Kardiologia Polska 2016; 74, 4: 380–384; DOI: 10.5603/KP.a2015.0195 ISSN 0022–9032

ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Cardiac effects of mitoxanthrone therapy in patients with multiple sclerosis

Żanna Pastuszak, Kazimierz Tomczykiewicz, Renata Piusińska-Macoch, Adam Stępień

Military Institute of Medicine, Warsaw, Poland

Abstract

Background: Mitoxanthrone (MTX) is a synthetic anthracycline antibiotic that has been used for several years in the treatment of patients with primary progressive, secondary progressive, and relapsing remitting multiple sclerosis (MS) who do not respond to other drugs. MTX has antineoplastic, immunomodulatory, and antibacterial properties. The most common adverse effects of MTX include nausea and vomiting, hair loss, increased risk of urinary and respiratory tract infections, and amenorrhea. Less frequent problems include leukopenia, thrombocytopenia, anaemia, and an increase in hepatic enzyme and bilirubin levels. Other severe sequelae of MTX treatment are drug cardiotoxicity and a potential to induce leukaemia. Drug toxicity results from its affinity to iron ions. The resulting complex strongly induces formation of free oxygen radicals and increases lipid peroxidation. Asymptomatic reduction in left ventricular ejection fraction (LVEF) by two-dimensional (2D) echocardiography, cardiomyopathy, and congestive heart failure have been observed in patients with MS at a rate of about 2.6–5%. Few studies evaluated cardiotoxicity of MTX in MS patients. Most previous studies were performed in small groups of cancer patients and cardiac evaluation was limited to physical examination.

Aim: To evaluate the effect of MTX treatment on LVEF by 2D echocardiography.

Methods: We studied 72 MS patients aged 25–63 years who were treated with MTX in 2002–2014. The diagnosis of MS was made using the 2001 McDonald criteria updated in 2005. The study group included primary progressive MS in 40 (56%) patients, secondary progressive MS in 5 (7%) patients, and relapsing remitting MS in 27 (37%) patients. MTX was administered at 12 mg/m^2 of body surface area every 3 months (up to the total dose of 140 mg/m^2). MTX treatment was initiated in patients with no signs of heart failure on physical examination, normal electrocardiogram (ECG), normal LVEF by 2D echocardiography, and normal laboratory test findings including complete blood count and hepatic and renal function parameters. Each MTX administration was preceded by 2D echocardiography with LVEF measurement, ECG, and physical examination of the cardiovascular system. The effect of MTX treatment on LVEF was evaluated by comparing baseline LVEF with LVEF measurements before the last MTX dose. Statistical analysis was performed using the Student *t* test.

Results: The mean LVEF before administration of the first MTX dose was 65 ± 3.3%. The lowest LVEF at the final 2D echocardiographic examination was 60 ± 2.1%. We did not find a significant LVEF reduction during MTX treatment in MS patients compared to baseline values. Severe myocardial dysfunction manifesting with significant LVEF reduction by 2D echocardiography or clinical evidence of heart failure was not noted in any patient in the study group.

Conclusions: Our study showed no significant LVEF reduction during MTX monotherapy in MS patients without a history of a cardiac disease and with normal echocardiographic findings at baseline. Long-term cardiac effects of MTX require further studies.

Key words: mitoxanthrone, echocardiography, multiple sclerosis

Kardiol Pol 2016; 74, 4: 380–384

INTRODUCTION

Mitoxanthrone (MTX) is a synthetic anthracycline antibiotic, an anthraquinone derivative that has antineoplastic, immunomodulatory, and antibacterial properties [1, 2]. In 1987, it was licensed for the treatment of leukaemias. It is also used in the treatment of breast, prostate, hepatic, ovarian, and

Address for correspondence:
Żanna Pastuszak, MD, PhD, Military Institute of Medicine, ul. Szaserów 128, 04–141 Warszawa, Poland, e-mail: zanna.pastuszak@hotmail.com
Received: 28.03.2015 **Accepted:** 31.08.2015 **Available as AoP:** 23.09.2015

gastric cancers. In the clinical practice, a beneficial effect of MTX has been observed on a decrease of the number of relapses and progression of disability in patients with primary progressive, secondary progressive, and relapsing remitting multiple sclerosis (MS) who do not respond to the treatment with interferon (IFN) β1a and β1b and glatiramer acetate [1, 3]. MTX is a small molecules that crosses the blood-brain barrier [4]. It affects both proliferating and non-proliferating cells. It inhibits topoisomerase II activity, DNA replication, and RNA synthesis. MTX reduces T lymphocyte, B lymphocyte, and macrophage activity, and decreases antibody production [1, 3, 5]. MTX is an inhibitor of antigen presentation, and secretion of INFγ, interleukin 2 and tissue necrosis factor α [6]. It induces apoptosis of other immunocompetent cells, such as T lymphocytes and dendritic cells [7]. Due to poor bioavailability following oral administration, MTX is administered in the treatment of MS at a standard dose of 12 mg/m^2 of body surface area (BSA) every 3 months up to the total dose of 120–140 mg/m^2 [3, 6, 8]. The most common adverse effects of MTX include nausea and vomiting, hair loss, increased risk of urinary and respiratory tract infections, and amenorrhea. Less frequent problems include leukopenia, thrombocytopenia, anaemia, and an increase in hepatic enzyme and bilirubin levels. Other severe limitations of MTX treatment are drug cardiotoxicity and a potential to induce leukaemia [3, 8, 9]. Congestive heart failure (HF) develops in about 2.6–5% of the treated patients [10]. Toxicity of MTX results from its quinone structure which may be reduced to semiquinone, releasing a free electron which is transferred to an oxygen moiety, initiating the free radical cascade. Cardiac toxicity of MTX is related to the presence of abundant amounts of lipids in the inner mitochondrial membrane, which bind to MTX particles. The drug also shows affinity to iron ions. The resulting complex strongly induces formation of free oxygen radicals. Few studies evaluated cardiotoxicity of MTX in MS patients. The aim of the study was to evaluate the effect of MTX treatment on left ventricular ejection fraction (LVEF) by two-dimensional (2D) echocardiography.

METHODS

Our study was a retrospective evaluation of 72 patients with MS aged 25–63 years who were treated at the Department of Neurology, Military Institute of Medicine, Warsaw, in 2002–2014. Multiple sclerosis was diagnosed based on the 2001 McDonald criteria updated in 2005 [11]. The study group included 72% women and 28% men. The mean age was 47 ± 10.64 years (47.9 years in women and 44.6 years in men). The study group included 40 (56%) patients with primary progressive MS, 5 (7%) patients with secondary progressive MS, and 27 (37%) patients with relapsing remitting MS. Patients were administered MTX in an intravenous infusion at 12 mg/m^2 of BSA every 3 months (up to the total dose of 140 mg/m^2). The patients received 1–5 drug doses. Total dose ranged from 18 to 144 mg, mean 65 mg. MTX treatment was initiated in patients with no signs of HF on physical examination, normal electrocardiogram (ECG), normal LVEF by 2D echocardiography, and normal laboratory test findings including complete blood count and hepatic and renal function parameters. Each MTX administration was preceded by 2D echocardiography with LVEF measurement, ECG, and physical examination of the cardiovascular system. LVEF was calculated using the formula: $LVEF = 7 / (D + 2.4) \times D^3$, where D is the left ventricular diameter. The effect of MTX treatment on LVEF was evaluated by comparing baseline LVEF with LVEF measurements before the last MTX dose at 3–15 months of treatment. The study did not include follow-up after termination of MTX therapy. Statistical analysis was performed using the Student *t* test.

RESULTS

The mean LVEF before administration of the first MTX dose was 65 ± 3.3% (lowest value 60%, highest value 78%). In the study group (n = 72), 2D echocardiography was normal in 58 (90%) patients and showed minor abnormalities in 7 (10%) patients, including left ventricular hypertrophy, interatrial septal aneurysm, right ventricular dilatation, trace aortic regurgitation, and mild atrioventricular valve insufficiency which were not contraindications to MTX therapy (Table 1). The lowest LVEF at the final 2D echocardiographic examination was 60% and the highest LVEF was 70% (mean 65 ± 2.1%). We did not find a significant LVEF reduction during MTX treatment in MS patients compared to baseline values (p = 0.083) (Table 2). Severe myocardial dysfunction manifesting with significant LVEF reduction by 2D echocardiography or clinical evidence of HF was not noted in any patient in the study group.

DISCUSSION

Severe limitations of MTX use include drug cardiotoxicity and a potential to induce leukaemia [3, 8, 9]. The mechanism of these adverse effects has not been fully elucidated. It is probably related to the ability of the drug to induce formation of chelate complexes with iron ions which stimulate formation of reactive oxygen species that damage cardiomyocytes [1, 12].

Table 1. Echocardiographic findings in multiple sclerosis patients selected for mitoxanthrone therapy

Echocardiography	Number (%) of patients
Normal	65 (90.28%)
Trace regurgitant jet	3 (4.17%)
Interatrial septal aneurysm	1 (1.39%)
Right ventricular dilatation	1 (1.39%)
Left ventricular hypertrophy	1 (1.39%)
Mild atrioventricular valve insufficiency	1 (1.39%)

Table 2. Left ventricular ejection fraction (LVEF) by two-dimensional echocardiography before and after mitoxanthrone treatment (Student t test)

Measurement timing	Mean LVEF	Standard deviation	Student *t* test	P
Before treatment	65.3%	3.3%	1.76	0.083
After treatment	64.7%	2.1%		

Another possible reason for MTX cardiotoxicity is the presence of abundant amounts of lipids in the inner mitochondrial membrane, which bind to MTX particles [1]. Other reports indicated that cardiac toxicity of MTX increases with the drug dose [13–15]. These data were obtained in patients who received MTX for the treatment of neoplastic disease. Few studies evaluated the effect of MTX on the myocardium during MTX monotherapy of MS. Single cases of asymptomatic LVEF reduction by 2D echocardiography, cardiomyopathy, and congestive HF were reported in MS patients. While symptomatic HF develops in about 0.2–0.5% of patients treated with MTX, asymptomatic LVEF reduction is 3 times more common [16]. It was shown that cardiac toxicity increases with higher infusion rate and dose of the drug. It is recommended to administer the drug in an intravenous infusion lasting no less than 30 min and not to exceed the total dose of 140 mg/m^2 of BSA [17]. MTX should not be used in patients with LVEF below 50% [3, 18]. The Food and Drug Administration recommends echocardiography with evaluation of LVEF before each MTX administration. A decrease in LVEF by more than 10 percentage points compared to baseline or below 50% is an indication to withdraw treatment [3]. In addition to cardiomyopathy and congestive HF, other manifestations of cardiac toxicity of MTX include tachycardia and cardiac arrhythmia [1]. The authors of the recommendations of the National Team of Cardiologic and Oncologic Supervision on cardiac safety of breast cancer patients described morphological and functional myocardial changes due to anthracycline administration as chemotherapy-related cardiac dysfunction (CRCD) type I. They also discussed three possible types of cardiac dysfunction resulting from the use of this class of drugs: perimyocarditis, early-onset HF developing during oncological treatment or soon after its termination, and late-onset HF manifesting several years after oncological treatment [19].

In our study, we did not find a significant reduction in LVEF by 2D echocardiography measured before the last dose of the drug compared to baseline pretreatment values. We also did not find any case of LVEF reduction below 50% or by 10 percentage points compared to baseline. It should be noted, however, that LVEF measured by 2D echocardiography is not a sensitive method, with differences of up to 10% noted between subsequent measurements without significant cardiac damage. A more sensitive method to monitor cardiomyocyte damage is troponin level measurement. The authors of the recommendations of the National Team of Cardiologic and Oncologic Supervision advise troponin measurement soon after the infusion is terminated, at 24 h and 72 h, and at 1 month after anthracycline administration [19]. Patients in our study did not report chest pain or palpitation, and we noted no case of HF symptoms during MTX treatment. Similar conclusions were arrived at by Zingler et al. [20] who evaluated LVEF by echocardiography in 73 patients with MS and found no significant LVEF reduction during treatment. In that study group, however, 1 case of atrial fibrillation episode was noted after the second MTX dose in a patients with hypertension and previous myocardial infarction. In another study by Ghalie et al. [21] in a much larger population of 1378 patients treated with MTX, symptoms of congestive HF developed in only 2 cases, and asymptomatic LVEF reduction below 50% was noted in 2.18% of patients, more frequently with higher drug doses above 100 mg/m^2 of BSA [21–23]. In another study in 93 patients, asymptomatic LVEF reduction resulted in treatment termination in 5 patients. In 4 of these patients, LVEF normalised within few months. In 1 patient, myocardial infarction occurred at 18 months after treatment termination [9]. Deobuverie et al. [1] noted 2 cases of LVEF reduction below 45% in a group of 307 patients with primary progressive and relapsing remitting MS treated with MTX. Fewer data are available on long-term cardiac effects of MTX treatment. Goffette et al. [10] described 3 patients in whom congestive HF developed at 24, 29, and 60 months after administration of the last MTX dose. Two of these patients were previously treated with cyclophosphamide which might have increased the cardiotoxic effect of MTX [10]. During 3 years of follow-up, Hartung et al. [8] reported 4 cases of asymptomatic LVEF reduction in a group of 196 patients, with no case of congestive HF resulting from MTX treatment [8].

CONCLUSIONS

In summary, previous studies indicate that the risk of cardiac damage during MTX monotherapy in MS patients without a history of cardiac disease and with normal baseline echocardiography is low. Further studies are required to investigate long-term cardiac effects of MTX. Cardiac damage manifesting with LVEF reduction may occur years after treatment completion. The utility of cardiac monitoring using more sensitive methods such as high-sensitivity cardiac troponins or cardiac magnetic resonance imaging should be considered [19].

Conflict of interest: *none declared*

References

1. Debouverie M, Taillandier L, Pittion-Vouyovitch S at al. Clinical follow-up of 304 patients with multiple sclerosis three years after mitoxantrone treatment. Multiple Sclerosis, 2007; 13: 626–31.
2. Szwed M: Mitoxantrone: an anthraquinone antibiotic with antitumor activity applied for the treatment of multiple sclerosis dvances. Hygiene Experimental Med, 2014; 68: 198–208.
3. Martinelli M, Radaelli L, Straffi M at al. Mitoxantrone: benefits and risks in multiple sclerosis patients. Neurological Sciences, 2009; 30: 167–170. doi: 10.1007/s10072-009-0142-7.
4. Repetto L, Vannozzi M, Balleari E et al. Mitoxantrone in elderly patients with advanced breast cancer: pharmacokinetics, marrow and peripheral hematopoietic progenitor cells. Anticancer Res, 1999; 19: 879–884.
5. Millefiorini E, Gasperini C, Pozzilli C et al. Randomized placebo-controlled trial of mitoxantrone in relapsing–remitting multiple sclerosis: 24-month clinical and MRI outcome. J Neurol, 1997; 244: 153–159.
6. Bennetto L, Burrow J, Sakai H et al. The relationship between relapse, impairment and disability in multiple sclerosis. Multiple Sclerosis J, 2011; 17: 1218–1224. doi: 10.1177/1352458511407368.
7. Zhang J, Hutton G. Role of magnetic resonance imaging and immunotherapy in treating multiple sclerosis. Ann Rev Med, 2005; 56: 273–302.
8. Hartung H, Gonsette R, Konig N et al. Mitoxantrone in progressive multiple sclerosis. A placebo-controlled, double-blind, randomised, multicentre trial. Lancet, 2002; 360: 2018–2022.
9. Wundes A, Kraft G, Bowen J et al. Mitoxantrone for worsening multiple sclerosis: tolerability, toxicity, adherence and efficacy in the clinical setting. Clin Neurol Neurosurgery, 2010; 112: 876–882. doi: 10.1016/j.clineuro.2010.07.018.
10. Goffette S, van Pesch V, Sindic C. Severe delayed heart failure in three MS patients previously treated with mitoxantrone. Multiple Sclerosis J, 2004; 10: 2–269.
11. Polman Ch, Reingold S, Giles E et al. Diagnostic criteria for Multiple Sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurology, 2005; 58: 840–846.
12. Brassat D, Recher C, Waubant E et al. Therapy-related acute myeloblastic leukemia after mitoxantrone treatment in a patient with MS. Neurology, 2002; 59: 954–955.
13. Herman E, Zhang J, Hasinoff B et al. Comparison of the structural changes induced by doxorubicin and mitoxantrone in the heart, kidney and intestine and characterization of the Fe(III)--mitoxantron complex. J Mol Cell Cardiol, 1997; 29: 2415.
14. Dukart G, Barone J. An overview of cardiac episodes following mitoxantrone administration. Cancer Treatment Symptoms, 1984; 3: 34–35.
15. Foster B, Lev K, Bergemann C et al. Cardiac advents in phase II trials with mitoxantrone. Cancer Treatment Symptoms, 1984; 3: 43–46.
16. Teichholz L, Kreulen T, Herman M et al. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol, 1976; 37: 7–11.
17. Goodin D, Arnason B, Coyle P et al. The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis. Neurology, 2003; 61: 1332–1338.
18. Douglas R, Chepuri N, Durden D at al. A pilot trial of combination therapy with mitoxantrone and interferon beta-1b using monthly gadolinium-enhanced magnetic resonance imaging. Multiple Sclerosis J, 2005; 3: 296–301.
19. Opolski G, Krzakowski M, Szmit S et al. Recommendations of National Team of Cardiologic and Oncologic Supervision on cardiologic safety of patients with breast cancer. The prevention and treatment of cardiovascular complications in breast cancer. Kardiol Pol, 2011; 69: 520–530.
20. Zingler V, Näbauer M, Jahn K et al. Assessment of potential cardiotoxic side effects of Mitoxantrone in patients with multiple sclerosis. Eur Neurol, 2005; 54: 28–33.
21. Ghalie R, Edan G, Laurent M et al. Cardiac adverse effects associated with mitoxantrone (novantrone) therapy in patients with MS. Neurology, 2002; 59: 909–913.
22. Edan G, Brochet B, Clanet M et al. Safety profile of mitoxantrone in a cohort of 800 multiple sclerosis patients. Multiple Sclerosis J, 2001; 7: 1–14.
23. Mauch E, Kornhuber H, Krapf H et al. Treatment of multiple sclerosis with mitoxantrone. J Clin Neuroscience, 1992; 242: 96–102.

Cite this article as: Pastuszak Ż, Tomczykiewicz K, Piusińska-Macoch R, Stępień A. Cardiac effects of mitoxanthrone therapy in patients with multiple sclerosis. Kardiol Pol, 2016; 74: 380–384. doi: 10.5603/KP.a2015.0195.

Wpływ leczenia mitoksantronem na serce u chorych na stwardnienie rozsiane

Żanna Pastuszak, Kazimierz Tomczykiewicz, Renata Piusińska-Macoch, Adam Stępień

Wojskowy Instytut Medyczny, Warszawa

Streszczenie

Wstęp: Mitoksantron (MTX) jest syntetycznym antybiotykiem antracyklinowym stosowanym od kilku lat w leczeniu chorych z postacią pierwotnie i wtórnie postępującą oraz rzutowo-remisyjną stwardnienia rozsianego (MS), nieodpowiadających na terapię innymi lekami. Wykazuje działanie przeciwnowotworowe, immunomodulujące i przeciwbakteryjne. Najczęstszymi działaniami niepożądanymi stosowania MTX są nudności i wymioty, wypadanie włosów, zwiększone ryzyko infekcji dróg moczowych i oddechowych, brak miesiączki. Rzadziej występują: leukopenia, trombocytopenia, niedokrwistość, wzrost stężenia enzymów wątrobowych i bilirubiny. Innym groźnym następstwem stosowania MTX jest kardiotoksyczność leku oraz możliwość wywołania białaczki. Toksyczność leku wynika z jego powinowactwa do jonów żelaza. Kompleks ten ma silne właściwości tworzenia rodników tlenowych, a także nasilenia peroksydacji lipidów. U chorych na MS obserwowano bezobjawowe klinicznie obniżenie frakcji wyrzutowej lewej komory (LVEF) w dwuwymiarowym badaniu echokardiograficznym (ECHO 2D), kardiomiopatię oraz zastoinową niewydolność serca, występującą z częstością 2,6–5%. W niewielu badaniach oceniono kardiotoksyczność MTX u chorych na MS. Większość dotychczasowych opracowań opiera się na małych grupach chorych leczonych onkologicznie i na ocenie funkcjonowania serca w badaniu przedmiotowym.

Cel: Celem niniejszej pracy była ocena wpływu leczenia MTX na LVEF określonej w ECHO 2D.

Metody: Badaniem objęto 72 pacjentów z MS w wieku 25–63 lat leczonych MTX w latach 2002–2014. Stwardnienie rozsiane rozpoznano na podstawie kryteriów McDonalda z 2001 r., uaktualnionych w 2005 r. W grupie z postacią pierwotnie postępującą było 40 (56%) osób, z wtórnie postępującą — 5 (7%) chorych oraz rzutowo-remisyjną MS — 27 (37%) pacjentów. Chorym podawano MTX w dawce 12 mg/m^2 powierzchni ciała co 3 miesiące (do maksymalnej łącznej dawki 140 mg/m^2). Warunkami włączenia pacjenta do leczenia MTX były: brak objawów niewydolności serca w badaniu przedmiotowym i prawidłowy zapis elektrokardiograficzny, prawidłowy wynik ECHO 2D z oceną LVEF, prawidłowe wyniki badań morfologicznych i biochemicznych krwi, w tym wartości enzymów wątrobowych i parametrów nerkowych. Przed każdorazowym podaniem MTX wykonywano ECHO 2D z pomiarem LVEF i elektrokardiogram oraz oceniano funkcjonowanie układu sercowo-naczyniowego w badaniu przedmiotowym. Wpływ leczenia MTX na wartość LVEF oceniano, porównując wartości LVEF przed rozpoczęciem terapii w stosunku do pomiaru wykonanego przed podaniem ostatniej dawki MTX. W analizie danych posłużono się testem t-Studenta.

Wyniki: W wyjściowym ECHO 2D serca u chorych na MS wykonanym przed podaniem pierwszej dawki MTX średnia wartość LVEF wynosiła 65 ± 3,3%. Najniższa wartość LVEF w końcowym ECHO 2D wynosiła 60 ± 2,1%. Nie wykazano istotnego statystycznie obniżenia LVEF w czasie leczenia MTX chorych na MS w stosunku do wartości sprzed terapii. W badanej grupie chorych nie odnotowano ciężkiego uszkodzenia mięśnia sercowego objawiającego się znacznym obniżeniem LVEF w ECHO 2D lub niewydolnością serca w badaniu przedmiotowym.

Wnioski: Wyniki badań nie wykazały istotnego obniżenia LVEF w trakcie monoterapii MTX u chorych na MS, nieobciążonych kardiologicznie, z prawidłowym wynikiem wstępnego badania echokardiograficznego. Dalszych badań wymaga ocena długoterminowego wpływu MTX na mięsień sercowy.

Słowa kluczowe: mitoksantron, badanie echokardiograficzne, stwardnienie rozsiane

Kardiol Pol 2016; 74, 4: 380–384

Adres do korespondencji:
dr n. med. Żanna Pastuszak, Wojskowy Instytut Medyczny, ul. Szaserów 128, 04–141 Warszawa, e-mail: zanna.pastuszak@hotmail.com
Praca wpłynęła: 28.03.2015 r. **Zaakceptowana do druku:** 31.08.2015 r. **Data publikacji AoP:** 23.09.2015 r.