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Chemotherapy cardiotoxicity: cardioprotective drugs and early identification of cardiac dysfunction

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Background **Chemotherapy cardiotoxicity is an emerging problem and it is very important to prevent cardiac dysfunction caused by anticancer drugs. The aim of this study was to assess the alterations of the cardiac function induced by chemotherapy in a follow-up of 2 years and to evaluate the cardioprotective role of angiotensin-converting enzyme inhibitors (ACEIs) in the prevention of cardiac dysfunction.**

Methods **A prospective study was carried out using patients with breast cancer (85 women; median age 57 ± 12 years) and other inclusion and exclusion criteria. On the basis of treatment, patients were divided into six groups: fluorouracil-epirubicincyclophosphamide, FEC (group A); FEC and trastuzumab (B); trastuzumab (C); FEC and taxotere (D); FEC, paclitaxel and trastuzumab (E); and chemotherapy and cardioprotective drugs (F). Cardiological evaluation including electrocardiogram and conventional echocardiogram with tissue Doppler imaging (TDI) was carried out at T0 (before starting chemotherapy), T1 (after 6 months from the start of chemotherapy) and T2 (2 years after the end of chemotherapy).**

Results **Significant changes in the TDI parameters of systolic and diastolic function were observed at T1 and T2 in all patients. A significant reduction of left ventricular ejection fraction (LVEF) was observed only at T2. In the patients treated with ACEI (F), these changes were less significant than in other groups and they do not have significant changes in the indices of diastolic function.**

Conclusion **TDI is more sensitive than conventional echocardiogram in the early diagnosis of cardiac dysfunction and ACEIs seem to have an important role in the prevention of cardiotoxicity.**

J Cardiovasc Med 2014, **16**:000–000

Keywords: angiotensin-converting enzyme inhibitor, cardiotoxicity, chemotherapy, prevention, tissue Doppler imaging

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Received 30 January 2014 **Revised** 22 September 2014
Accepted 23 September 2014

Introduction

Chemotherapy cardiotoxicity is an emerging problem. Some drugs, such as anthracyclines and other biological agents, can cause cardiovascular complications (left ventricular dysfunction, heart failure, myocardial ischemia, hypertension, arrhytmias, pericarditis, cardiac tamponade).[1] Anthacycline-induced cardiotoxicity has been categorized into acute, early-onset chronic progressive and late-onset chronic progressive.[2] Late anthracycline cardiotoxicity is cumulative, dose related and high dosages can result in congestive heart failure and left ventricular dysfunction.[3] Usually, cardiac damage caused by anthracycline is irreversible (Type I cardiotoxicity). Trastuzumab induces predominantly reversible dysfunction (Type II cardiotoxicity).[4] This classification system does have limitations; for example, trastuzumab, a Type II drug, can trigger irreversible cardiac damage in patients with severe preexisting cardiac disease or potentiate anthracycline Type I cardiotoxicity. In Type I cardiotoxicity, usually pathophysiology is related to cell loss, and in Type II, cellular dysfunction (mitochondrial and protein alterations) underlies the reversible damage.[5] Thus, it is very important that the early diagnosis of left ventricular dysfunction induced by anticancer drugs using tissue echocardiographic parameters [such as tissue Doppler imaging (TDI) and speckle tracking] is more sensitive than conventional echocardiography and the prevention of severe forms of cardiac dysfunction using early cardioprotective drugs [such as angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARBs) and beta-blockers] when subclinical cardiotoxicity has been identified.[6]

The aim of this study was to assess the alterations of the cardiac function induced by chemotherapy in a follow-up of 2 years (using conventional echocardiographic parameters associated with tissue Doppler parameters) and to evaluate the protective role of drugs (ACEI, ARBs and beta-blockers) in the prevention of severe forms of cardiac dysfunction.

1558-2027 © 2014 Italian Federation of Cardiology DOI:10.2459/JCM.0000000000000232

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Table 1 Patients studied

	Number of patients
Total number	85
Age	57 ± 12
Family history of cardiovascular disease	51 (60%)
Diabetes	13 (15%)
Hypertension	38 (44%)
Obesity	9 (10%)
Dyslipidemia	13 (15%)
Smoking	16 (19%)

Materials and methods

This study was designed and conducted as a prospective study using 85 patients [85 women, mean age (±SD) 57 ± 12 years] with breast cancer treated with antineoplastic agents. Patients were treated at University Hospital of Palermo, Department of Medical Oncology, and several criteria of inclusion and exclusion were used to recruit patients. Inclusion criteria were early stage of disease (presence of lymph nodes metastases but absence of distant metastases), any histological cancer, treatment with anthracyclines [regimen fluorouracil–epirubicin–cyclophosphamide (FEC), taxanes (taxol, taxotere) and trastuzumab], left ventricular ejection fraction (LVEF) of more than 50% at baseline, normal indices of hepatic and renal function, absence of major known diseases, availability of patients to perform periodic electrocardiograms and echocardiograms during follow-up at University Hospital of Palermo, Department of Cardiology. Exclusion criteria were presence of known heart disease, prior exposure to mediastinal irradiation and earlier chemotherapy (factors that increase the risk of cardiotoxicity). All patients had cardiovascular risk factors such as hypertension (44%) treated with ACEIs, ARBs and beta-blockers, diabetes (15%), obesity (10%), cardiovascular familiarity (60%), dyslipidemia (15%) and cigarette smoke (19%) (Table 1).

Patients treated with ACEIs were 64% of the population, 20% with ARBs and 16% with ß-blockers (Fig. 1).

On the basis of chemotherapy treatment and concomitant treatment with ACEI, ARBs and beta-blockers, patients were divided into six groups: A, six cycles of FEC; B, three cycles of FEC and three cycles of trastuzumab; C, six cycles of trastuzumab; D, three cycles of FEC and three cycle of taxotere; E, three cycles of FEC and three cycles of taxol and trastuzumab; and F, chemotherapy and ACEI/ARBs/ß-blockers (Table 2). Cardiological evaluation including electrocardiogram and echocardiogram was made at baseline (T0), at 6 months after the start of chemotherapy (T1) and at 2 years after the end of chemotherapy. The median length of chemotherapy was 1 year.

Echocardiographic evaluation was carried out by means of echocardiographic machine Acuson. Chamber dimension, LVEF and systolic function, valve function and morphology, Doppler pattern and diastolic function were assessed with conventional echocardiography. Parameters of conventional echocardiography were integrated with tissue Doppler parameters.

Echocardiographic evaluation considered LVEF, E/A and TDI [Em/Am = ratio between myocardial early diastolic velocity (Em) and myocardial atrial velocity (Am); myocardial systolic velocity (Sm), isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT) and global performance index (TEI)]. LVEF was measured by a modified biplane Simpson method. E/A ratio was measured with standard Doppler. Em, Am and Sm were obtained with TDI by placing the sample volume at mitral annulus lateral, at the junction between the left ventricular lateral wall and mitral annulus, in the apical four-chamber section. The TDI parameters were always measured by the same investigator.

Statistical methods

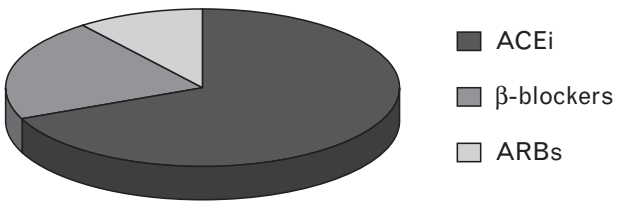
Data are reported as mean ± standard deviation SD. Differences between values measured at different times (T0, T1, T2) were assessed using Student's *t*-test and were considered significant for a P value less than 0.05.

Results

During echocardiographic follow-up, we did not find significant reductions in LVEF at T1, but we found significant changes at T2 (62% ± 0.15 at baseline, 60% ± 0.08 at T2, $P < 0.0001$) when considering the patient population as a whole.

Conversely, significant changes in the tissue Doppler parameters of systolic function (Sm and IVCT) were

Fig. 1



Patients treated with angiotensin-converting enzyme inhibitor, beta-blockers and angiotensin receptor blockers.

Table 2 Groups

Group	Number of patients	Mean age	Chemotherapy
Group A	14 (16%)	59 ± 9	FEC
Group B	14 (16%)	55 ± 6	FEC and trastuzumab
Group C	15 (18%)	62 ± 15	Trastuzumab
Group D	36 (43%)	54 ± 8	FEC and taxotere
Group E	6 (7%)	63 ± 20	FEC and taxol and trastuzumab
Group F	38 (44%)	66 ± 7	Chemotherapy and ACEi/ARBs/β-blockers

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; FEC, regimen fluorouracil–epirubicin– cyclophosphamide.

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Table 3 Changes in Em and Sm

	Sm (*P*)	Em (*P*)
T0	14.43 ± 3.21	15.78 ± 3.7
T1	12 ± 2.15 (*P* < 0.0001)	14.38 ± 2.3 (*P* = 0.003)
T2	11.90 ± 2.21 (*P* < 0.0001)	12.19 ± 3.05 (*P* < 0.0001)

Table 4 Changes in E/A and Em/Am

	E/A	*P*	Em/Am	*P*
T0	1.05 ± 0.24		0.88 ± 0.23	
T1	0.95 ± 0.19	0.003	0.80 ± 0.12	0.005
T2	0.93 ± 0.24	0.001	0.78 ± 0.15	0.001

observed not only at T2 but also early at T1 in the whole population. Sm decreased significantly at T1 and T2 (Table 3). IVCT was significantly increased in the general population at T1 and T2 (Fig. 2).

A significant reduction was found in the E/A ratio and in the Em/Am ratio, but the Em/Am ratio measured with the tissue Doppler was more sensitive than the E/A ratio in showing the early presence of diastolic dysfunction at baseline and after chemotherapy because in 65% of the population, Em/Am inversion at T1 preceded E/A inversion at T2 (Table 4). Significant changes were found in Em and Am at T1 and T2 (Table 3). IVRT measured with the tissue Doppler and TEI index showed a significant increase at T1 and T2.

TEI index, a parameter of global left ventricular function, was found significantly increased at T1 (0.36 ± 0.09 at T0, 0.47 ± 0.13 at T1, 0.54 ± 0.09 at T2, $P < 0.05$) in the whole population (Fig. 3). Evaluation of patients within several groups (A, B, C, D, E, F) showed significant changes in the echocardiographic parameters of systolic function and diastolic function in some groups, but not in all groups.

In group A (14 patients, mean age 59 ± 9 years), we found significant changes in the echo parameters of systolic and diastolic function. Sm showed a significant reduction at T1 and T2 and LVEF showed a significant reduction at T2 but not at T1 (Table 5).

IVRT and TEI index were increased significantly at T1 and T2. The E/A ratio and the Em/Am ratio were significantly reduced at T1 and T2.

In the other groups (B, C, D, E), changes in the TDI indices have been less significant than the same indices in group A and changes in the echo parameters followed the same trend as the whole population. Maybe in A group, the alterations were more significant because these patients were treated with a high dose of anthracyclines compared with other groups and anthracycline cardiotoxicity is dose related.

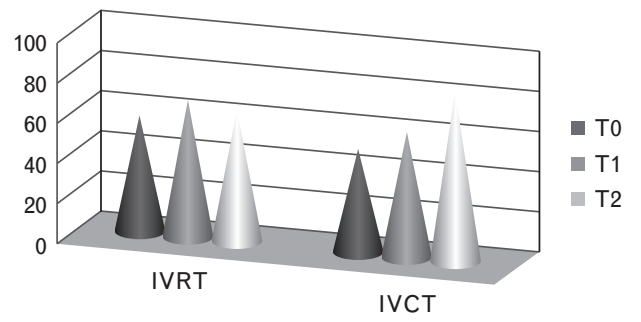
Additional and important observations were made in F group. In this group, significant changes in the echo parameters of systolic function were found. Sm showed a significant reduction at T1 and T2. IVCT has increased significantly at T1 and T2 (Table 6).

The TEI index showed a significant increase at T1 and T2. These modifications of systolic function parameters were less significant than those found in the general population and in the subgroup of patients who are not treated with antihypertensive drugs. In addition, for this group, we did not find significant changes in the echo parameters of diastolic function at T1 and T2 (IVRT, E/A ratio and Em/Am ratio). We did not find significant changes in LVEF at T1 and T2 (Table 6). We evaluated the intra-observer variability that was not statistically significant.

Discussion

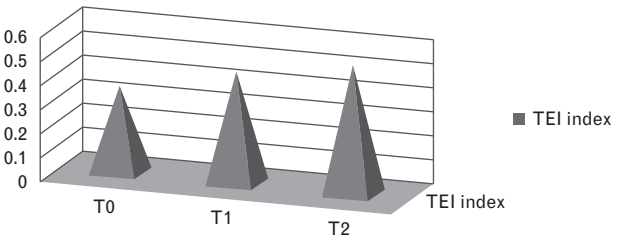
Chemotherapy cardiotoxicity is an emerging problem and the early diagnosis of left ventricular dysfunction induced by anticancer drugs using tissue echocardiographic parameters (such as TDI and speckle tracking) is very important to prevent the development of severe forms of

Fig. 2



Changes in isovolumic relaxation time and isovolumic contraction time in the whole population.

Fig. 3



Changes in global performance index in the whole population. ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; FEC, regimen fluorouracil–epirubicin–cyclophosphamide; Group A, six cycles of FEC; Group B, three cycles of FEC and three cycles of trastuzumab; Group C, six cycles of trastuzumab; Group D, three cycles of FEC and three cycles of taxotere; Group E, three cycles of FEC, three cycles of taxol and trastuzumab; Group F, chemotherapy and ACEI/ARBs/ß-blockers; IVCT, isovolumic contraction time; IVRT, isovolumic relaxation time; Sm, Em and Am, tissue Doppler imaging parameters; TEI index, global performance index.

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Table 5 Changes in systolic function in A group

	Sm	*P*	LVEF	*P*
T0	14.9 ± 2.95		62 ± 0.15	
T1	12.03 ± 0.5	<0.05	62 ± 0.10	>0.05
T2	11.7 ± 1.87	<0.05	60 ± 0.08	<0.0001

LVEF, left ventricular ejection fraction.

cardiac dysfunction, using cardioprotective agents early, when subclinical dysfunction is detected.

Our results are in agreement with the literature data and confirmed by the results reported in our previous work, but various important novel findings were demonstrated.[7] For example, limited data are present in the literature regarding the correlation between the early identification of cardiac dysfunction detected by TDI and clinical dysfunction detected by LVEF. In our study, we found a significant reduction in the LVEF only at T2 and not at T1. A significant reduction in the TDI parameters of systolic function was observed not only at T2 but early at T1. Thus, TDI parameters are more sensitive in the early diagnosis of left ventricular dysfunction than LVEF and the monitoring of TDI parameters would be used during chemotherapy treatment such as integration to conventional echocardiography. Several studies demonstrated the superiority of TDI compared with LVEF in the early diagnosis of left ventricular dysfunction.[8–10] Thus, our study confirms that significant changes in the TDI echo parameters predict the later occurrence of cardiotoxicity and the later reduction of LVEF.

It is demonstrated that longitudinal dysfunction is the first subclinical step towards a further degree of myocardial deterioration. Longitudinal left ventricular mechanics are predominantly governed by the subendocardial layer, which are the most vulnerable and most sensitive to the presence of myocardial disease, ischemic heart disease as well as cardiomyopathy induced by drugs.[11]

In the subendocardium, the fibres are roughly longitudinally oriented, with an angle of about 80° with respect to the circumferential direction. The angle decreases towards the midwall, wherein the fibres are oriented in the circumferential direction (0°) and decrease further to an oblique orientation of about −60° in the subepicardium.[12]

Thus, TDI evaluating mitral annulus velocity and the global longitudinal left ventricular function is more sensitive than ejection fraction in the early diagnosis of left ventricular dysfunction induced by anticancer drugs (Table 7).

In addition, we found that oncological patients treated with ACEI, ARBs and beta-blockers compared with the whole population showed less significant changes in the TDI parameters of systolic function (Sm and IVCT) at T1 and T2. LVEF did not show a significant decrease in this group and diastolic impairment did not occur (E/A and Em/Am ratio did not change significantly). Thus, our data confirm and support previous studies about the cardioprotective role of ACEI in the chemotherapy cardiotoxicity.[13] ACEIs reduce afterload and systolic ventricular wall stress, increase cardiac output, improve ventricular geometry, prevent the growth effects of angiotensin II on myocytes, attenuate aldosterone-induced cardiac fibrosis and reduce apoptosis of cardiac cells.[14] In animal models, cardiac ACE activity was found to be increased after chemotherapy compared with control individuals. Notably, treatment with lisinopril started after chemotherapy significantly inhibited cardiac ACE activity and improved mortality, cardiac remodelling and cardiac dysfunction in an animal model. A previous study[15] demonstrates that in rats treated with temocapril, collagen accumulation was inhibited and fibrosis was avoided in the cardiac interstitium.

Thus, these findings suggest that beneficial effects of ACEI in anthracycline-treated animals depend on inhibition of cardiac ACE and that its activation plays a pivotal role in the development of this kind of cardiomyopathy. ACEIs have been shown to be potent scavengers of free radical and they exert antioxidant effects.[16]

Other studies showed a protective effect of ARBs after treatment with anthracyclines, which was demonstrated in rats; it was shown that pretreatment with the ARBs elicited a normalization of significant biochemical parameters and reduced cardiac tissue damage.[17,18] ACEI, beta-blockers and angiotensin II receptor blockers seem to prevent the development of late cardiotoxicity in patients treated with high doses of chemotherapy.[13,19,20]

A recent study[21] showed an improvement of global longitudinal strain in cancer patients treated with beta-blockers. Thus, the early diagnosis of cardiotoxicity is very important to prevent the development of late cardiotoxicity and heart failure using cardioprotective agents such as ACEI, beta-blockers and ARBs.

Table 6 Changes in E/A, Em/Am, isovolumic relaxation time and Sm in F group

	E/A (*P*)	Em/Am (*P*)	IVRT (*P*)	Sm (*P*)
T0	0.8 ± 0.17	0.82 ± 0.13	64 ± 10	15 ± 3
T1	0.8 ± 0.2 (*P* = 1)	0.8 ± 0.12 (*P* = 0.48)	66 ± 19 (*P* = 0.057)	13.9 ± 1.5 (*P* = 0.047)
T2	0.79 ± 0.19 (*P* = 0.8)	0.8 ± 0.02 (*P* = 0.35)	70 ± 17 (*P* = 0.06)	12.94 ± 3.14 (*P* = 0.0046)

IVRT, isovolumic relaxation time.

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Table 7 Differences between A group and F group

	A group		F group	
	Sm (*P*)	LVEF (*P*)	Sm (*P*)	LVEF (*P*)
T0	14.9 ± 2.95	62 ± 0.15	15 ± 3	62 ± 0.15
T1	12.03 ± 0.5 ($P = 0.030$)	62 ± 0.10 ($P > 0.05$)	13.9 ± 1.5 ($P = 0.047$)	62 ± 0.10 ($P > 0.05$)
T2	11.7 ± 1.87 ($P = 0.002$)	60 ± 0.08 ($P < 0.0001$)	12.94 ± 3.14 ($P = 0.0046$)	62 ± 0.22 ($P > 0.05$)

LVEF, left ventricular ejection fraction.

But further study is necessary. European Society for Medical Oncology (ESMO) clinical practice guidelines recommend serial evaluation of LVEF and the start of treatment with enalapril when there is a significant reduction of ejection fraction (LVEF) and in the patients with subclinical cardiotoxicity induced by Type I agents also identified by an increase in cardiac troponin.[22] However, it would be desirable to start cardioprotective therapy in all patients with subclinical cardiotoxicity identified by new echocardiographic parameters.

Study limitation

The main limitation of the study was the number of patients included in the study, especially the number of patients treated with ACEI and ARBs. Furthermore, a larger population will be necessary in the future. Another limitation of the study was the use of TDI without the assessment of left ventricular longitudinal strain.[23] TDI represents a good, easy and reliable method to measure left ventricular longitudinal performance, particularly in the early phases of cardiac toxicity from chemotherapy. However, it is a Doppler technique and its main intrinsic limitation is represented by the angle dependency.

Conversely, two-dimensional (2D) speckle-tracking echocardiography (STE) is a relatively new, largely angle-independent technique used for the evaluation of myocardial function. Strain describes myocardial deformation that is the fractional change in the length of a myocardial segment. Strain and strain rate analysis increases sensitivity in detecting subclinical cardiac involvement in conditions such as amyloidosis, diabetes and hypertensive heart disease, as well as changes in left ventricular function after cancer treatment.[24] Assessment of 2D strain by STE is a semiautomatic method, which requires manual definition of the myocardium. Training and experience are needed for proper interpretation and recognition of artifacts.[25] We have not used 2D STE in our study because we evaluated cardiac dysfunction induced by anticancer agents in a follow-up of 3 years (2 years after the end of chemotherapy with median length of treatment 1 year), and 3 years ago at baseline in our central hospital, adequate software for the assessment of left ventricular longitudinal strain was not available. Another limitation of the study was not dose cardiac biomarkers such as T-Brain natriuretic peptide (T-BNP) and Troponin. The role of biochemical markers is still controversial in literature; however, the dosage of Troponin and T-BNP is quite accepted in the early detection of cardiac damage, particularly if it is associated with imaging techniques.[26–29]

In our study, dosage of T-BNP and Troponin levels was not available because serial dosages were needed and patients had poor compliance. Furthermore, in the future, it is necessary to correlate biomarker levels, TDI, strain and cardioprotective role of drugs in long-term follow-up for the early diagnosis of cardiotoxicity.

Conclusion

TDI is more sensitive than LVEF in the early diagnosis of left ventricular dysfunction and it may help target patients who could benefit from closer cardiac monitoring, earlier initiation of cardioprotective medical therapy or less cardiotoxic novel tyrosine kinase inhibitors and anticancer drugs. In addition, ACEI, ARBs and beta-blockers have a cardioprotective role in the prevention of chemotherapy cardiotoxicity.

Thus, patients with subclinical cardiotoxicity detected using TDI and significant changes in the echo parameters of systolic and diastolic function, during chemotherapy and during follow-up, would start cardioprotective treatment with ACEI or ARBs to prevent the development of severe forms of cardiac dysfunction after chemotherapy. Further studies are needed to support the use of these drugs when subclinical cardiotoxicity is detected by new echocardiographic parameters.

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