Background: There are few treatment options for patients with secondary progressive and worsening relapsing-remitting multiple sclerosis. Mitoxantrone is an antineoplastic drug, recently approved for treatment of multiple sclerosis. Mitoxantrone is, however, associated with dose-related cardiotoxicity, which limits its use.

Objective: To investigate the possible cardiotoxicity of mitoxantrone in multiple sclerosis.

Methods: We studied 96 patients with worsening relapsing-remitting or secondary progressive multiple sclerosis, to evaluate cardiotoxicity within one year of mitoxantrone therapy. This study was performed in the Multiple Sclerosis Clinic of Isfahan University of Medical Sciences from October 2003 through October 2004. Analysis of mitoxantrone therapy (12 mg/m²), in terms of cardiac toxicity, was conducted on patients who received at least 4 doses. Cardiac assessment was carried out every 6 months with electrocardiogram, as well as a spectral and color-flow Doppler echocardiographic examination at the time of enrollment and 6 and 12 months later.

Results: Ninety-six patients were assessed over 12 months. There was no evidence of clinically-significant cardiac dysfunction. Three patients had a left ventricular ejection fraction of <10% of the base-line value and three had <50%.

Conclusion: Mitoxantrone (12 mg/m²) is effective and generally well tolerated by patients with worsening relapsing-remitting and secondary progressive multiple sclerosis. Our findings suggest that the risk for developing cardiotoxicity is low in patients with multiple sclerosis within one year of the treatment with mitoxantrone.

Introduction

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system. The disease is histopathologically characterized by multifocal inflammation, demyelination, and axonal loss. Clinical pattern of MS was defined by international consensus. Around 85% of patients initially experience one or more relapses, followed by complete or incomplete recovery. This clinical pattern is referred to as the relapsing-remitting phase. Over 10 years, roughly 50% of these patients experience a transition to a secondary progressive phase, which is characterized by gradual worsening of the condition and disability with or without superimposed relapses. Nearly 50% of patients will require assistance with ambulation within 15 years of diagnosis; the majority will be forced into premature retirement.

There are few treatment options for patients with secondary progressive and worsening relapsing-remitting MS. Mitoxantrone is an antineoplastic drug, recently approved for treatment of patients with MS. Several immunosuppressant properties of this drug justify its use in the treatment of MS, which is associated with dysregulated responses of T and B cells to antigens in the central nervous system and macrophage-mediated myelin damage and axonal injury.

Intravenous mitoxantrone treatment improved neurological disability and delayed progression of MS in patients with worsening relapsing-remitting
Mitoxantrone-induced cardiotoxicity in patients with MS

Mitoxantrone probably reduces the clinical attack rate and reduces attack-related magnetic resonance imaging (MRI) outcome in patients with relapsing MS. Cardiac side effects are the most serious adverse effects associated with mitoxantrone treatment. Nonetheless, these side effects fortunately occur infrequently in MS patients. After one year of monotherapy with mitoxantrone, 3.4% of patients had a reduction in their left ventricular ejection fraction (LVEF) to ≤50%, as compared to 0% of the placebo-administered group of patients. At the end of the second year, respective incidences were 1.9% and 2.9% (total cumulative dose of mitoxantrone for each patient was 96 mg/m² after a 2-year treatment course).

Cardiotoxicity associated with mitoxantrone therapy is dose-related. Mitoxantrone blocks cardiac muscarinic receptors and prolongs the duration of the action potential. Probably, this mechanism induces early after-depolarization and may signify a potential cardiac adverse effect of the drug.

The aim of this study was to investigate the cardiotoxicity of mitoxantrone in patients with MS. It seems that cardiotoxicity happens earlier in Iranian patients with MS, as compared with other countries.

Patients and Methods

Our study included 96 patients who received mitoxantrone for treatment of worsening relapsing-remitting and secondary progressive MS. All patients were registered in the MS Clinic of Isfahan University of Medical Sciences. This study was performed from October 2003 through October 2004. The study was approved by the Ethics Committees of Isfahan University of Medical Sciences and the Isfahan Society of MS. All patients signed a consent document, approved by the institutional review board, at the study site.

The inclusion criteria were age between 18 – 55 years; stepwise progression of disability between clinical relapses (worsening relapsing-remitting MS) or gradual progression of disability with or without superimposed clinical relapses (secondary progressive MS); score on the Kurtzke expanded disability status scale (EDSS) of 2 – 6; worsening of 1.0 or more EDSS points during the 18 months before enrollment; no previous treatment with mitoxantrone or other cytotoxic drugs; and LVEF of >50%. All patients had a confirmed diagnosis of MS, based on the diagnostic criteria for MS as specified by McDonald et al. Mitoxantrone was administered slowly via intravenous infusion over at least five minutes every three months, for a period of one year (a total of four courses). Treatment with other immunomodulatory or cytotoxic agents was prohibited during the study. All patients received 12 mg/m² of intravenous mitoxantrone, every three months.

Each patient had an electrocardiogram and a spectral and color-flow Doppler echocardiographic examination at the beginning and 6 and 12 months later. Two experienced cardiologists, who were unaware of the treatment regimen, performed each echocardiography. The mean of the two measurements of LVEF was used for statistical analysis. Cardiac monitoring consisted of a rhythm-controlled print-out and measurement of LVEF by echocardiography.

Administration of mitoxantrone was discontinued, if the LVEF decreased by ≥10% of the baseline value or if the measured value was <50%.

Results

Ninety-six patients completed the 12-month course of the study. All 96 patients received 12 mg/m² mitoxantrone during this study. All patients underwent cardiac monitoring.

Seventy-nine patients had relapsing-remitting (16 males and 63 females) and the remaining 17 had secondary progressive MS (4 males and 13 females).

The mean ± SD age of patients was 29.9 ± 7.3 years. The mean ± SD LVEF at the beginning and 6 and 12 months after the study, were 61.5% ± 4.1%, 59.9% ± 5.1%, and 59.6% ± 4.7%, respectively. The interobserver correlation coefficient between the results of LVEF of the two cardiologists was 0.92. No patient suffered from congestive heart failure (CHF) before the treatment. No significant difference in the electrocardiogram or the LVEF findings was noted during the follow-up, except in six patients. None of the patients had any signs or symptoms of CHF. Three patients had LVEF of 10% below the base line, and three (3.1%) had LVEF of <50%. The decrease in LVEF in two patients happened after the administration of the second dose and in one after the third dose. No CHF or other clinically-
significant cardiac dysfunction occurred during the one-year monitoring. Data obtained from six patients are summarized in Table 1.

### Table 1. Characteristics of six patients with cardiac side effects.

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Type of MS</th>
<th>Duration of MS</th>
<th>Attack rate in previous 12 months</th>
<th>LVEF at …</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>32</td>
<td>PRMS</td>
<td>4</td>
<td>2</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>19</td>
<td>PRMS</td>
<td>3</td>
<td>3</td>
<td>55%</td>
</tr>
<tr>
<td>3</td>
<td>Female</td>
<td>22</td>
<td>PRMS</td>
<td>6</td>
<td>2</td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>19</td>
<td>PRMS</td>
<td>2</td>
<td>2</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>17</td>
<td>PRMS</td>
<td>9</td>
<td>4</td>
<td>60%</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>22</td>
<td>PRMS</td>
<td>3</td>
<td>0</td>
<td>70%</td>
</tr>
</tbody>
</table>

*PRMS = progressive-relapsing multiple sclerosis.*

In our study, we did not find any significant cardiac dysfunction. Three and point one percent of our patients had LVEF of <50%. These patients had no cardiac failure. In our patients, decrease of LVEF happened earlier than that reported in other studies; it also happened with a lower cumulative dose (<60 mg/m²).

We believe that mitoxantrone provides a new therapeutic modality for patients with worsening relapsing-remitting and secondary progressive MS. It was observed that cardiotoxicity could happen earlier in the Iranian patients. Therefore, it is recommended that LVEF be determined before the start of the therapy and during the course of the treatment, following every injection. We did not start mitoxantrone therapy in patients with LVEF of <50%. More data are needed to clarify the tolerance of mitoxantrone at higher cumulative doses and longer durations of therapy and follow-up.

### References

Mitoxantrone-induced cardiotoxicity in patients with MS


