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Early Effects of Breast Cancer Chemotherapy by Fluorouracil, Epirubicin and Cyclophosphamide with or without Docetaxel Regimen on the Right and Left Ventricle Functions

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Abstract

Objectives: to investigate global cardiac functional status during adjuvant chemotherapy with Fluorouracil, Epirubicin and Cyclophosphamide (FEC) and FEC-Docetaxel protocol for breast cancer.

Material and Method: 51 women treated with adjuvant chemotherapy for breast cancer at the oncology department.

Results: LVEF decreased from baseline values of 66%±3 to 64.5%±4.4, p=0.001 at six month calculations as compared to the beginning. There was increase in the Left Ventricular MPI values from the baseline records of 0.45±0.1 to 0.58±0.15, p=0.0001 at six months follow-up. Mean TAPSE values were 2.45±0.42 and 2.05±0.35 cm respectively, p=0.0001. There was increase in the right ventricular TDI MPI values after the therapy as compared to the baseline calculations (0.23 and 0.37, p=0.0001) at six months. When we compare the delta values of LEVF, LV MPI, TAPSE and RV TDI MPI in group of FEC alone and FEC followed by Docetaxel regimen, we did not find any significant changes before and after the chemotherapy (p= 0.08, p=0.38, p=0.43 and p=0.2, respectively).

Conclusion: Chemotherapy with FEC is associated with subclinical right and left ventricular dysfunction as assessed by TAPSE, left ventricular Doppler myocardial performance index, and right ventricular tissue Doppler myocardial performance index.

Keywords: Chemotherapy, FEC-Docetaxel regimen, Echocardiography,TAPSE, tei index

Özet

Amaç: Meme kanseri tedavisi Fluorouracil, Epirubicin and Cyclophosphamide (FEC) VEFEC-Docetaxel ile yapılan anjuvan protokolü sırasında global kardiyak fonksiyon durumunun incelenmesi.

Gereç ve Yöntem: Onkoloji bölümünde meme kanseri nedeniyle adjuvant tedavi gören 51 hasta çalışmaya alındı.

Bulgular: Tedavi başlangıcı ile karşılaştırıldığında 6 aylık tedavi sonrası LVEF 66%±3 den 64.5%±4.4 e düştü, p=0.001. 6 aylık takipte Sol Ventriküler MPI değerleri bazal değerler olan 0.45±0.1 dan 0.58±0.15 e yükseldi, p=0.0001. Tedavi öncesi ve sonrası ortalama TAPSE değerleri sırasıyla 2.45±0.42 ve 2.05±0.35 cm, p=0.0001 idi. Altı aylık tedavi sonrasında, bazal ölçümlerler kıyaslandığında Sağ Ventriküler TDI MPI değerlerinde tedavi sonrası anlamlı artış saptandı (0.23 ve 0.37, p=0.0001). Yalnızca FEC ve Docetaxel fonrası FEC rejimlerine ait tedavi öncesi ve sonrası LVEF, LV MPI, TAPSE ve RV TDI MPI ölçümlerinin Delta değerleri karşılaştırıldığında, anlamlı bir değişiklik saptanmadı (sırasıyla p= 0.08, p=0.38, p=0.43 and p=0.2).

Sonuç: TAPSE, LVD TDI MPI ve RD TDI MPI ile değerlendirildiğinde, FEC kemoterapisi subklinik Sağ Ventrikül disfonksiyonuyla ilişkilidir.

Anahtar Kelimeler: Kemoterapi, FEC-Docetaxel rejimi, Ekokardiografi, TAPSE, tei index

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Introduction

Cardiovascular complications of cancer chemotherapy such as, arrhythmia, myocardial ischemia, arterial and venous thrombosis and congestive heart failure are associated with poor prognosis and they may become determinant of patients' life expectancy instead of cancer. Almost all cancer drugs can damage to cardiovascular system in varying degrees and severity and importance of chemotherapy complications necessitate for oncologists, radiologists, internist and cardiologists to approach the disease as teamwork [1-3]. Previous studies monitored the cardiovascular complications of chemotherapy by Electrocardiography (ECG), B and M-mode echocardiography, radionuclide angiography (MUGA), cardiac MRI and cardiac Tomography. Among them, echocardiography is a cheap, non-invasive, and highly accurate tool for monitoring. Furthermore, echocardiography is a rapidly developing imaging tool and it has many advantages when compared with other techniques. In last decade, many articles about the monitoring of cardiovascular complications of cancer chemotherapy were published. But, most of them have evaluated the cardiovascular complications by ECG changes only, biomarker changes, left ventricular diastolic or systolic dysfunctional changes, right ventricular functions by TAPSE, right ventricle area/volume changes, tissue Doppler imaging (TDI), stress or strain imaging techniques [3-5]. But there is not enough data about the effects of Fluorouracil, Epirubicin and Cyclophosphamide (FEC) with or without Docetaxel (FEC/T) regimen on the right and left ventricle functions. In this study, we aimed to investigate global cardiac functional status during breast cancer chemotherapy by FEC or FEC/T protocol.

Patients and Methods

Study population

58 women treated with adjuvant chemotherapy for non-metastatic breast cancer at the Medical Oncology Department of Bülent Ecevit University, Zonguldak, Turkey between May 2011 and Sep 2012 were included in the study.

Local Ethics Committee approved the study and the study was conducted according to the recommendations of Declaration of Helsinki on Biomedical Research involving human subjects. All the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, which was revised in 1983. Written informed consent was obtained from each patient before enrollment. Women who had breast cancer surgery due to confirmed breast cancer by histology and left ventricular ejection fraction (LVEF) of more than 50% at baseline were included in the study. Exclusion criteria were defined as the existence or history of cardiac disease, diabetes mellitus, renal failure, arrhythmia on ECG or arrhythmia history, hypertension and existence of systolic or diastolic dysfunction. Patients, who had poor echocardiographic image quality, since some of the patients have limited access after left-sided breast surgery, were also excluded. According to the exclusion criteria 7 patients excluded from the study and remaining 51 patients were analyzed in the study.

Participants received either FEC protocol (5-FU 500 mg/m2 iv d1+Epirubicin 100 mg/m2 iv d1 and Cyclophosphamide 500 mg/m2 iv d1 Q3w x 6 cycles) or FEC-Docetaxel protocol (5-FU 500 mg/m2 iv d1+Epirubicin 100 mg/m2 iv d1 and Cyclophosphamide 500 mg/m2 iv d1 Q3w x 3 cycles followed by Docetaxel 100 mg/m2 i.v. Q3w x 3 cycles) according to the treating physician's choice.

Complete physical examination was performed in all participants before first cycle of chemotherapy and evaluated prospectively before each cycle. Blood samples were obtained before each cycle for complete blood count and biochemistry.

Echocardiographic analysis

Cardiac evaluation including echocardiography and electrocardiography (ECG) was performed on the day before the onset of chemotherapy and after the end of 6th cycle in all patients. The same cardiologist using a General Electric Vivid-7 Echocardiography with a 2.5–3.5 MHz transducer in the left lateral decubitus position performed all echocardiographic examinations and investigator did not know the patients status and blinded to the study. Each examination was performed and recorded by the same expertise cardiologist blinded to the chemotherapeutic status of the patients. Parasternal and apical projections were obtained according to the recommendations of American Society of Echocardiography

[5,6]. The left ventricle volumes and ejection fraction were obtained by the modified biplane Simpson's method. Left atrial left ventricular end diastolic and end systolic dimensions were measured from the parasternal long axis view. From apical four-chamber view, E, A, isovolumic relaxation time (IVRT), isovolumetric contraction time (IVCT) and ejection time (ET) were calculated. Left ventricular index or myocardial performance index (MPI) was calculated as (IVRT+ICT)/ET by conventional Doppler study.

Right ventricular end-diastolic and end-systolic diameters were measured from the apical four-chamber view to calculate right ventricular dimensions and volumes. To determine the Tricuspid annular plane systolic excursion (TAPSE), an M-Mode cursor was placed at the junction of the tricuspid valve plane with the right ventricular free wall, using the images of the apical four-chamber view. TDI values of the left ventricle were obtained from the apical four-chamber view using a sample volume placed at the lateral corner of the mitral tricuspid annulus; and anterior, inferior, medial, and lateral sections of the mitral annulus.

For evaluation of Right Ventricular TDI, apical four-chamber view was chosen. TDI cursor was placed on the right ventricular free wall, 1 cm apical to the tricuspid annulus. From TDI of the RV tricuspid annulus: systolic velocity (Sm), early diastolic velocity (Em), and late diastolic velocity (Am) were recorded. In the TDI images, time interval between the start and end of Sm duration was measured as the ejection time (ET), the time between the end of the Sm and the beginning of the Em as isovolumetric relaxation time (IRT or isovolumetric acceleration time), and the time between the end of Am and the beginning of Sm as isovolumetric contraction time (ICT); a time is the sum of IRT, ICT and ET; b time is equal to the ET. Right ventricular Tei index (TDI MPI) was calculated as (a-b)/b. In this study, a Doppler velocity range of -20 to 20 cm/s was selected. The differences observed before and after therapy might be related to the variability of the measurements so investigator measure all the parameters three times and calculated the average values.

Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version 17 software (SPSS Inc., Chicago, IL, USA). For the continuous variables, parametric test conditions were first tested. The Shapiro–Wilk test was used to determine whether the continuous variables were normally distributed. Descriptive statistics were shown as mean standard deviation or median + IR (minimum– maximum) where appropriate. Degrees of association between continuous variables were calculated by Spearman's correlation analysis. The measurements of before and after the treatment were analyzed by Paired T test. The Parameters were considered to be significant if P value was less than 0.05.

Results

Basal characteristics of the study population were presented in the table 1.

Table-1: Baseline and 6 months characteristics of the study population

	Baseline	End of the treatment	P value
	n=51	n=51	
Age, years, sd	53±2		
Systolic BP (mmHg), sd	120±11	126±9	0.7
Diastolic BP (mmHg), sd	75±6	78±10	0.80
BMI, sd	27±4	26±2.5	0.7
WBC(10□), sd	5.8±0.5	6±0.8	0.9
PLT (10□), sd	185±20	190±40	0.85
Hb, g/dL, sd	11.5±0.2	11.2±0.8	0.9
AST gr/dl, sd	31±5	33±4	0.6
ALT gr/dl, sd	28±6	30±5	0.7
CK IU/L, sd	75±10	83±7	0.8
CK-MB IU/L, sd	13±6	18±8	0.6

BP: Blood pressure, BMI: Body mass index, WBC: white blood cell, HB: hemoglobin,
Liver function tests: AST and ALT, CK: creatine kinase

The mean age of the patients was 53±2 years. All patients had surgery before chemotherapy and none of them had metastases. None of the patients terminated chemotherapy due to cardiotoxicity. All patients completed all cycles of chemotherapy. At the baseline none of the patients had diabetes mellitus, hypertension and cardiac rhythm problem on the ECG. Any patient received regular medication except the chemothe-

rapy protocol. Twenty-nine patients received six cycles of FEC regimen and remaining 22 patients received FEC-Docetaxel regimen. No significant changes occurred after six months at the end of chemotherapy as compared to the baseline values in age, systolic blood pressure, weight, hematological and biochemical as well as cardiac data. Also there were no changes in cardiac rhythm and heart rate on the control ECG.

No patient described dyspnea, palpitation and chest pain during therapy and follow-up period.

LVEF decreased from baseline values of 66%±3 to 64.5%±4.4, p=0.001 at six month calculations as compared to the beginning. There was increase in the Left Ventricular MPI values from the baseline records of 0.45±0.1 to 0.58±0.15, p=0.0001 at six months follow-up which suggest both systolic and diastolic impairment of cardiac functions (Table 2). We did not find any significant difference in the TDI values of left ventricle, including LV Sm-lat, LV Sm-inf, LV Sm-Sep (Table 2). Those results confirmed that, left ventricular systolic and diastolic dysfunction occurs during chemotherapy but left ventricle myocardial tissue velocity does not change significantly. Mean TAPSE values were 2.45±0.42 and 2.05±0.35 cm respectively, p=0.0001. There was increase in the right ventricular TDI MPI values after the therapy as compared to the baseline calculations (0.23 and 0.37, p=0.0001) at six months. Differences of the TAPSE, MPI and Tei index before and after the treatment were depicted in figure-1.

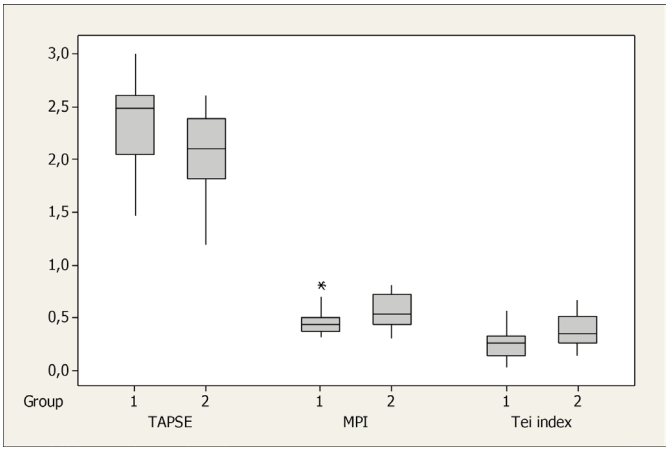

Figure-1:
Differences of the TAPSE, MPI and Tei index before and after the treatment.
TAPSE, tricuspid annular plane systolic excursion; MPI, myocardial performance index.

Decrease in TAPSE and the increase in RV TDI MPI values give rise to thought us that there was remarkable dysfunction in global right ventricle during the therapy. RVEDD, RVSD, vena cava diameter at inspirium and expirium were all remained unchanged (Table 2).

Table2: Echocardiographic parameters of the study population before and after the treatment.

Parameters	Before ±SD n=51	After ±SD n=51	P
Left Ventricular			
LAD, cm	3,5±0,6	3,48±0,78	0,27
LVESD cm	2,86±0,50	2,92± 0,6	0,8
LVEDD, cm	4,69±0,7	4,78±0,54	0,1
LVEF%	66%± 3	64,5%± 4,4	0,001
E velocity, m/s	0,72±0,22	0,67±0,27	0,35
A velocity, m/s	0,75±0,23	0,76±0,25	0,9
IVCT	42±14	46±2	0,2
IVRT	78±14	93±16	0,004
ET	273±23	250±40	0,001
LV Tei İndex	0,45±0,10	0,58±0,15	0,0001
LV Sm-lat, cm/s	8,5±1,8	8.6±1,9	0,5
LV Sm-inf, cm/s	7,8±1,5	7,8±1,3	0,8
LV Sm-Sep, cm/s	7,1±1	7,2±1,1	0,6
Right Ventricular			
RV WT, cm	0,5±0,10	0,43±0,15	0,02
RVESD cm	2,2±0,5	2,1±0,6	0,8
RVEDD cm	3,5±0,6	3,5±0,5	0,8
TAPSE, cm	2,45±0,42	2,05±0,35	0,0001
VC Diam. ins.	1,19 ±0,5	1,16±0,3	0,6
VC Diam. exp.	1,62±0,4	1,70±0,5	0,5
P vel. m/s	0,94±0,33	0,91±0,2	0,55
Sm-RV, cm/s	11,6±2	10,9±3,3	0,2
Em RV cm/s	11±6	9,6±3	0,08
Am RV cm/s	14,7±3	13,4±4,1	0,47
IVA-RV, m/sec(2)	8,3±2,5	12,5±2,5	0,0001
RV TDI Tei index	0,23±0,11	0,37±0,14	0,0001

LVEF: Left ventricular ejection fraction, LVESD: Left ventricular end- systolic diameter, LVEDD: Left ventricular end-diastolic diameter, AAD: Ascendan aortic diameter, MPI: Myocardial performance index, LAD: left atrial diameter, RVT: right ventricular thickness, ICT: isovolumetric contraction time, ET: ejection time, TAPSE: tricuspid annular plane systolic excursion, RVEDD: right ventricular end diastolic diameter,
RVESD: right ventricular end systolic diameter, VCins: vena cava diameter at inspirium, VCexp: vena cava diameter at expirium, IVRT: isovolumic relaxation time, IVA-RV: isovolumic myocardial acceleration, TAE: tricuspid annular early diastolic velocity, TAA: tricuspid annular late diastolic velocity, Pvel: pulmonary velocity, Avel: aortic velocity,

When we compare the delta values of LEVF, LV MPI, TAPSE and RV TDI MPI in-group of FEC alone and FEC followed by Docetaxel regimen, we did not find any significant changes before and after the chemotherapy (p= 0.08, p=0.38, p=0.43 and p=0.2, respectively).

Discussion

This prospective study showed that FEC regimen with or without Docetaxel is associated with global cardiac functional deteriorations in early six months period. In this study, we have prospectively evaluated overall cardiac functions mainly by echocardiography and tissue Doppler. Although all the changes remained at sub-clinical level, LVEF decreased and MPI increased at six months echocardiographic evaluations. The decrease in the LVEF might have some concerns due to intra observer variability of LVEF calculations. But, the significant increase in the LV MPI values confirms the remarkable impairment in the left ventricular systolic and diastolic functions.

We assessed the right ventricle functions using both TAPSE and RV TDI MPI. Both methods have shown us that there is also significant impairment in global right ventricular functions [6,7].

Our study is unique for three reasons: firstly, we monitored both ventricles in one study by echocardiography. Secondly, we have used as tools for the evaluations of both ventricular functions by standard LVEF calculations and TAPSE; besides we have used especially new and more detailed methods such as left ventricular MPI and RV TDI MPI. Thirdly, we also evaluated the both ventricular myocardial velocities by TDI.

The MPI (a combined myocardial performance index, Tei index) is an echocardiographic method for evaluation of global left ventricle systolic and diastolic function [8-10]. Calculation of MPI by echocardiography is easy and time saving method. So, we chose MPI for assessment of global left ventricle functions including diastolic and systolic functions. Our study showed marked increase in MPI during six months follows up in patients with breast cancer treated by FEC protocol. Although those changes remained at subclinical findings, long-term follow-up of those changes carries prognostic value. The Tissue Doppler Tei index of left ventricle also has been shown to correlate with pulsed wave measurements[11]).

Imaging of right ventricle functions has difficulties by conventional echocardiographic methods. Geometric shape, marked regional differences in the extent of fiber shortening, very close localization to the sternum, previous thoracic and cardiovascular surgery, existence of obesity and chronic pulmonary disease, existence of right ventricular dysfunction and previous mastectomy all often lead to poor image quality by conventional echocardiographic imaging and evaluation of right ventricle[12]. For those reasons we used TAPSE and RV TDI MPI for monitoring of right ventricle functions. It has been shown that, RV TDI parameters are correlated with invasive measurement and magnetic resonance imaging [12].

Anthracyclines, alkylating agents and newer drugs such as taxanes are effective and active drugs for breast cancer. Compared with the combination of cyclophosphamide, methotrexate, and fluorouracil (CMF), 4 cycles of standard dosing of anthracycline-based therapy is equivalent to 6 cycles of CMF[1]. Sequential therapy as adjuvant setting with FEC followed by docetaxel significantly improves disease-free and overall survival and also has a favorable safety profile[2]. Studies revealed that FEC and FEC-Docetaxel regimens had 86.7% and 90.7% of five-year overall survival rates respectively [1,2]. For the monitoring of cardiac complications of FEC chemotherapy in breast cancer, baseline and regular follow-up by LVEF on echocardiography and MUGA were used in the majority of previous studies. Both of them still have very important and accurate role in LEVF follow-up but, they are not sensitive for early detection of pre-clinical cardiac disease (subclinical), and contractility and pre-load/afterload effects leading to transient changes influence it. Other parameters of echocardiography such as measurements of fraction shortening and diastolic function (e.g., E/A ratio) have been used to detect early cardiotoxicity in addition to LVEF [1-6]. Furthermore, MUGA mainly shows the changes in LVEF with low sensitivity and specificity, but does not give us enough information for early toxicity detection.

Contrary to MUGA, echocardiography identifies both systolic and diastolic dysfunction, as well as valvular and pericardial disease. Some cardiac specific or cardiac tissue bounded biochemical markers may also indicate myocardial injury before

the changes in LVEF are apparent such as Troponin and natriuretic peptides [2]. In our study group we have used only echocardiography being as accurate, time consuming, safe for doctors and patients with standard and highly sophisticated methods.

Conclusion: Although incidence of cardiotoxicity about FEC/T containing cancer drugs was shown by LVEF and MUGA, our study showed that, there are occult cardiac dysfunctions, which may be important for those patients. We advise that measurements of left ventricular MPI, right ventricle TAPSE and RVVTDI MPI in all FEC/T regimen patients should be done for early, definite detection and prevention of cardiac complications.

Limitation: We do not have a control group in this study but also we excluded the patients who have abnormal basal echocardiographic findings. Small sample size and data acquisition between first therapy and after the completion of six months are limitations. Also this is not the first study addressing the cardiac effects of chemotherapeutic drugs but it is not well known the effects of tissue Doppler and right ventricular functions.

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