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Suppression of Mitoxantrone Cardiotoxicity in Multiple Sclerosis Patients by Dexrazoxane

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Objective: **To explore the potential of dexrazoxane to suppress subclinical cardiotoxicity in MS patients receiving mitoxantrone.** ***Methods:*** **An open-label study was performed to evaluate possible subclinical cardiotoxicity in multiple sclerosis patients treated quarterly with mitoxantrone (48mg/m^2 cumulative), with and without concomitant dexrazoxane, using blinded serial radionucleide ventriculography.** ***Results:*** **No patient experienced symptoms of heart failure. Patients receiving dexrazoxane, which is cardioprotective for anthracyclines, exhibited a significantly lesser decline in left ventricular ejection fraction (mean change, −3.80% vs −8.55%, $p < 0.001$).** ***Interpretation:*** **These results support a cardioprotective effect of dexrazoxane in mitoxantrone treated multiple sclerosis patients.**

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Dose-dependent cardiomyopathies can result from anthracyclines and structurally related anthracenediones such as mitoxantrone (MX), although cardiotoxic risk is greater for anthracyclines.[1] For doxorubicin, the risk of congestive heart failure (CHF) is 3% at a threshold of 400mg/m^2, 7% at 550mg/m^2, and 18% at 700mg/m^2.[2] In view of an approximate potency ratio of 1 to 5,[3] 700mg/m^2 of doxorubicin corresponds to approximately140mg/m^2 of MX (the recommended limit in MS); oncological studies suggest that the risk of CHF at this threshold is approximately 2.6%.[4]

Subclinical decline in cardiac function likely occurs more frequently than CHF.[1,5] Of 1,378 MS patients receiving a mean of 60.5mg/m^2 MX, two cases of CHF were seen, but of the 779 patients who underwent serial measurements, 17 (2.18%) had an asymptomatic

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decrease in left ventricular ejection fraction (LVEF) below 50%.[6] The number of patients whose LVEF decreased by 10% or more was not reported in this cohort, but an absolute decrease by greater than or equal to 10% is grounds for withholding further treatment.[4,7]

Dexrazoxane (DRZ) is an iron-chelating cardioprotective agent approved for use with doxorubicin.[2] DRZ has not been carefully tested in humans receiving MX, but in animals it does protect against MX-associated cardiotoxicity.[8] Here, we examine pretreatment and posttreatment LVEF and, as an exploratory outcome, postinfusion cardiac troponin (cTn)-I, in 47 MS patients treated with four quarterly MX infusions with and without DRZ.

Materials and Methods

The primary aims of this study were to assess change in LVEF after 48mg/m^2 MX and a possible cardioprotective effect of DRZ. There were no clinical or MRI end points in this open-label study. All patients (n = 47) initiating quarterly MX infusions at the University of Michigan MS Center between July 2000 and May 2003 received at least four quarterly infusions and are included in this analysis. Importantly, the multiple gated acquisition scan (MUGA) interpreter was blinded regarding DRZ administration. Prior treatment with anthracyclines or anthracenediones, pregnancy, or history of cardiac disease precluded MX treatment. Because of variable cumulative dose administered, no data were analyzed beyond 48mg/m^2. Patients in the "DRZ+" group were drawn from a previously reported safety (including LVEF assessment) and tolerability study of MX plus DRZ[9]; the majority of patients in the DRZ− group were enrolled after the safety study, although there was overlap of several patients. Baseline demographics among DRZ+ and DRZ− groups were compared regarding age and baseline LVEF (two sample t tests) and sex (Fisher's exact test). All data were examined for outliers and normality using scatterplots, histograms, and normal probability plots. This study was approved by the University of Michigan Institutional Review Board.

All patients received intravenous MX (12mg/m^2) over 15 to 30 minutes. In individuals receiving DRZ (600mg/m^2), it was administered intravenously 30 minutes before MX. The ratio of DRZ to MX (50:1) was chosen because in oncology DRZ generally has been used in a 10 to 1 combination with doxorubicin. Given the approximately 1 to 5 potency ratio for doxorubicin to MX, this corresponds to a 50 to 1 DRZ to MX ratio.

In addition to routine preinfusion laboratory monitoring, cardiac troponin (cTn)-I was checked within 7 days of infusion and repeated 24 to 72 hours and 8 to 12 days after treatment, based on reports that both acute and delayed cTn increases can occur after anthracycline treatment.[10] MUGA scans performed at baseline and at end of study, 2 to 3 months after the fourth infusion, were analyzed by the same evaluator, who was completely blinded, having no knowledge of dexrazoxane coadministration. Mean (paired t test) and median (Wilcoxon signed ranks test) change in LVEF for each group were compared, whereas the mean change in LVEF between groups was compared using the two sample t test. Between group comparison of the number of subjects with absolute LVEF change greater than or equal to −10% was assessed using the Fisher's exact test. A linear regression model was also considered to assess the effect of DRZ, adjusted for baseline factors.

Results

Overall, 47 patients were enrolled (28 DRZ+, 19 DRZ−), including 30 females (63.8%; 66.7% DRZ+, 33.3% DRZ−) and 17 males (36.2%; 47.1% DRZ+, 52.9% DRZ−). Mean and median ages were 45.6 and 48, respectively (45 and 47.5 for the DRZ+ group; 46.5 and 49 for the DRZ− group). Neither outliers nor departure of the data for continuous variables from normal distribution were detected in our data set. There are no significant differences between the DRZ+ and DRZ− groups regarding age ($p = 0.6$), sex ($p = 0.22$), or baseline LVEF ($p = 0.18$), and none of the baseline factors has a statistically significant impact on the cardioprotective effect of DRZ. None of our patients experienced CHF or other clinical signs of cardiac dysfunction at any time during the study.

As shown in Tables 1 and 2, the mean absolute LVEF change for all 47 subjects was −5.72%, a significant decrease from baseline ($p < 0.001$; 95% confidence interval, −4.62 to −6.83). Mean LVEF change was −8.55% for the DRZ− group ($p < 0.001$; 95% confidence interval, −6.88% to −10.23%) and −3.80% for the DRZ+ group ($p < 0.001$; 95% confidence interval −2.80% to −4.80%), indicating a cardioprotective effect for DRZ ($p < 0.001$). Perhaps more striking, LVEF decreased by greater than or equal to 10% in 7 of 19 (37%) DRZ− subjects, compared with 0 of 28 in the DRZ+ group ($p < 0.001$). As an exploratory measure, we assessed the potential utility of cTn-I as an early marker of susceptibility to MX-associated cardiac injury. None of the patients' cTn-I values obtained at two time points after each of four infusions, as specified in Materials and Methods, exceeded the upper limit of normal, 0.39ng/ml (data not shown).

Discussion

Our results reinforce that subclinical cardiac toxicity secondary to MX may be much more common than symptomatic cardiac injury, which has also been observed in small case series.[11] Although MUGA assessment of LVEF may have intrinsic variability, it is an objective and blinded outcome, and the decreases in LVEF observed are not simply a result of measurement variability, given that LVEF did not increase in any of the 47 individuals. A smaller change in LVEF (−3.80%) was seen in the DRZ+ versus the DRZ− group (−8.55%; $p < 0.001$), and LVEF decreased by greater than or equal to 10% in 0 of 28 DRZ+ patients, compared with 7 of 19 DRZ− patients ($p <$

Table 1. Change in LVEF (MUGA) for DRZ+ and DRZ− subjects—Individual Results

	DRZ+ Group				DRZ− Group		
	MUGA				MUGA		
Patient	Pre	Post	LVEF Change	Patient	Pre	Post	LVEF Change
1	71%	64%	− 7%	1	72%	64%	− 8%
2	62%	56%	− 6%	2	71%	65%	− 6%
3	67%	62.5%	− 4.5%	3	66%	58%	− 8%
4	74%	71%	− 3%	4	66%	57%	− 9%
5	57%	50%	− 7%	***5***	***83%***	***71%***	***− 12%***
6	79%	71%	− 8%	6	60%	51%	− 9%
7	66%	64%	− 2%	*7*	75%	62%	− 13%
8	77%	71%	− 6%	8	67%	57.5%	− 9.5%
9	57%	54%	− 3%	***9***	***75%***	***61%***	***− 14%***
10	65%	56%	− 9%	10	58%	58%	0%
11	77%	70%	− 7%	***11***	***83%***	***72%***	***− 11%***
12	68%	65%	− 3%	***12***	***73%***	***63%***	***− 10%***
13	62%	62%	0%	13	51%	44%	− 7%
14	58%	50%	− 8%	***14***	***73%***	***63%***	***− 10%***
15	62%	58%	− 4%	***15***	***64%***	***54%***	***− 10%***
16	64%	63%	− 1%	16	78%	77%	− 1%
17	56%	53%	− 3%	17	***71%***	***62%***	***− 9%***
18	63%	62%	− 1%	18	70%	63%	− 7%
19	67%	64%	− 3%	19	65%	56%	− 9%
20	69%	63%	− 6%				
21	70%	68%	− 2%				
22	72%	71%	− 1%				
23	70%	68%	− 2%				
24	63%	60%	− 3%				
25	61%	59%	− 2%				
26	72%	72%	0%				
27	73%	70%	− 3%				
28	60%	58%	− 2%				

Individual LVEF results (MUGA) before and after treatment with quarterly MX infusions (12mg/m^2 each, 48mg/m^2 cumulative) are shown for subjects in DRZ+ and DRZ− groups. The eight subjects (all in DRZ− group) whose LVEF decreased by greater than or equal to 10% are indicated in bold italics.

LVEF = left ventricular ejection fraction; DRZ = dexrazoxane.

0.001), demonstrating a cardioprotective effect, which has also been observed experimentally.[8] Although this was not a randomized study, MUGA assessment was blinded regarding DRZ, and no patient receiving the four infusion regimen at our MS Center during the study period was excluded. This work does not address whether DRZ affects the therapeutic benefit of MX. However, it is reassuring that DRZ does not compromise the antileukemic efficacy of doxorubicin.[12] Furthermore, both DRZ and MX have separately been

Table 2. Change in LVEF (MUGA) for DRZ+ and DRZ− subjects—Group Results

	DRZ+ Group			DRZ− Group		
	Baseline LVEF	1-year LVEF	*p*	Baseline LVEF	1-year LVEF	*p*
Mean (%)	66.5	62.7	<0.001	69.5	61.0	<0.001
SD (%)	6.4	6.6		8.1	7.6	
95% Confidence interval (%)	64.0–69.0	60.1–65.3		65.6–73.4	57.3–64.6	
Median (%)	66.5	63.0	<0.001	71.0	62.0	<0.001
Range (%)	56–79	50–72			51–83	44–77
Mean change in LVEF (%)	−3.8			−8.6		<0.001

Group pre- and post-MX LVEF outcomes are shown. Mean LVEF decreased for DRZ+ and DRZ− groups ($p < 0.001$). The mean change in LVEF was significantly less for the DRZ+ group (−3.8% compared with −8.6%; $p < 0.001$).

LVEF = left ventricular ejection fraction; DRZ = dexrazoxane.

shown to ameliorate disease in experimental allergic encephalomyelitis, and together DRZ + MX is more efficacious than either agent alone.[13]

The occurrence and severity of MX cardiotoxicity is unpredictable. Preexisting cardiac disease seems a logical risk factor,[14] but there remains a need for an early marker of myocardial injury that can predict subsequent impairment in ventricular function. cTn isoforms are sensitive markers of ischemic myocardial damage, and animal studies demonstrate that the pathological severity of doxorubicin or MX-induced cardiomyopathy correlates with serum cTn levels, although cTn may not increase until after several infusions.[8] Here, we show that post-MX cTn-I is not an effective predictor of cardiac injury through 48mg/m^2 MX. Further studies are needed to investigate the possible utility of cTn-I or cTn-T as biomarkers for subclinical cardiotoxicity beyond 48mg/m^2. In the meantime, frequent cardiac monitoring seems prudent. Note that product labeling for MX was updated in March 2005, in view of postmarketing surveillance showing that cardiac function may diminish early in the treatment course, such that cardiac monitoring is now recommended before each MX infusion.[15]

Despite the potential for cardiac and other toxicities associated with MX, its potential benefit may outweigh these risks in the individual patient. If cardiac risk could be mitigated, such as with DRZ, the risk to benefit ratio could be improved, and this might enable the current dose limit of MX to be surpassed in at least some individuals benefiting from therapy. A larger randomized, prospective clinical trial of MX with and without DRZ seems warranted before considering DRZ for general use.

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