Early onset cardiotoxicity associated with mitoxantrone in patients with multiple sclerosis

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Multiple sclerosis (MS) is an autoimmune disease, involving predominantly the white matter of the brain and spinal cord. Approximately 85% of patients initially experience one or more relapses followed by complete or incomplete recovery; this clinical pattern is called the relapsing–remitting phase. Over 10 years, roughly 50% of these patients experience a transition to the secondary progressive phase, which is characterized by gradually worsening disability with or without superimposed relapses.[1] Mitoxantrone is an antineoplastic drug recently approved for patients with MS. Intravenous mitoxantrone treatment improved neurological disability and delayed progression of MS in patients with worsening relapsing–remitting or secondary progressive disease.[2] Cardiac side effects are the most serious adverse effects associated with mitoxantrone treatment.[3] Cardiotoxicity associated with mitoxantrone may be characterized by changes in ECG, indicating possible tachycardia and arrhythmia, symptomatic decrease in measures of left ventricular ejection fraction (LVEF), or symptomatic congestive heart failure (CHF).[4] After one year of monotherapy, 3.4% of mitoxantrone treated patients had a reduction in LVEF to ≤50% compared to 0% of placebo group patients; at the end of the second year respective incidences were 1.9% and 2.9%; the total cumulative dose of mitoxantrone per patient was 96 mg/m^2 after a 2-year treatment course.[2] Cardiotoxicity associated with mitoxantrone therapy is dose related.[4] Mitoxantrone blocks cardiac muscarinic receptors and prolongs action potential duration (APD). Probably, this mechanism induces early after depolarization and may signify a potential cardiac adverse effect of the drug.[5] Our study included 96 patients who received mitoxantrone for worsening relapsing-remitting and secondary progressive MS to evaluate probable cardiotoxicity associated with the drug during a one-year follow–up period.

All the patients were registered in the clinic for MS at Isfahan University of Medical Sciences, Isfahan, Iran. This study was performed from October 2003 to October 2004. The study was approved by the ethics committees at Isfahan University of Medical Sciences, and by Isfahan Society of Multiple sclerosis. All patients signed a consent document approved by the institutional review board at the study site. The inclusion criteria were: age 18-55 years: stepwise progression of disability between clinical relapses (worsening relapsing–remitting multiple sclerosis) 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 greater than 50%. Mitoxantrone was administered via slow intravenous infusion over at least 5 minutes every 3 months, for one year (a total of 4 courses). Treatment with other immunomodulatory or cytotoxic agents was prohibited during the study. All patients received mitoxantrone 12 mg/m^2 intravenously every 3 months. Each patient had an ECG and a spectral and color flow Doppler echocardiographic (ECHO) examination at the beginning, and 6, and 12 months later. Two experienced cardiologists who were unaware of the treatment regimen performed each ECHO. The mean of 2 measures of LVEF was the basis of statistical analysis. Cardiac monitoring consisted of rhythm-control print out and measurement of LVEF by ECHO. Administration of mitoxantrone was discontinued if the LVEF decreased by 10% or more from baseline, or if the measured value were less than 50%.

Ninety-six patients completed the 12 months course of the study. All 96 patients received mitoxantrone with a dose of 12mg/m^2 during this study. All patients underwent cardiac monitoring. Seventy-nine patients had relapsing–remitting (16 male, 63 female) and the remaining 17 had secondary progressive MS (4 male, 13 female). The mean age of patients was 29.89 (SD 7.3). The mean LVEF at beginning, 6 and 12 months later was 61.5 (SD 4.1), 59.9 (SD 5.1), 59.6 (SD 4.7). The inter observer correlation coefficient between results of LVEF of 2 cardiologist was 0.92. No patients suffered congestive heart failure (CHF) before treatment. No significant differences in the ECG or the LVEF were noted during the follow-up, except in 6 patients. None of the patient had any signs or symptoms of congestive heart failure. Three patients had LVEF of 10% below baseline, and in another 3, it was below 50% (3.1%). Decrease in LVEF in 2 of them occurred after the 2nd dose, and one after the 3rd dose. Heart rate and blood pressure were normal in all patients and none had cardiac risk factors other than mitoxantrone therapy to explain the decline in their LVEF. No congestive heart failure or other clinically significant cardiac dysfunction occurred during one year of monitoring. The data of these 6 patients are summarized in **Table 1.**

Mitoxantrone 12 mg/m^2 as administered during this study was effective and generally well tolerated by patients with worsening relapsing–remitting and secondary progressive MS. The benefits of

Table 1 - Characteristics of the 6 patients with cardiac side effects.

Sex	Age (Years)	Type of MS	Duration of MS (Years)	Attack rate in previous 12 months	LVEF %		
					0 months	6 months	12 months
Male	32	RRMS	4	2	65	40	discontinued
Male	19	RRMS	3	3	55	45	discontinued
Female	22	RRMS	6	2	70	60	60
Female	19	RRMS	2	2	70	60	60
Female	17	RRMS	9	4	60	45	discontinued
Male	22	RRMS	3	0	70	55	55

RRMS - relapse-remitting multiple sclerosis, LVEF - left ventricular ejection fraction

mitoxantrone therapy were observed without any evidence of short–term toxic effect. Feuillet et al[6] reported a single case of an acute heart failure occurring in a cohort of more than 800 patients treated with mitoxantrone. Although, mitoxantrone was generally well tolerated, oncologists reported drug-related congestive heart failure in 2.6–6% of patients who received cumulative doses of mitoxantrone up to 140 mg/m^2, as in the treatment regimen for leukemia or solid tumors. Notably, nearly all mitoxantrone recipients in those studies who experienced clinically significant cardiac dysfunction had pre-existing cardiovascular diseases or had also been treated with other cardiotoxic anthracyclines and mediastinal irradiation. Ghalie et al[4] demonstrated that the incidence of CHF in patients with MS who received a mean cumulative dose of 60.5 mg/m^2 was <0.2%. In one study of 28 patients, 5 had a significant decline in LVEF from baseline. In our patients, the decrease of LVEF happened earlier than in other studies and with a lower cumulative dose (<60 mg/m^2). We believe mitoxantrone provides a new therapeutic modality for patients with worsening relapsing–remitting and secondary progressive MS. We observed that cardiotoxicity might be happening earlier in Iranian patients. However, it should be considered that, cardiotoxicity in our patients is not related to cumulative dose but was idiosyncratic. Further studies are needed to identify this different result and the tolerance of mitoxantrone at higher cumulative doses, and longer duration of therapy and follow up. Therefore, we recommend a test of LVEF before therapy and on the course of treatment following every injection.

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