Chemotherapy-induced cardiotoxicity: role of the tissue Doppler in the early diagnosis of left ventricular dysfunction

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Cardiotoxicity is a common complication of chemotherapy. The aim of this study was to assess the cardiotoxicity of anticancer drugs using tissue Doppler imaging. A prospective study was carried out using patients with early breast cancer (72 women, median age: 57 ± 12 year) and other inclusion and exclusion criteria. Inclusion criteria were treatment with epirubicin, trastuzumab, fluorouracil, cyclophosphamide, taxotere, and taxolo; left ventricular ejection fraction (LVEF) of more than 50%; and absence of important pathologies. Exclusion criteria were presence of known heart disease, earlier exposure to mediastinal irradiation, and earlier chemotherapy. On the basis of treatment, patients were divided into five groups: A = fluorouracil–epirubicin–cyclophosphamide (FEC), B = FEC + trastuzumab, C = trastuzumab, D = FEC + taxotere, and E = FEC + taxol + trastuzumab. Cardiological evaluation including electrocardiogram and echocardiogram was carried out at baseline, 3 months, and 6 months after the start of chemotherapy in all patients. The Doppler patterns were integrated with other echo parameters (tissue Doppler). Significant changes ($P < 0.05$) in the echo parameters of the tissue Doppler were observed in treated patients during follow-up but not in LVEF. In conclusion, the tissue Doppler is more sensitive than standard Doppler in the study of diastolic function and LVEF in the study of systolic function. The tissue Doppler should integrate conventional echocardiography in the study of left ventricular function in patients treated with anticancer drugs. It is very important to reduce the risk of cardiovascular complications, especially heart failure, in breast cancer survivors. *Anti-Cancer Drugs* 22:468–472 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2011, **22**:468–472

Keywords: cardiac monitoring, cardiotoxicity, chemotherapy, heart failure, left ventricular dysfunction, tissue Doppler imaging

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Received 26 October 2010 **Revised form accepted** 30 December 2010

Introduction

Cardiotoxicity of anticancer drugs is a very important problem. It is defined, by the National Cancer Institute, as the 'toxicity that affects the heart'. This definition not only includes a direct effect of the drug on the heart but also an indirect effect due to enhancement of hemodynamic flow alterations or due to thrombotic events [1]. Cardiotoxicity can develop in a subacute, acute, or chronic manner. Acute or subacute cardiotoxicity is characterized by either the occurrence of abnormalities in ventricular repolarization and electrocardiographic QT-interval changes, by supraventricular and ventricular arrhythmias, by acute coronary syndromes, and pericarditis-like and/or myocarditis-like syndromes, observed at any time from the initiation of therapy to up to 2 weeks after termination of treatment. Chronic cardiotoxicity may be differentiated in two subtypes based on the onset of clinical symptoms. The first subtype occurs early, within 1 year after termination of chemotherapy, and the second occurs late, more than 1 year after chemotherapy. The most typical sign of chronic cardiotoxicity is asymptomatic systolic and/or diastolic left ventricular dysfunction that leads to severe congestive cardiomyopathy and that may ultimately lead to death [1,2]. Each anticancer agent has a cardiotoxic action. Anthracyclines can generate congestive heart failure and left ventricular dysfunction and their cardiotoxicity is irreversible and dose dependent [1,3]. Trastuzumab, a recombinant humanized IgG_1 monoclonal antibody that selectively binds to the human epidermal growth factor receptor 2 protein, increases the risk of cardiotoxic adverse events if it is administered with anthracyclines or other anticancer agents [1]. Taxanes (taxotere and taxolo) can cause sinus bradycardia, atrioventricular block, and ventricular tachycardia; cyclophosphamide can induce pericarditis, myocarditis, and heart failure; and 5-fluorouracil can cause myocardial ischemia [1]. Cardiovascular complications include all adverse effects of anticancer drugs on the heart and the vascular system (arrhythmias, systolic and diastolic dysfunction, heart failure, ischemia/infarction, myocarditis, thromboembolism, and hypertension/hypotension) [2]. Cardiovascular complications were observed in 5–65% of patients

0959-4973 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e3283443704

treated with chemotherapy; the proportion is dependent on the type of cardiac abnormalities and the duration of follow-up [3–8]. For example, acute cardiotoxicity of anthracyclines occurs in less than 1% of patients immediately after infusion. The early-onset chronic progressive form occurs in 1.6–2.1% of patients, during therapy or within the first year after treatment. Late-onset chronic progressive anthracycline-induced cardiotoxicity occurs at least 1 year after completion of therapy in 1.6–5% of patients [3,9]. The risk of clinical cardiotoxicity increases with a cumulative dose of anthracycline. The risk of heart failure with doxorubicin occurs in 35% with 400 mg/m^2, 7–26% at 550 mg/m^2, and 18–48% at 700 mg/m^2 [3–10]. However, in a retrospective review of three trials, the incidence of heart failure was found to be 26% with cumulative doses of 550 mg/m^2 [3]. For this reason, the maximum lifetime cumulative dose for doxorubicin is 400–550 mg/m^2. However, epirubicin seems to have less incidence of heart failure and its maximum lifetime cumulative dose is 900 mg/m^2 [3,9,10]. Risk factors for anthracycline toxicity include cumulative dose, intravenous bolus administration, higher single doses, history of earlier irradiation, the use of other concomitant agents known to have cardiotoxic effects (cyclophosphamide, trastuzumab, and paclitaxel) female sex, underlying cardiovascular disease, age (young and old age), and increased length of time since anthracycline completion [8,9,11–14]. The overall incidence of trastuzumab varies in the literature from 2 to 28%. The incidence of cardiac dysfunction ranges from 2 to 7% when trastuzumab is used as monotherapy, 2–13% when trastuzumab is used in combination with paclitaxel, and up to 27% when trastuzumab is used concurrently with anthracyclines plus cyclophosphamide [9,15]. It is very important to assess the cardiotoxicity of anticancer drugs by monitoring cardiac function with different methods such as echocardiography, electrocardiography, ECG HOLTER 24 h, and other methods more expansive and more invasive (scintigraphy, magnetic resonance imaging, endomyocardial biopsy, and stress echocardiography) [16]. Echocardiography is a widely used noninvasive method of monitoring cancer therapy. Parameters of systolic [left ventricular ejection fraction (LVEF)] and diastolic function [E/A = ratio between the early diastolic peak velocity (E, early) and the atrial peak velocity A (A, atrial)] and valvular function can be assessed. The international oncological guidelines recommend evaluating LVEF before starting treatment and during follow-up. The indication for treatment interruption is a decrease in LVEF greater than 10 percentage points, combined with a reduction to a value below the limit of normality (50%) [16–18]. However, LVEF is not sensitive for early detection of preclinical cardiac disease (subclinical). Moreover, it is influenced by contractility and preload/afterload effects leading to transient changes. Therefore, other measurements of systolic function and diastolic function should be used to detect early cardiotoxicity in addition to LVEF [16,19].

Conventional echocardiography should be integrated with the tissue Doppler imaging (TDI) that provides parameters more sensitive in the study of left ventricular function. TDI allows the measurement of the diastolic and systolic velocities of the ventricular walls and mitral annulus, and measures of TDI are less influenced by loading conditions [20].

Methods

This study was designed and conducted as a prospective study using patients with breast cancer (72 women, median age: 57 ± 12 years) treated with antineoplastic agents. Patients were treated in the Department of Medical Oncology at the University Hospital of Palermo, 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] 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 in the Division of Cardiology at the University Hospital of Palermo. Exclusion criteria were presence of known heart disease, earlier exposure to mediastinal irradiation, and earlier chemotherapy (factors which increase the risk of cardiotoxicity). All patients had early stages of diseases and cardiovascular risk factors such as hypertension treated with ACE inhibitors, Sartans, or β-blockers (41% of patients), diabetes (15%), obesity (10%), cardiovascular familiarity (60%), dyslipidemia (15%), or smoking (19%) (Table 1). On the basis of treatment and chemotherapy doses, patients were divided into five groups: A = six cycles of FEC, B = three cycles of FEC + three cycles of trastuzumab, C = six cycles of trastuzumab, D = three cycles of FEC + three cycles of taxotere, and E = three cycles of FEC + three cycles of taxol + trastuzumab (Table 2). Doses of fluorouracil were 800 mg/m^2 by cycle, epirubicin 140 mg/m^2, cyclophosphamide 800 mg/m^2, trastuzumab 420 mg/m^2, taxolo and taxotere 150 mg/m^2 or more or less depending on the patient's conditions. Cumulative doses of epirubicin were 840 mg/m^2 in the patients of groups A and 420 mg/m^2 in

Table 1 Patients studied

	Number of patients (%)
Total number of patients (*N*)	72
Age (years)	57 ± 12
Cardiovascular familiarity	43 (60)
Diabetes	10 (15)
Hypertension	30 (41)
Obesity	7 (10)
Dyslipidemia	10 (15)
Smoking	13 (19)

the patients of groups B, D, and E. It is very important to know the cumulative doses of anthracyclines because cardiotoxicity of anthracyclines is dose dependent. Cardiological evaluation including electrocardiogram and echocardiogram was made at baseline (T0), at 3 months (T1), and at 6 (T2) months after the start of chemotherapy. Echocardiography and electrocardiography were performed in all patients at 3 months after the start of treatment and in 90% of patients (65 patients) at 6 months. The median length of chemotherapy was 1 year. All patients at 6 months were still on chemotherapy and should continue chemotherapy. Echocardiographic evaluation was carried out with echocardiography 'Acuson Sequoia'. 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 total ejection isovolumic index (TEI) index]. 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-chambered section. IVRT and IVCT were measured using the tissue Doppler. TEI index (IVCT + IVRT)/ejection time is a Doppler echocardiographic parameter of global function.

The TDI parameters were always measured by the same investigator (F.B., cardiologist, with an earlier Master's degree in echocardiography). The same investigator assessed LVEF. There was an independent evaluation of these parameters. Most of the time other investigators as well as D.D.L. were present during the echocardiographic evaluation. Only one time (one patient), were TDI measures and LVEF determined by another cardiologist (G.N.). The results of parameters were reported as mean ± standard deviation. Differences were assessed using Student's *t*-test and were considered to be significant if *P* value was less than 0.05.

Results

During echocardiographic follow-up, we did not find significant reductions in LVEF (62% ± 5 at baseline, 61% ± 3 at 3 and 6 months, $P > 0.05$) but we found significant changes in the tissue Doppler parameters of systolic function (Sm and IVCT) at 3 (T1) and 6 months (T2) after the start of chemotherapy (Table 3), when considering patients as a whole, but not for several individual groups. A significant reduction was found in the E/A ratio (Doppler parameter of diastolic function) and in Em/Am ratio, but Em/Am ratio measured with the tissue Doppler was more sensitive than E/A ratio in showing the early presence of diastolic dysfunction at baseline and after chemotherapy (Table 4). At baseline, 32 patients (45%) reported reversal E/A but 53 (76%) reported reversal Em/Am. After chemotherapy, patients with reversal Em/Am showed reversal E/A. Patients without diastolic dysfunction at baseline (14 patients) reported reversal Em/Am at 3 months (T1) after chemotherapy and reversal E/A at 6 months (T2). We did not find diastolic dysfunction after chemotherapy in four patients. IVRT measured with the tissue Doppler and TEI index showed significant increase at 3 (T1) and 6 months (T2) after the start of the treatment (Table 3). We did not find any correlation between reversal Em/Am and E/A after chemotherapy and different therapies. Evaluation of patients within several groups (A, B, C, D, E) showed statistically significant changes in the echocardiographic parameters of systolic function (Sm), diastolic function (E/A, Em/Am, and IVRT), and TEI

Table 2 Groups

	No. of patients (%)	Median age	Anticancer drugs Number of cycles
Group A	12 (16)	59 ± 9	Six FEC
Group B	12 (16)	55 ± 6	Three FEC + three trastuzumab
Group C	13 (18)	62 ± 15	Six trastuzumab
Group D	29 (43)	54 ± 8	Three FEC + three taxotere
Group E	6 (7)	63 ± 20	Three FEC + three taxolo + trastuzumab

FEC, fluorouracil–epirubicin–cyclophosphamide.

Table 4 Changes in E/A and Em/Am

	E/A	*P* value	Em/Am	*P* value
T0	1.05 ± 0.24		0.88 ± 0.23	
T1	0.98 ± 0.22	0.07	0.83 ± 0.15	0.12
T2	0.96 ± 0.19	0.01	0.79 ± 0.12	0.005

E/A, ratio between the early diastolic peak velocity (E, early) and the atrial peak velocity A (A, atrial); Em/Am, ratio between myocardial early diastolic velocity (Em) and myocardial atrial velocity (Am).

Table 3 Changes in LVEF, Sm, IVRT, and TEI index

	LVEF	*P* value	Sm	*P* value	IVRT	*P* value	TEI index	*P* value
T0	62 ± 5		14.43 ± 3.21		58 ± 14		0.36 ± 0.09	
T1	61 ± 3	0.14	13.00 ± 2.5	0.002	70 ± 10	0.0001	0.43 ± 0.08	0.0001
T2	61 ± 3	0.14	12.00 ± 2.15	0.0001	69 ± 17	0.0001	0.45 ± 0.08	0.0001

IVRT, isovolumic relaxation time; LVEF, left ventricular ejection fraction; Sm, myocardial systolic velocity; TEI, total ejection isovolumic index.

index in group A but not in other groups. In other groups, changes in the echocardiographic parameters were not significant ($P > 0.05$) but they followed the same trend as the whole population.

Discussion and conclusion

Anticancer drugs cause asymptomatic alterations of systolic and diastolic cardiac functions. These alterations were showed using two-dimensional echocardiography with standard Doppler and pulsed TDI. Significant changes in systolic and diastolic cardiac functions occurred at 3 and 6 months after starting chemotherapy but these changes were more pronounced for most TDI measurements when compared with conventional echocardiography (standard Doppler and LVEF). A significant reduction in the echo parameters of the tissue Doppler and standard Doppler was observed during follow-up but not in LVEF, considering patients as a whole and not as several groups. The Em/Am ratio measured with the tissue Doppler was more sensitive than E/A ratio at baseline and after chemotherapy. In effect, reversal Em/Am preceded reversal E/A at baseline (T0) and after chemotherapy, in the presence of diastolic dysfunction. Therefore, TDI seems to offer significant advantage over traditional techniques when trying to determine the presence of cardiac dysfunction as a result of chemotherapy [21]. In the assessment of left ventricular diastolic performance, the tissue Doppler is more reliable than the conventional Doppler because the influence of loading conditions is less and TDI measures are more reproducible [22]. We did not find any correlation between reversal Em/Am and reversal E/A after chemotherapy and different therapies. IVRT (TDI parameter of diastolic function) and TEI index (parameters of global function) changed significantly at T1 and T2, showing an early impairment of cardiac function in the early months after starting the treatment. We did not find significant reductions in LVEF during the study in all patients. We found significant reductions in Sm, the TDI parameter of systolic function. Therefore, on the basis of our results, on the basis of the assessment of LVEF in individual patients (at baseline, T1, and T2), and in accordance with earlier studies, we believe that there were no significant reductions in LVEF during the study. Earlier studies showed that in patients treated with epirubicin (300–400 mg/m^2), LVEF did not change significantly up to 18 months after chemotherapy but TDI parameters (Em/Am and Sm) showed significant reduction during the first few months of treatment [21]. Other studies showed that in patients treated with anthracyclines, alteration of diastolic function (E/A and IVRT) precedes alteration of systolic function [23]. Other researchers used strain rate, a measure of deformation rate of regional myocardial fibers, in the early evaluation of cardiac dysfunction in patients treated with antineoplastic agents [24]. In our study, we have measured other TDI parameters (IVRT, IVCT, and TEI index), in addition to Em/Am and Sm, in patients treated with epirubicin and other anticancer agents. TDI should integrate LVEF evaluation in the assessment of cardiac function in patients treated with anticancer agents, to identify early alterations of cardiac function induced by chemotherapy and to prevent heart failure, disease with mortality of 50% at 5 years, and high costs of hospitalization [4]. TDI evaluation does not have limitations because it is cheaper, noninvasive, and shows greater reproducibility [22]. Considering several groups (A, B, C, D, E), we found significant changes in the echocardiographic parameters (E/A, Em/Am, IVRT, TEI index) in group A but not in other groups in which alterations of echocardiographic parameters followed the trend of the AscoltaTrascrizione fonetic whole population, but they were not significant. It is probable that significant changes in group A were due to the higher dose of epirubicin administered (cumulative doses of 840 mg/m^2). In effect, anthracycline-induced cardiotoxicity is dose dependent [10]. Alterations that were not significant in the echocardiographic parameters were found in groups B, D, and E probably due to lower dose of epirubicin (cumulative doses of 450 mg/m^2). Human epidermal growth factor receptor 2 + patients treated with trastuzumab (group C) have been studied but we did not find significant alterations in echocardiographic parameters. Cardiotoxicity of trastuzumab increases in the presence of earlier chemotherapy but we did not find significant alterations in groups B and E, probably because earlier doses of epirubicin were lower and the population evaluated was small. On the basis of our results in the groups and in agreement with the literature, anthracyclines are more cardiotoxic than other anticancer agents and their cardiotoxicity is dose dependent. On the basis of our results, considering the entire patient population, anticancer drugs cause alterations of systolic and diastolic functions and TDI is more sensitive than conventional echocardiography in the early diagnosis of left ventricular dysfunction. In effect, asymptomatic alteration of systolic and diastolic functions was showed using TDI but not conventional echocardiography, in the early months after starting chemotherapy. TDI offers parameters more sensitive than conventional echocardiography in showing the presence of systolic and diastolic dysfunctions and TDI parameters are less influenced by loading conditions and are more reproducible [22]. Patients studied were treated with anticancer drugs; the median length of chemotherapy was 1 year but echocardiographic evaluation was carried out after 3 months and after 6 months after starting chemotherapy and chemotherapy should be continued. These women were not treated with anticancer agents earlier. It is very important to identify, in women, who must continue chemotherapy, early alteration of cardiac function by using TDI to prevent the progression of the cardiac dysfunction. In conclusion, the tissue Doppler should integrate conventional echocardiography

in the study of cardiac function in patients treated with anticancer drugs. Early diagnosis of left ventricular dysfunction is very important to reduce the risk of congestive heart failure in cancer survivors. Cardiologists and oncologists should collaborate to reduce chemotherapy-associated cardiotoxicity, changing dose–treatment modalities, and introducing cardioprotective agents [4]. It is unacceptable for cancer survivors to develop treatment-related cardiovascular complications, especially heart failure.

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