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ORIGINAL ARTICLE

Chemotherapy-Induced Cardiotoxicity: Subclinical Cardiac Dysfunction Evidence Using Speckle Tracking Echocardiography

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ABSTRACT

Objectives: In our study, we aimed to identify early markers of cardiac dysfunction in patients treated with mitoxantrone. We also looked at cardiac functional changes during therapy by analyzing longitudinal deformation and by measuring left ventricular (LV) and left atrial (LA) global strain. **Materials and Methods:** LA and LV global longitudinal strain were analyzed in 20 patients affected by multiple sclerosis and treated with mitoxantrone. Patients underwent echocardiography before treatment, after every drug administration during the 12-months treatment period, and finally after 6 and 12 months of drug discontinuation. **Results:** Compared with baseline values, patients showed a significant reduction of both LA and LV longitudinal global strain at the end of treatment with mitoxantrone (LA_GS% T10 vs. T0 values: 15,2 ± 12,5 vs. 20,2 ± 11,1; LV_GS%: −16,4 ± 2,5 vs. −17,4 ± 3,8). Strain reduction reverted after treatment discontinuation (LA_GS% FU vs. T0 values: 20,4 ± 15,7 vs. 20,2 ± 11,1; LV_GS%: −17,3 ± 3,3 vs. −17,4 ± 3,8). **Conclusions:** Impairment of longitudinal deformation during mitoxantrone therapy may indicate a dysfunction related to early myocardial damage. These findings appear to be reversible after treatment discontinuation.

Key Words: Cardiac dysfunction, cardiotoxicity, echocardiography, longitudinal deformation

INTRODUCTION

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system with a chronic course and autoimmune pathogenesis. MS is characterized by an abnormal activity of the immune system (especially T-lymphocyte and macrophage) against myelin leading to its progressive destruction. Due to its autoimmune pathogenesis, immunosuppressive drugs, especially Mitoxantrone (MTX), have an important role in the therapeutic strategies for the treatment of MS.[1] MTX belongs to the family of anthracyclines and is used to treat relapsing-remitting and secondary progressive MS. These two types of MS are characterized by intense inflammatory activity, rapid worsening of symptoms and increased disability and relapses.[1,2]

The most important limitation to the use of MTX is myelosuppression. Another side effect observed is cardiotoxicity due to the formation of free radicals. The anthracycline-iron complex causes in fact damage to mitochondrial and cellular membranes with a consequent reduction in the number of contractile cells.[3,4] Anthracycline cardiotoxicity can be classified into *acute*, *chronic* and *late* varieties. *Acute* cardiotoxicity occurs very prematurely, right after drug administration, in the form of myopericarditis syndrome, arrhythmias, ST segment's alteration and acute heart failure. However, these effects are often reversible after drug discontinuation.

Chronic toxicity is characterized by refractory heart failure that can occur one month after the last administration or even after one or two years from the treatment. *Late* onset cardiotoxicity is secondary to the accumulation of the drug in the body tissues and can be evident many years after the end of the drug administration. It is mainly seen when the

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antracycline therapeutic dose range is exceeded.[5,6] Many studies reported the incidence of antracycline related cardiotoxicity between 18% and 36% with a relationship to the cumulative dose of the drug. Subclinical cardiac alterations can be found even in patients treated with a low dose of anthracyclines.[7,8]

Both in common practice and in clinical trials, left ventricular ejection fraction and shortening fraction at rest, obtained with echocardiography or with radio-isotopic ventriculography, are usually used to reveal chemotherapy-induced cardiomiopathy. However, an impairment of these parameters is a late event and therefore they are not sensitive to reveal early signs of cardiac functional alterations. In fact, a decrease of ejection fraction occurs when the deterioration of cardiac function is already irreversible.[9]

Many clinical studies have demonstrated the usefulness of parameters derived by new echocardiographic methods, such as, Tissue Doppler Imaging (TDI) and 2 dimensional (2D)-speckle tracking (STE),[10-13] to detect cardiac dysfunction during the earlier phases. The analysis of myocardial longitudinal velocities curves, obtained by TDI and detected at medial and lateral mitral annulus, is considered as an index of ventricular relaxation related with the left ventricular end-diastolic pressure.[14,15] Moreover, myocardial performance index (MPI), obtained by the ratio between isovolumetric contraction time (ICT), isovolumetric relaxation time (IRT) and ejection time (ET), is also considered an index of global cardiac function.[16-17] 2D-STE analysis is a more sensitive technique and allows the identification of early markers of myocardial dysfunction before the impairment of conventional echocardiographic parameters and frequently reveals subclinical LV alterations. It is also helpful to clarify mechanisms related to myocardial functional impairment.[18]

The aim of our study was to identify early markers of cardiac damage in patients affected by MS and treated with MTX before the impairment of conventional echocardiographic parameters like ejection fraction.

MATERIALS AND METHODS

Study's population

20 outpatients (9 women and 11 men, mean age 43.4 ± 9.2 years old) affected by MS, in treatment with MTX, without cardiovascular co-morbidities, were clinically evaluated and underwent trans-thoracic echocardiography at the beginning of MTX therapy (MS_T0), after any administration during 12 months (In particular, after 5th MTX administration (MS_T5), and after 10th MTX administration (MS_T10), and in the long term after 6 and 12 months of treatment's discontinuation (MS_FU). Two patients were affected by "Progressive Relapsing" MS while all the other patients by "Relapsing-Remitting" MS.

Echocardiography

All the echocardiographic studies were performed with a Vivid 7 ultrasound system (GE Healthcare, Horten, Norway) equipped with multi-frequency probe S3. All images were obtained in the lateral decubitus position. Cardiac chamber size quantification, including systolic and diastolic thickness of left ventricular (LV) septum, posterior wall thickness and LV systolic and diastolic diameters (LVIDd, LVIDs) were obtained by M-Mode echocardiography. LV ejection fraction (LVEF) and left atrial volume indexed for body surface (LAVi) were assessed by 2D-echocardiography from the apical 4-chamber view. All parameters were evaluated according to the recommendations of the American Society of Echocardiography.[19] The sample volume of pulsed-wave Doppler imaging was placed at the tip level of the mitral leaflets in the apical 4-chamber view obtaining the peak velocities for mitral inflow during early diastole and atrial filling (E and A, respectively); their ratio (E/A) was also obtained. Color Doppler TDI acquisitions with a frame rate between 100 and 120 frames per second (fps) were acquired. The sample volume of the pulsed TDI was placed at the septal and lateral margins of the mitral annulus, obtaining peak systolic (S'), early and late diastolic (E' and A') velocities, isovolumetric relaxation time (LV-IRT), ejection time (LV-ET) and isovolumetric contraction time (LV-ICT). MPI was calculated according to formula: MPI = (*ICT* + *IRT*)/ET. This was measured directly on the spectral display and the averaged values of septal and lateral velocities were used to calculate ratio between E and E' (E/E') as a surrogate of the LV filling pressures.[14-18, 20]

Longitudinal global strain of the left ventricle (LV_GS) and left atrium (LA_GS) was obtained by 2D-Speckle Tracking analysis, from the apical 4 chamber view using conventional 2-dimensional gray-scale echocardiography. Three consecutive heart cycles were recorded; the frame rate was between 47 and 57 fps. The analysis was performed offline using the ECHOPAC software (ver. 11.0.0), which was able to follow and analyze the speckles movement, frame by frame, after delineation of the endocardial border. LV endocardial border was manually traced and then a region of interest (ROI) was automatically displayed by the software. ROI was adjusted to ensure that all the myocardium was inside the ROI avoiding pericardial inclusion. Likewise, the evaluation of left atrial longitudinal strain was performed from the apical four-

chamber view, delineating the ROI that then was subdivided into 6 segments (2 correspond to the interatrial septum, 2 to the lateral wall, and 2 to the roof of the left atrium). After segmental tracking quality validation, the software generated longitudinal strain curves.

Statistical analysis

Data are expressed as mean ± standard deviation (SD). Analysis of Variance (ANOVAs) was performed to test for statistically significant differences in the observation before the treatment, between the treatments and also after the treatment. Data were also compared to a control group of 30 healthy normal subjects (N), matched for age and weight in the beginning. Three levels of statistical significance ($p < 0.05$, $p < 0.01$, $p < 0.001$ respectively) were considered.

The study complied with the Declaration of Helsinki. A written informed consent was achieved from all subjects. The local ethical committee approved this study.

RESULTS

All patients were treated with one MTX administration per month. The highest MTX individual dose was 117 ± 39 mg. Follow up duration without therapy was 10.7 ± 1.1 months.

Echocardiographic characteristics of values of MS group at the time before therapy (MS_T0), after 5th and 10th MTX administration (MS_T5 and MS_T10), in the follow up after treatment's discontinuation (MS_FU), all of which compared to N group, are depicted in Table 1.

No significant group differences were found for the following parameters: LVIDd, LVIDs, A, E/A, A'. At T0, MPI was significantly increased in patients affected by MS when compared with N. At T5, (6.5 ± 1.6 months and 55,8 ± 15,67mg/m^2 MTX mean dose) LV_GS was reduced and MPI was further increased when compared with N. LVEF and LV_GS were significantly reduced when compared to T0.

At T10, (12,4±2,0 months and 112,09 ± 26,49 mg/m^2 MTX mean dose) LAVi, E/E', MPI were increased compared to N group. E, S', E', LV_GS and LA_GS were reduced compared to N and T0.At FU without therapy, all parameters of patients with MS were comparable to those at T0, whereas LAVi and E/E' decreased, and E, S', E' LV_GS, LA_GS increased compared to T10. None of the patients showed acute toxicity. At the end of therapy (cumulative dose 130 mg/m^2), one patient showed frequent ventricular ectopic beats; however, he did not have echocardiographic alterations.

In one patient, after 5th MTX administration (cumulative dose 50 mg/m^2), a 20% LVEF reduction compared to the initial value he was seen (LVEF decreased from a value of 69% to a value of 50). In three patients, a reduction of LVEF on an averaged value of 13%, as compared to the initial values, was seen but LVEF did not reach a pathological value. In all of these patients, LVEF returned to the initial value after MTX therapy modulation, consisting of either the reduction of the drug dosage or by distancing the drug administration with a three-monthly cycle instead of a monthly cycle. MS group

Table 1: Results and echocardiographic characteristics of the patients in the study

	N	MS_T0	MS_T5	MS_T10	MS_FU
Months	—	0	6,5 ±2	12,4±2	10,7±1,1
LVIDd mm	50,1±3	49,3±5	48,8±6	49,1±6	49,6±6
LVIDs mm	31,1±4	30,7±4	30,5±4	30,8±6	31,2±6
LVEF %	66,8±4	68,3±4	66,1±5$^{\#}$	66,5±5	66,6 ±6
LAVi ml/m^2	24,8±6	25,7±6	24,7±7	26,5±6°	24,8±4 (*)
E cm/s	79,2±28	68,2±15	67,2±16	60,9±14° $^{\#}$	68,6±11
A cm/s	57,7±16	59,3±13	56,4±16	57,4±12	59,7±13
E/A	1,2±0,4	1,2±0,4	1,3±0,4	1,2±0,4	1,2±0,3
S' cm/s	7,1±1,7	7,3±1,6	7,0±1,4	6,1±1,4° $^{\#}$	6,7±1,5 (*)
E' cm/s	9,5±0,1	9,7±2,4	9,7±2,0	7,9±2,4° $^{\#\#}$	9,9±2,5 (**)
A' cm/s	8,9±1,9	8,9±2,0	8,8±2,2	8,9±1,8	8,7±1,8
E/E'	7,4±2,5	7,3±2,1	7,1±1,9	8,7±2,2°	7,3±1,6 (**)
MPI	0,48±0,2	0,55±0,1°	0,65±0,2°°	0,66±0,2°°	0,55±0,1°
LV_GS %	–17,5±3,8	–17,4±3,8	–16,4±3,5° $^{\#}$	–16,4±2,5°$^{\#}$	–17,3±3,3 (*)
LA_GS %	20,0±6.8	20,2±11,1	20,7±14,8	15,2±12,5°$^{\#}$	20,4±15,7 (**)

°p<0.05°° p<0.001°°° p<0.0001: MS (To, T5, T10, FU) vs N;$^{\#}$ p<0.05 $^{\#\#}$ p<0.001 $^{\#\#\#}$ p<0.0001: MS (To, T5, T10, FU) vs MS_To;(*) p<0.05(**) p<0.001 (***) p<0.0001: MS_FU vs MS_T10 Where, LV=Left ventricle; LVIDd=LV Dimension diastolic; LVIDs=LV Dimension systolic; LVEF=LV ejection fraction; LAVi=left atrial volume indexed for body surface area. Peak mitral inflow velocity: E early diastolic filling andA late diastolic filling, E/A=ratio between E and A. Tissue velocity at mitral annulus: S' longitudinal peak systolic,E' longitudinal peak early diastolic, A' longitudinal peak late diastolic; E/E'=ratio between E and E'; MPI=myocardialial performance index; LV_GS=LV longitudinal global strain; LA_GS=left atrial longitudinal global strain. MS=multiple sclerosis. MS_To=time at the beginning of mithoxantrone therapy; MS_T5=time after five months of therapy; MS_T10=time after ten months of therapy; MS_FU=follow up without treatment

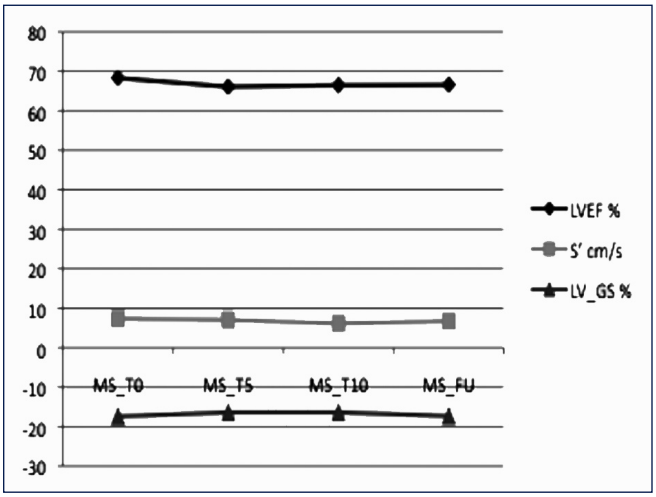

Figure 1: Values of left ventricle ejection fraction (LVEF %), longitudinal peak systolic velocity at mitral annulus (S' cm/s) and left ventricle longitudinal global strain of (LV_GS %) at the beginning of mithoxantrone therapy (MS_T0), after five (MS_T5) and ten months (MS_T10) of therapy, and follow up without treatment (MS_FU). MS = patients with multiple sclerosis

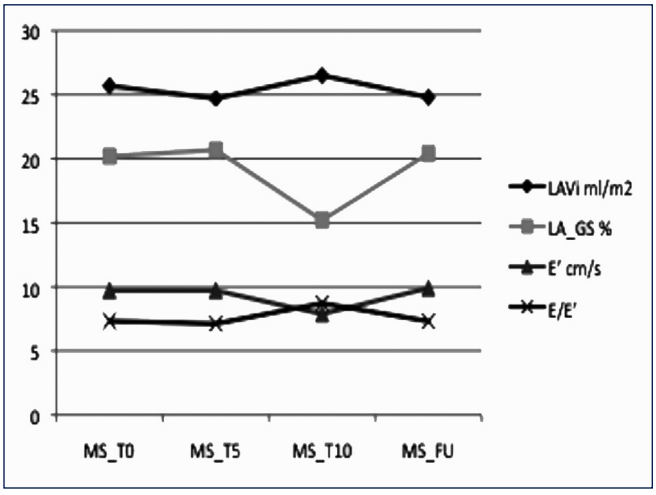

Figure 2: Values of left atrial volume indexed for body surface (LAVI ml/m²), left atrial longitudinal global strain of (LA_GS %), longitudinal peak early diastolic velocity at mitral annulus (E' cm/s) and ratio between peak mitral inflow early diastolic filling (E) and E' (E/E'), at the beginning of mithoxantrone therapy (MS_T0), after five (MS_T5) and ten months (MS_T10) of therapy, and follow up without treatment (MS_FU). MS = patients with multiple sclerosis

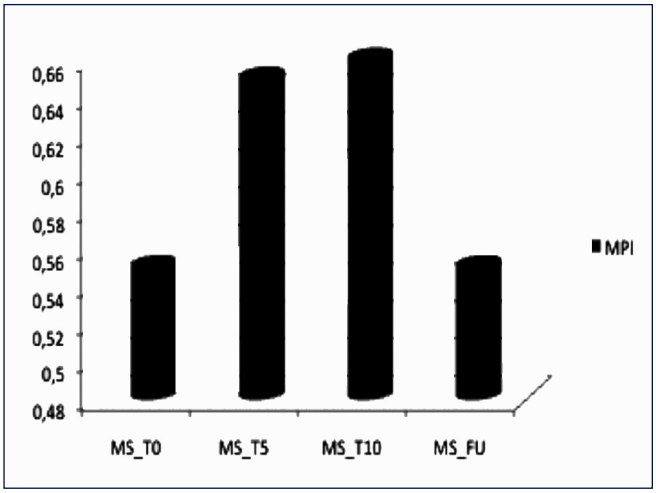

Figure 3: Values of myocardial performance index (MPI) at the beginning of mithoxantrone therapy (MS_T0), after five (MS_T5) and ten months (MS_T10) of therapy, and follow up without treatment (MS_FU). MS = patients with multiple sclerosis

showed a decrease of LVEF and LV_GS after 5th therapy cycle and of S' at T10 that remained at FU time [Figure 1], increase in LAVi and E/E' and decrease of LA_GS and E' at T10 with normalization at FU [Figure 2]. MPI gradually increased during the treatment [Figure 3].

DISCUSSION

In the group of examined patients, although not significant, an LVEF reduction was seen after the 5th therapy cycle. This reduction is in agreement with data in the literature and must be considered as an expression of the drug toxicity on the cardiac muscle. LVEF was maintained over the observation period and the size of the cardiac chambers did not change. A decrease in LVEF is considered as the main indicator of anthracycline toxicity (7-10): Usually, when there's a 10% reduction as compared to baseline LVEF values, associated with an absolute value <50%, it is necessary to immediately discontinue the treatment. When all the global functions are preserved and only LVEF reduction is seen, the modulation of the drug dosage and administration usually suffices. LVEF changes are correlated directly with the mortality of patients treated with anthracycline, but are usually late, and sometimes they're more difficult to resolve. LVEF is, however, not very sensitive for the early diagnosis of preclinical heart disease.[8,11]

In our study, we noticed a decrease of S' and LV_GS, as index of LV longitudinal function and deformation in patients suffering from MS. Global longitudinal strain has been introduced as an index of global LV function.[21] This study confirmed the findings (reduced global longitudinal strain) of a previous study performed by Tsai *et al*., showing reduced global longitudinal strain in adult survivors of Hodgkin's lymphoma receiving anthracyclines.[22] At present, there is no strain or strain rate value that provides a cut-off beyond which clinically manifest symptoms are more likely to occur. However, strain analysis can improve the detection of subclinical cardiac damage secondary to the anticancer therapy.

Experimental and clinical studies using Eco-TDI in patients treated with anthracyclines showed early alterations of diastolic function and of longitudinal left ventricular

contractile function, in absence of changes in LVEF, detected earlier than changes in ejection fraction.[11,23-27] In patients examined, those parameters were changed, but not significantly, and showed a rapid return to baseline values at the follow-up after discontinuation of the therapy. Furthermore an increase in LAVi and E/E', a decrease of myocardial velocity E' and atrial strain, markers of increased LV filling pressures, at the end of treatment may be related to late cardiotoxicity of chemotherapy agents. Normalization of these parameters at follow up may be an indicator of a reversible myocardial dysfunction after discontinuation of therapy and seems to be interesting. Despite similar changes of E and E' (both of them are increased similarly), the ratio of E/E' was decreased in untreated patients. However, the persistent abnormal myocardial performance index and longitudinal systolic velocity may be related to a subtle alteration of cardiac function.[28,29]

We can say that parameters derived from TDI are considered useful for evaluating the impact of subclinical anthracycline therapy on heart function and in particular to monitor long-term cardiac function in patients treated with Mitoxantrone.[30] In the available clinical trials, Mitoxantrone provided effective treatment for worsening multiple sclerosis, but long-term use of this drug may compromise left ventricular function. The risks of substantial myelosuppressive and cardiotoxic effects can be reduced by careful patient selection, drug administration and monitoring.

CONCLUSIONS

Patients with subclinical dysfunction have an elevated risk of developing symptomatic congestive heart failure and increased mortality, and hence it is important to detect subtle changes of cardiac function.[31] Given the wide individual variability in the onset and progression of cardiotoxic anthracycline damage and the great clinical and prognostic impact that it has on the patient,[32] it is very important to identify cardiac involvement at an early stage, when it's still possible to obtain a full functional recovery.[29]

This may help the cardiologist and oncologist in decision-making regarding the management of cancer treatment, including discontinuation of the therapy, reformulation of the therapeutic regimen, addition of potential supportive therapies (angiotensin converting enzyme inhibitors and beta blockers). All these strategies are warranted to preserve and improve cardiac function in patients receiving cardiotoxic agents.

Study limitations

We included only 20 cases of a population admitted to a single center. Our patients were examined in a stable condition to avoid changes in the loading conditions, after excluding patients with possible confounding variables that can reduce myocardial function in patients with antracycline therapy (i.e. valvular heart disease, old myocardial infarction). However, studies including a larger sample size are warranted to further explore the effect of possible confounding variables.

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