Mitoxantrone Reduced Disability in Iranian Patients with Multiple Sclerosis

Ali Hamzehloo MD*, Masood Etemadifar MD*

Background: Multiple sclerosis is a leading cause of disability in young adults. Mitoxantrone has recently been shown to be effective in ameliorating multiple sclerosis activity and reducing the relapse rate. This study aimed to assess the efficacy of mitoxantrone on disease activity and decreasing relapse rate in patients with multiple sclerosis in Iran.

Methods: This was a clinical trial on patients who received intravenous mitoxantrone, 12 mg/m² every 3 months. The study was performed at Isfahan Multiple Sclerosis Clinics, affiliated to Isfahan University of Medical Sciences. This clinical trial was conducted from October 2003 through April 2005.

One hundred and forty-seven patients with worsening relapsing-remitting and secondary progressive multiple sclerosis received mitoxantrone, 12 mg/m² every 3 months. Clinical assessment was made every 3 months for one year.

Results: Of the 147 patients, 129 (93 females and 36 males) could successfully complete the course of our study. A significant therapeutic effect ($P < 0.0001$) was detected for the attack rate before and after treatment. The mean attack rate 12 months before treatment was 1.10 (SD = 0.95), which reduced to 0.09 (SD = 0.29) during treatment.

The mean expanded disability status scale at the beginning of the treatment was 4.32, which declined to 3.62 ($P < 0.0001$) after one year.

Conclusion: Mitoxantrone was generally well tolerated and reduced progression of disability and clinical exacerbation in our patients. Physicians must be careful about the complications of mitoxantrone especially cardiotoxicity.

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS). The disease is one of the most common neurologic disorders of younger adults and is a major nontraumatic reason for disability in the ages of 20 to 50.¹

Clinical pattern of MS has been defined by international consensus.² About 85% of patients initially experience one or more relapses followed by complete or incomplete recovery; this clinical pattern is referred to as relapsing-remitting phase. Over 10 years, about 50% of these patients will experience a transition to the secondary progressive phase,³ which is characterized by gradually worsening disability with or without superimposed relapses. About 10% of patients experience a clinical course with a progressive onset termed primary progressive multiple sclerosis. The remaining 5% of patients suffer from progressive disability, which is later accompanied by one or more superimposed relapses; this pattern is referred to as progressive relapsing MS. At least half of the patients, who initially present with relapsing-remitting multiple sclerosis (RRMS) will develop secondary progressive multiple sclerosis (SPMS).⁴

The National Multiple Sclerosis Society and the American Academy of Neurology recommended
Mitoxantrone reduced disability in Iranian patients with MS.\textsuperscript{5, 6} Atrophy occurs early in RRMS and a recent report suggests that the rate of axon damage is most prominent in the first year after diagnosis, so early treatment may be important in limiting the long-term disability. The report suggests that early treatment with mitoxantrone can be beneficial for certain groups of patients.\textsuperscript{7}

Mitoxantrone is a synthetic anthracenedione recently approved by the Food and Drug Administration (FDA) for the treatment of worsening relapsing-remitting, secondary progressive, and progressive relapsing MS.\textsuperscript{8} Mitoxantrone suppresses both B and T lymphocytes and seems more effective on helper subsets than on suppressors, resulting in a down regulation of the inflammatory cascade. In addition, mitoxantrone has a marked suppressive effect on macrophage function.\textsuperscript{9} Because macrophages are found in large numbers in acute lesions, their suppression may be associated with a decrease in the extent of tissue damage caused by inflammation.\textsuperscript{8}

In a pivotal randomized double-blinded, multicenter trial, mitoxantrone 12 mg/m\textsuperscript{2} administered once every 3 months for 2 years provided significant improvement on neurologic disability rating, including Kurtzke Expanded Disability Status Scale (EDSS), Ambulatory Index (AI), and Standardized Neurologic Status (SNS) scores compared with placebo.\textsuperscript{10} The drug also significantly reduced the mean number of relapses and prolonged the time to the first treated relapse, with the beneficial effects on disease progression supported by magnetic resonance imaging.\textsuperscript{11 – 13}

Mitoxantrone hydrochloride is a cost-effective treatment for patients with SPMS or progressive relapsing MS.\textsuperscript{14}

In our study, we evaluated the efficacy of mitoxantrone on MS patients in Isfahan, Iran, and hypothesized that after 12 months, mitoxantrone 12 mg/m\textsuperscript{2} would significantly decrease progression of disability with fewer relapses.

Materials and Methods

Study design
The study was a clinical trial on patients who received the treatment regimen of mitoxantrone 12 mg/m\textsuperscript{2} intravenously every 3 months for 12 months. This study was performed at Isfahan Multiple Sclerosis Clinic, affiliated to Isfahan University of Medical Sciences in October 2003 to April 2005. The study was approved by ethics committees of Isfahan University of Medical Sciences and by Isfahan Society of Multiple Sclerosis. All patients signed an informed consent approved by the institutional review board at the study site.

Patients
The inclusion criteria were; age between 15 and 55 years, patients whose neurological status was significantly abnormal between relapses (worsening relapsing-remitting multiple sclerosis), and gradual progression of disability with or without superimposed clinical relapses (secondary progressive multiple sclerosis), Kurtzke EDSS\textsuperscript{15} score of 2 – 6.5, worsening of 1.0 point or more of EDSS score during the 18 months before enrollment, no clinical relapses or treatment with glucocorticoids for at least 8 weeks before enrollment, no previous treatment with mitoxantrone, glatiramer acetate, cytotoxic drugs, or total-body lymphoid irradiation, left ventricular ejection fraction greater than 50%, and normal range values for white cell count (more than 4 × 10\textsuperscript{9}/l), neutrophil count (more than 2 × 10\textsuperscript{9}/l), and platelet count (more than 100 × 10\textsuperscript{9}/l). All patients had been diagnosed as having RRMS or SPMS based on the diagnostic criteria for MS according to McDonald et al.\textsuperscript{16}

Treatment and assessment
Mitoxantrone was administered by slow intravenous infusion over at least 5 minutes every 3 months for 1 year (a total of four doses). The antiemetic drugs were administered peroral 1 hour before and 8 hours after drug infusion. Treatment with other immunomodulatory or cytotoxic agents was prohibited during the study.

The attack was defined as an episode of neurological disturbance. The causative lesions were likely to be inflammatory or demyelinating in nature. The event should last for at least 24 hours.\textsuperscript{16} Those patients who experienced a severe attack were treated with a 5-day course of intravenous methylprednisolone, 1000 mg/day.

EDSS was evaluated at each scheduled and nonscheduled visit by a neurologist who was unaware of treatment. Another physician carried out all medical assessments, reviewed laboratory data, adjusted the dose of the drug according to the protocol, treated the patients’ symptoms, and diagnosed and graded the severity of clinical relapses. This physician was unaware of treatment.
assignment. The primary efficacy outcome consisted of two clinical measures: change from baseline EDSS at 12 months, and number of relapses treated with corticosteroids.

Cardiac monitoring was done before treatment and after 6 and 12 months. The monitoring included electrocardiography and measurement of left-ventricular ejection fraction (LVEF) via echocardiography. Administration of mitoxantrone was discontinued if the LVEF decreased 10% or more from the baseline or if the measured value was less than 50%.

Statistical analyses

The main aim of this study was to assess the change of EDSS in the 3-month periods and relapse rate before and after the treatment. For each two interval periods $t$-test was applied for analysis and multivariate repeated measure test was applied for analysis of linear progression of EDSS.

Results

One hundred and forty-seven patients were studied between October 2003 and April 2005 at the MS Clinic, affiliated to Isfahan University of Medical Sciences. All of the patients received at least two doses of mitoxantrone and had at least two clinical assessments.

Eighteen patients were excluded from the study for following reasons: seven patients for cardiotoxicity, two patients for noncompliance to the drug, three patients discontinued the treatment because of financial problems, and the remaining one for inadequate follow-up.

A total of 129 patients could successfully complete the course of our study. Of them, 93 were females and 36 were males, 108 had RRMS and 21 had SPMS. The mean age of the patients was 31.57 (SD = 8.5). The mean duration of MS was 6.9 years (SD = 3.7) and the mean attack rate during 12 months before treatment was 1.10 (SD = 0.9). Thirty nine patients had no relapse one year before treatment. The mean cumulative dose for the 12 mg/m² dose over 12 months was 46.7mg/m² (SD = 2.1).

A significant treatment effect ($P < 0.0001$) was detected for the attack rate before and after the treatment. The mean attack rate during 12 months before treatment was 1.10 (SD = 0.95) and during the treatment period was 0.09 (SD = 0.29). Of all patients on treatment, 117 had no relapse and 12 suffered from only one attack during the course of the treatment. All but one of the attacks during the treatment happened in the first 6 months of treatment (cumulative dose <24mg/m²).

EDSS progression decreased significantly during the treatment. The mean EDSS is depicted in Figure 1.

Comparison of the mean of EDSS during the treatment by multivariate test (repeated measure test) showed a highly significant effect of the drug on reducing EDSS progression ($P < 0.0001$).

A high significant effect ($P < 0.0001$) of mitoxantrone on reducing the mean of EDSS was

![Figure 1. EDSS was decreased significantly during the treatment. The mean EDSS at the beginning and during the treatment of 3-month intervals.](image-url)
Mitoxantrone reduced disability in Iranian patients with MS

Mitoxantrone reduced disability in Iranian patients with MS

detected between the two visits. Paired t-test showed a highly significant difference ($P < 0.0001$) between EDSS at the beginning of the treatment and EDSS at 6, 9, and 12 months later. The mean EDSS change from baseline to 12 months was 0.7.

Mitoxantrone was generally well tolerated during this study. Nausea, urinary tract infection, menstrual disorders, amenorrhea, and mild alopecia occurred more frequently during the study. One patient discontinued the study for severe hair loss.

The severity is defined by intensity that drug is withdraw by patients or physician. There were no deaths or serious drug-related adverse events. The drug was discontinued as a result of adverse effects in 11 patients (leukopenia, decreased LVEF, amenorrhea and pregnancy).

Leukopenia occurred in 20 (15.5%) patients. In all of these patients’, white cell count returned to normal range after cessation of the treatment. No changes in liver function tests were detected. Secondary amenorrhea (cessation of menses for at least 3 months) was seen in 21.5 % of female patients. Amenorrhea did not persist in the patients 6 months after cessation of the treatment.

During the one-year follow-up, LVEF decreased to less than 50% in 4 patients and to less than 10% below baseline in 3 patients. No congestive heart failure or other clinically significant cardiac dysfunction occurred during the one-year monitoring period.

**Discussion**

Mitoxantrone 12 mg/m$^2$ was effective and was generally well tolerated by the patients with worsening relapsing-remitting and secondary MS. Significant treatment effect was observed with multivariate test of EDSS variable that collectively captured clinically relevant features of the disease.

In a small phase II pilot trial 10 patients with clinically definite MS were studied. The average Disability Status Scale (DSS) was 6. The Patients received mitoxantrone 12 mg/m$^2$ at 3-month intervals over 1 year. After 1 year of treatment, the mean DSS score decreased to 5.1.

In two trials with different MS populations, the results were statistically significant. The reduction in the confined one point in EDSS was 63% and 83%, with a significant improvement of the disability score. There was an important reduction of the relapse rate, between 68% and 77%, respectively.$^{18}$

Cursiefen and colleagues studied 15 patients retrospectively for a one-year treatment with mitoxantrone every 3 months. They observed that relapse rate reduced from 3.0 (SD = 1.5) in the year before treatment to 0.5 (SD = 0.5) during the treatment.$^{19}$

In another study, 27 (42%) of 64 patients in the placebo group and 36 (60%) of 60 patients in mitoxantrone group did not progress in their EDSS score by 1 or more after 3 years ($P = 0.047$).$^{20}$

Edan and co-workers showed a significant improvement in EDSS change at months 2 – 6 in the mitoxantrone group, with a final mean improvement of more than one point (-1.1 vs. +0.3, $P < 0.001$). There was a significant reduction in the number of relapses (7 vs. 31, $P < 0.001$), and an increase in the number of patients who were free of exacerbation (14 vs.7, $P < 0.05$).$^{12}$

In our study, after mitoxantrone treatment, only 8 of 129 patients had 0.5 point increase in EDSS. This finding in another study was seen in three out of 13 patients.$^{21}$ The mean EDSS change in our study during 1 year was 0.7. The effect of mitoxantrone on the clinical attack rate measure was stronger statistically. This effect was -90% ($P < 0.0001$) in our study compared with another study, which was -67% ($P = 0.0002$).$^{22}$

For using this drug in relapsing MS, however, the physicians have to consider its potential toxicity. Patients treated with mitoxantrone are at increased risk for cardiac toxicity manifested by cardiomyopathy, reduced LVEF, and irreversible congestive heart failure.$^{23 – 24}$ Oncologists have reported drug-related congestive heart failure in 2.6 – 6.0% of patients who had received cumulative dose of mitoxantrone up to 140 mg/m$^2$ for treatment of leukemia or solid tumors.$^{25}$

Recently, an analysis of the data from three clinical trials of mitoxantrone (mean cumulative dose = 60.5 mg/m$^2$) in MS has been reported.$^{26}$

In our study, LVEF reduced 10% below baseline in three (2.3%) patients and below 50% in four (3.1%) patients. None of the patients experienced symptoms of congestive heart failure or other clinically significant cardiac dysfunction. However, in our study lower incidence of reduced LVEF was related to lower cumulative dose compared with other studies. Of the seven patients with reduction of LVEF, in two patients the reduction happened after the second dose and in the remaining patients after the third dose. We
recommended evaluating LVEF before the treatment and a repeat test before every scheduled visit for injection of mitoxantrone.

Secondary amenorrhea was observed in 25% of female patients in some studies. Edan and co-workers reported secondary amenorrhea in 6.7% of women younger than 35 years who had received mitoxantrone to a cumulative dose of 79 mg/m². Secondary amenorrhea was detected in our study in 21.5% of female patients.

Transient leukopenia was seen in 13.5% of patients; there was no evidence of treatment-related leukemia or other drug-related malignant disorders.

We believe that mitoxantrone provides a new therapeutic option for patients with worsening relapsing-remitting and secondary progressive MS. Efficacy of mitoxantrone in our patients to decrease relapse rate and EDSS progression was significant. For administration of the drug in Iranian patients, physicians must be careful about cardiac toxicity, which is presumed to be related to lower cumulative doses of the drug.

Acknowledgment

We would like to appreciate Mrs. Baseri for cooperating in providing the data and injection of the drug.

References

24. Strotmann JM, Spindler M, Weilbach FX. Myocardial function in patients with multiple sclerosis treated with
Mitoxantrone reduced disability in Iranian patients with MS


