Late Cardiotoxicity in MS Patients Treated with Mitoxantrone

Abstract

Context: Mitoxantrone (MTX) is an antracyclin drug that is used for treatment of patients with chronic refractory multiple sclerosis (MS). Congestive heart failure (CHF) is a rare complication of this drug that may occur early, during therapy, or later, months or years after termination of therapy.

Aims: The aim of this study is to evaluate the long-term adverse effect of MTX on cardiac function.

Methods: The study involved 49 MS patients on MTX therapy because of their disease was refractory to other treatments (18 men and 31 women). They were treated in two centers related to Esfahan University of Medical Sciences. The mean age was 34.65 ± 9.56 years. Systolic and diastolic left ventricular (LV) functions were measured by echocardiography. The baseline echocardiographic data were collected from patients’ file. Echocardiography was repeated by a single cardiologist in 2016.

Results: After MTX therapy, one patient’s ejection fraction (EF) reduced below 50% (2%). In spite of their normal diastolic function before therapy, two patients developed diastolic dysfunction (4%). Nonparametric binomial analysis reveals that MTX therapy increased the probability of developing systolic dysfunction, early or late P < 001. Conclusions: MS patients treated with MTX are at increased risk of developing early and late-LV dysfunction, so all patients on MTX therapy must be periodically evaluated for these late complications.

Keywords: Heart failure, mitoxantrone, multiple sclerosis

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune disease of central nervous system in which axonal damage in brain and spinal cord is observed. It is one of the most common cause of disability in young adults in West Europe and North America.[1] There are 2.5 million people suffered from MS worldwide.[2] In a case-controlled study on patients with worsening relapsing–remitting MS mitoxantrone (MTX), 12 mg/m² was generally well tolerated and reduced progression of disability and clinical exacerbations.[1]

MTX (Novantrone), a synthetic anthrancedione derivative, is an antineoplastic, immunomodulatory, and anti-inflammatory agent. Its presumed mechanism of action in patients with MS is via immunomodulatory mechanisms, although these remain to be fully elucidated. MTX interfered with the antigen-presenting capabilities of monocyte-derived dendritic cells and induced their apoptosis at low concentrations, whereas higher concentrations caused cell lysis.[4,5]

MTX also exerts both cytotoxic and immunomodulatory effects on microglia in the CNS, the latter being mediated by increased levels of IL-10 production and impaired IL-23p19 production.

Intravenous MTX treatment improved neurological disability and delayed progression of MS in patients with worsening relapsing–remitting or secondary-progressive disease.[4-10]

MTX is licensed in the United States and some European countries, as a disease-modifying therapy for MS.[2]

The drug was allowed in treatment of leukemia. It is also used in treatment of breast, prostate, ovarian, stomach, and liver cancer. MTX inhibits topoisomerase II activity, matches to DNA molecule, and damage her structure. The drug inhibits lymphocyte T, B, and macrophages activity and antibody synthesis.[11]

MTX monthly for 6 months as induction therapy followed by maintenance treatment showed sustained clinical benefit for up to 5 years with an acceptable adverse event profile in patients with aggressive relapsing–remitting MS.[12,13]
There is, however, concern that it may cause irreversible cardiomyopathy with reduced left ventricular (LV) ejection fraction (EF) and congestive heart failure (CHF).\[^9\] CHF, potentially fatal, may occur during therapy with MTX or months to years after termination of therapy. Cardiotoxicity risk increases with cumulative MTX dose and may occur whether or not cardiac risk factors are present.\[^4,5,8-10\] Presence or history of cardiovascular disease, radiotherapy to the mediastinal/pericardial area, previous therapy with other anthracyclines or anthracenediones, or use of other cardiotoxic drugs may increase this risk. The aim of this study is to evaluate the long-term adverse effect of MTX on cardiac function of MS patients.

**Methods**

We examined long-term cardiotoxicity of MTX on MS patients treated with this drug. Cases selected from MS patients that were treated in two centers related to Isfahan University of Medical Sciences (al-Zahra Hospital and Isfahan MS Center). The time span between end of treatment and follow-up evaluation was between 1 and 5 years.

**Inclusion criteria**

All MS patients that had at least two sessions of MTX therapy and had no exclusion criteria.

**Exclusion criteria**

Patients with congenital heart disease, valvular heart disease, heart failure, coronary hear disease, pregnant patients, and patients who were treated with other cardiotoxic drugs excluded from the study.

Demographic and baseline data were collected by a questionnaire. The baseline echocardiographic data were collected from patients file and echocardiography was repeated by a single cardiologist in 2016.

**Echocardiography**

Systolic function evaluated by measurement of ejection fraction (EF) diastolic function evaluated by measurement of E/A, deceleration time E’/A’, and E/E’. Pulmonary arterial pressure was estimated with measurement of trans-tricuspid gradient.\[^14\] All new cardiac adverse events during treatment including reduction of resting LVEF measured by transthoracic echocardiogram (<50% or an absolute reduction of ≥10% from the baseline), diastolic and systolic contraction abnormalities, and newly emerging arrhythmias that could not be attributed to any other origin were regarded as therapy-related cardiac dysfunction. Mean values and standard deviations are given for the descriptive analyses, because of small sample size, the data were analyzed by nonparametrical binominal test of significance. \( P \) value <0.05 was considered significant.

All statistical analyses were performed using SPSS version 15.0.

**Table 1: Cardiovascular complication of mitoxantrone therapy**

| Characteristics                        | \( n (\%) \) or mean±SD |
|----------------------------------------|-------------------------|
| Age                                    | 34.65±9.56              |
| Sex                                    |                         |
| Male                                   | 18 (36.7)               |
| Female                                 | 31 (63.3)               |
| Cardiovascular complication            |                         |
| No complication                        | 45 (92)                 |
| Systolic dysfunction                   | 1 (2)                   |
| Diastolic dysfunction                  | 2 (4)                   |
| Arrhythmia                             | 1 (2)                   |
| Pericardial effusion                   | 0                       |
| Total                                  | 4 (8)                   |

SD=Standard deviation

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**Results**

Forty-nine patients (18 men and 31 women) enrolled in this study. The mean age was 34.65 ± 9.56 [Table 1].

Out of 31 female patients, only one person developed systolic heart failure (reduced EF below 50%); this means that 3.2% of female or 2% of all patients developed this complication. The EF reduction was over 10% and patient had no clinical symptom. Two other patients developed diastolic dysfunction in spite of normal diastolic function before therapy [Table 2 and Figure 1].

None of our patients had pericardial effusion or arrhythmia as a complication of drug therapy [Table 3].

Nonparametric binominal analysis reveals that after MTX therapy the probability of developing systolic dysfunction early or late is 2% [Table 4].

**Discussion**

Subclinical cardiotoxicity is commonly defined on cardiac imaging as clinically asymptomatic left ventricular systolic dysfunction with a fall in LVEF by >10% to a value of EF <50%.\[^14,15\] One patient out of our 49 patients (2%) developed late subclinical cardiotoxicity and another one developed early cardiotoxicity that healed after discontinuation of drug. None of our patients had clinically symptomatic heart failure. Two patients also developed grade II diastolic dysfunction. Diastolic dysfunction is a physiological process that is caused by age-related reduction in cardiac compliance. These patients were 37- and 40-year old, so this mild reduction on diastolic function may not be a complication of MTX therapy.

Paul reported that from a total number of 18 patients with secondary progressive MS who were treated with MTX at...
In this study, left ventricular ejection fraction reduction under 50% was reported in 27 (5.3%) patients during the treatment phase and 14 (5.6%) patients during the follow-up phase. Predictors of cardiotoxicity include cumulative dose, cardiovascular risk factors, and age of treatment.

Comparing the cardiotoxicity of MTX in MS patients with cancer patients, MTX is slightly less cardiotoxic in MS patients. This may be due to lower therapeutic dose of drug in MS patients; another description of this difference may be different in mean age of patient. MS patients are usually younger than cancer patients and have less comorbid disease.

So, MTX is an appropriate drug for MS patients who have worsening relapsing–remitting MS despite prior therapy. Clinical trials show that MTX would reduce relapse, the number of new lesions visualized on magnetic resonance imaging, and stop or reduce the progression of the disease in many patients.

The important limitations of our study were the small number of patients and variability on follow-up duration and inequality in cumulative dose of drug.

**Conclusions**

MTX is a disease-modifying drug that could be used in patients with progressive MS that are not controlled by other drugs. Late cardiotoxicity is a rare but significant complication that must be detected early by appropriate screening of cardiac function at least during first 5 years after therapy.

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**Table 2: The frequency of cardiovascular complication according to number of sessions of mitoxantrone therapy**

| Number of injection | Complication | Diastolic dysfunction, n (%) | Systolic dysfunction, n (%) | Arrhythmia, n (%) | Total number |
|---------------------|--------------|-------------------------------|-----------------------------|-------------------|--------------|
| 2                   |              | 0                             | 0                           | 0                 | 3            |
| 3                   |              | 0                             | 0                           | 0                 | 5            |
| 4                   |              | 0                             | 0                           | 0                 | 3            |
| 5                   |              | 1 (2.9)                       | 1 (2.9)                     | 1 (2.9)           | 34           |
| 6                   |              | 1 (25.0)                      | 0                           | 0                 | 4            |

**Table 3: Age distribution of complication of mitoxantrone therapy**

| Sex      | Age   | Frequency | Diastolic dysfunction | Systolic dysfunction | Arrhythmia |
|----------|-------|-----------|-----------------------|----------------------|------------|
| Male     | 15-29 | 3         | 0                     | 0                    | 0          |
|          | 30-39 | 9         | 0                     | 0                    | 0          |
|          | ≥40   | 6         | 0                     | 0                    | 0          |
| Female   | 15-29 | 13        | 0                     | 1                    | 0          |
|          | 30-39 | 0         | 0                     | 0                    | 0          |
|          | ≥40   | 8         | 2                     | 0                    | 0          |

**Table 4: Binominal analysis for probability of cardiac complication**

| Complication        | Category | n  | Observed_prop | Test_prop | P     |
|---------------------|----------|----|---------------|-----------|-------|
| Systolic dysfunction | Yes      | 5  | 0.1           | 0.05      | <0.001|
| early               | Yes      | 1  | 0.02          | 0.01      | <0.001|
| Systolic dysfunction | Yes      | 1  | 0.02          | 0.01      | <0.001|
| late                |          |    |               |           |       |
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