. Fog T, Linnemann F (1970) The course of multiple sclerosis. Acta Neurol Scand 46 [Suppl]:47–58
6. Gonsette RE, Demonty L (1989) Mitoxantrone: A new immunosuppressive agent in multiple sclerosis. In: Gonsette RE, Delmotte P (eds) Recent advances in multiple sclerosis therapy. Elsevier, Amsterdam, pp 161–164
7. Grossman RI, Braffman BH, Brorson JR, Goldberg HI, Silberberg DH, Gonzalez-Scarano F (1988) Multiple sclerosis: serial study of gadolinium-enhanced MR Imaging. Radiology 169: 117–122
8. Gruener A, Ingenhag W, Clark J (1985) Mitoxantron – Klinische Pharmakologie, Untersuchungen und Analysen zur Verträglichkeit. Fortschr Antimikrob Antineoplast Chemother 387–399
9. Harris JO, Frank JA, Patronas N, McFarlin DE, McFarland HF (1991) Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: implications for clinical trials and natural history. Ann Neurol 29:548–555
10. Kappos L, Städt D, Rohrbach E, Keil W, Clauss W (1988) Time course of gadolinium enhancement in MRI of patients with multiple sclerosis: effects of corticosteroid treatment. J Neurol 235:10
11. Kesselring J, Miller DH, MacManus DG, Johnson G, Milligan NM, Scolding N, Compston DAS, McDonald WI (1989) Quantitative magnetic resonance imaging in multiple sclerosis: the effect of high dose intravenous methylprednisolone. J Neurol Neurosurg Psychiatry 52:14–17
12. Lenzhofer R (1985) Kardiotoxizität von Mitoxantron. Fortschr Antimikrob Antineoplast Chemother 4:379–386
13. Lublin FD, Lavasa M, Viti C, Knobler RL (1987) Suppression of acute and relapsing experimental allergic encephalomyelitis with mitoxantrone. Clin Immunol Immunopathol 45:122–128
14. Miller DH, Rudge P, Johnson G, Kendall BE, MacManus DG, Moseley IF, Barnes D, McDonald WI (1988) Serial gadolinium-enhanced magnetic resonance imaging in multiple sclerosis. Brain 111:927–939
15. Miller DH, Barkhof F, Berry I, Kappos L, Scotti G, Thompson AJ (1991) Magnetic resonance imaging in monitoring the treatment of multiple sclerosis: Concerted Action Guidelines. J Neurol Neurosurg Psychiatry 54:683–688
16. Phadke JG (1990) Clinical aspects of multiple sclerosis in North-East Scotland with particular reference to its course and prognosis. Brain 113:1597–1628
17. Polman CH, Van der Wiel HE, Netelenbos JC, Teule GJJ, Koetsier JC (1991) A commentary on steroid treatment in multiple sclerosis. Arch Neurol 48:1011–1012
18. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13:227–231
19. Ridge SC, Sloboda AE, McReynolds RA, Levine S, Oronsky AL, Kerwar SS (1985) Suppression of experimental allergic encephalomyelitis by mitoxantrone. Clin Immunol Immunopathol 35:35–42
20. Sloboda AE, Oronsky AL, Kerwar SS (1986) Studies of the effect of mitoxantrone on adjuvant induced arthritis in rats. Clin Immunol Immunopathol 40:236–243