

Effects of folinic acid and fluorouracil chemotherapy on right ventricle functions as assessed with tricuspid annular plane systolic excursion

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Abstract

Aim: This study aimed to investigate the effects of folinic acid and fluorouracil (bolus FUFA regimen) chemotherapy on right ventricle (RV) functions.

Materials and Methods: Thirty-four gastrointestinal (GI) cancer patients treated with antineoplastic drugs were included the study. All participants received FUFA chemotherapy protocol for colorectal, gastric and pancreatic cancer (i.e. fluorouracil 400-425 mg/m² intravenous day 1-5 + folinic acid 20-25 mg/m² intravenous day 1-5 every 28 days x6 cycles) with or without radiation therapy according to the cancer and patient status. All participants have undergone complete physical and laboratory examination and complete echocardiographic evaluation including detailed right ventricle functional evaluations before the onset of chemotherapy and 6 months after the start of treatment.

Results: Mean RV thickness was 0.49 cm before chemotherapy and 0.62 cm at the end of the treatment (p=0.29). Mean tricuspid annular plane systolic excursion (TAPSE) values were 2.08 ± 0.3 and 2.00 ± 0.39 cm, respectively (p=0.25). RV total ejection isovolumic (Tei) index related to the chemotherapy did not change significantly (0.24 and 0.29, respectively, p=0.07). Also we did not find significant chance in the RV end diastolic diameter, RV end systolic diameter, vena cava diameter on inspiration and expiration.

Conclusion: Bolus FUFA regimen chemotherapy does not diminish the RV functions as assessed by TAPSE and RV Tei index in GI cancer patients. Hippokratia 2014; 18 (4): 346-349.

Keywords: Tricuspid annular plane systolic excursion, total ejection isovolumic index, right ventricular function, folinic acid, fluorouracil, chemotherapy

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Introduction

Chemotherapy drugs such as anthracyclines, cyclophosphamide, 5-fluorouracil (5-FU), platins, taxanes and a newer drug trastuzumab may cause cardiotoxicity¹. Cardiovascular complications of the chemotherapy are cardiac arrhythmia, myocardial ischemia or infarction, vascular thrombosis and heart failure and all of these complications are associated with poor prognosis and they decrease the quality of life and life expectancy².

Although there are many studies about the left ventricular systolic and diastolic functions after the chemotherapy, there have not been enough investigations about right ventricular functions in patients even they have normal left ventricular systolic functions³. The assessment of right ventricle by echocardiography is difficult due to its anatomical and morphological structure so M-mode echocardiography, Doppler echocardiography and myocardial Doppler tissue imaging are all used to evaluate right heart and provide accurate prognostic information especially when used in combination⁴. The systolic move-

ment of the base of the right ventricle (RV) free wall provides one of the most visibly obvious movements on normal echocardiography. Tricuspid annular plane systolic excursion (TAPSE) is a method to measure the distance of systolic excursion of the RV annular segment along its longitudinal plane, from a standard apical 4-chamber window⁵. In this study we investigated early effects of cancer chemotherapy, if any, on right ventricle in a relatively short time period in cancer patients who received folinic acid and fluorouracil (FUFA regimen) who have been treated with chemotherapeutics for the first time in their life.

Material and Methods

Study population

This study was done prospectively in patients with gastrointestinal system cancer (34 patients) treated with antineoplastic drugs at the Medical Oncology department of the Bulent Ecevit University School of Medicine between May 2010 and November 2012. The study was

conducted according to the recommendations of Declaration of Helsinki on Biomedical Research involving human subjects and was approved by the local Ethics Committee. Written informed consent was obtained from each participant. Inclusion criteria were disease of breast cancer with confirmed by histological cancer and left ventricular ejection fraction (LVEF) of more than 50% at baseline. We did not involve patients with a history of cardiac disease, diabetes mellitus, renal failure, arrhythmia on electrocardiography (ECG) and hypertension. Patients who had left or right ventricle dysfunction, pulmonary arterial hypertension or known valvular disease were excluded. Patients who had abnormal TAPSE values, RV dilatation and patients who had inadequate echocardiographic view since some of the patients have limited access after left-sided breast surgery were also excluded. All participants received FUFA chemotherapy protocol for colorectal, gastric and pancreatic cancer (fluorouracil 400-425 mg/m² intravenous day 1-5 + folinic acid 20-25 mg/m² intravenous day 1-5 every 28 days x6 cycles) with or without radiation therapy according to the cancer and patient status. All participants have undergone complete physical examination before the beginning of the chemotherapeutic regimen. Blood samples were obtained before the each cycle for complete blood count and biochemistry.

Echocardiographic analysis

Echocardiography (ECG) and electrocardiography were performed in all patients before the onset of chemotherapy and 6 months after the start of treatment. All echocardiographic examinations were performed using a General Electric Vivid-7 Echocardiography (GE-Vingmed Ultrasound AS, Horten, Norway) with a 2.5-3.5 MHz transducer in the left lateral decubitus position. Each examination was performed and recorded by the same expertise cardiologists, blinded to the chemotherapeutic status of the patients. Parasternal and apical projections were obtained according to the recommendations of the American Society of Echocardiography. Standard two-dimensional echocardiographic evaluation for left and right ventricular size and function was performed. Parameters of conventional echocardiography were integrated with tissue Doppler parameters.

Echocardiographic evaluation considered LVEF, early to late ventricular filling velocities (E/A), and tissue Doppler imaging (TDI) as Em/Am ratio [ratio between myocardial early diastolic velocity (Em) and myocardial atrial velocity (Am)] and total ejection isovolumic (Tei) index. LVEF was measured from the apical four-chamber view. To determine the TAPSE, an M-Mode cursor was placed at the junction of the tricuspid valve plane with the RV free wall, using the images of the apical four-chamber view. To measure the pulmonary acceleration time, pulsed Doppler was used to record the RV outflow tract systolic spectral signal, and time-to-peak duration of the spectral signal across the pulmonic valve was measured from the short-axis view. TDI values of the right and left

ventricles were obtained from the apical four-chamber view using a sample volume placed at the lateral corner of the tricuspid annulus; and anterior, inferior, medial, and lateral sections of the mitral annulus.

Statistical analysis

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) software, version 17 (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 and standard deviation or median and interquartile range (IR) (minimum–maximum) where appropriate. Degrees of association between continuous variables were calculated by Spearman's correlation analysis. Parameters were considered to be significant if p value was less than 0.05.

Results

Baseline characteristics of the study population (34 patients) showed in Table 1. There were no statically significant differences between the baseline and end of the treatment results according to the general characteristics. The mean age of the participants was 52.9 ± 5 years. All patients had surgery before the chemotherapy. Eighteen patients had rectal cancer, 11 patients had gastric cancer and the remaining 5 patients had pancreatic cancer. Fourteen patients received radiation therapy with the second or third chemotherapy cycles. Twenty five patients (74%)

Table 1: There is no significant change in baseline characteristics of the study population (34 gastrointestinal cancer patients), before and end of the chemotherapy with folinic acid and fluorouracil (FUFA regimen) chemotherapy, on right ventricle (RV) functions.

	Baseline	End of the treatment	p value
Age (years)	52.9 ± 5		
Systolic BP (mmHg)	129 ± 9	127 ± 12	0.6
Diastolic BP (mmHg)	82 ± 7	83 ± 10	0.75
BMI	23 ± 3.5	21 ± 2.5	0.4
WBC(10 ³)	6.8 ± 1.2	7 ± 0.9	0.9
PLT (10 ³)	210 ± 45	225 ± 40	0.7
Hb (g/dL)	11.5 ± 0.6	10.5 ± 0.8	0.6
AST (gr/dl)	37 ± 10	41 ± 5	0.3
ALT (gr/dl)	29 ± 8	30 ± 9	0.45
CK (IU/)	68 ± 12	75 ± 10	0.85
CK-MB (IU/L)	15 ± 6	20 ± 8	0.7

Values are shown as means ± standard deviation, BP: blood pressure, BMI: body mass index, WBC: white blood cell, Hb: hemoglobin, AST: Aspartate transaminase, ALT: Alanine transaminase, CK: creatine kinase.

completed all cycles of therapy while 5 patients (15%) had 5 cycles and 4 patients (11%) had 4 cycles of chemotherapy. None of the patients terminated the chemotherapy related to cardiotoxicity. At the baseline none of the patients had diabetes mellitus, hypertension and cardiac rhythm problem on the ECG. Following the 6 cycles of chemotherapy we did not find any cardiac arrhythmia on the last ECG evaluation; but there was a significant prolongation of QT dispersion (450 ± 30 ms vs 490 ± 44 ms, $p=0.006$), within no ventricular dysrhythmia. In addition we did not find any significant changes in P dispersion.

RV Functions

Echocardiographic measurements for the RV, mean RV thickness (RVT) C was 0.49 cm before chemotherapy and 0.62 cm at the end of the treatment ($p=0.29$). Mean TAPSE values were 2.08 ± 0.3 and 2.00 ± 0.39 cm, respectively ($p=0.25$). RV Tei index related to the chemotherapy did not change significantly (0.24 and 0.29, $p=0.07$, respectively). Also we did not find significant change in the RV end-diastolic diameter (RVEDD), RV end-systolic diameter, vena cava diameter on inspiration and expiration (Table 2).

Tissue Doppler and Left Ventricular Functions

We found a non-significant decrease in the isovolumic relaxation time (IVRT) related to the chemotherapy (92 ± 22 and 90 ± 24 , $p=0.83$) and there was no significant change in the isovolumic myocardial acceleration (IVA-

Table 2: Following folinic acid and fluorouracil chemotherapy there is no significant deterioration in the left ventricular ejection fraction value assessed by echocardiography as well as in right ventricular functions.

Parameter	Before (\pm SD)	After (\pm SD)	p
Left Ventricle			
LVEF (%)	$66\% \pm 3.3$	$64.8\% \pm 3.7$	0.069
MPI	0.53 ± 0.15	0.62 ± 0.18	0.065
Right Ventricle			
RVT (cm)	0.49 ± 0.12	0.62 ± 0.07	0.29
TAPSE (cm)	2.08 ± 0.3	2.00 ± 0.39	0.25
Tei index	0.24 ± 0.16	0.31 ± 0.21	0.19
RVEDD	3.65 ± 0.56	3.76 ± 0.56	0.25
RVESD	2.26 ± 0.4	2.24 ± 0.4	0.84
VCins.	1.17 ± 0.2	1.12 ± 0.2	0.44
VCexp.	1.76 ± 0.3	1.70 ± 0.3	0.88

LVEF: left ventricular ejection fraction, MPI: myocardial performance index, RVT: right ventricular thickness, TAPSE: tricuspid annular plane systolic excursion, Tei: total ejection isovolumic, RVEDD: right ventricular end diastolic diameter, RVESD: right ventricular end systolic diameter, VCins: vena cava diameter at inspiration, VCexp: vena cava diameter at expiration, SD: standard deviation.

RV), (7.2 and 7.0, $p=0.74$). LVEF decreased $66.0\% \pm 3.3$ to $64.8\% \pm 3.7$ following the chemotherapy ($p=0.069$) but there was no statistical significance. Myocardial performance index (MPI) was non-significantly slightly increased after the chemotherapy ($p=0.065$).

Discussion

In this study we examined in 34 cancer patients, echocardiography parameters and tissue Doppler, and we found that bolus FUFA regimen did not change significantly RV functions and LVEF clinically.

5-FU is in the center of the cancer chemotherapy especially in gastrointestinal tract adenocarcinomas. Beside been an effective agent, 5-FU has also several undesired cardiac side effects, such as coronary vasospasm, coronary thrombosis, cardiomyopathy, and sudden cardiac death⁶. It has been shown that treatment with 5-FU chemotherapy causes cardiac adverse events with an incidence of 1.6 to 8.0%⁷ and this incidence could be increased nearly 10 times, in patients with underlying cardiac pathology compared to those without cardiac problems⁸. In their study Oztop et al, revealed that, echocardiography did not show any significant change in either systolic or diastolic functions in 22 patients with gastrointestinal cancer who received FUFA chemotherapy⁹. In addition, the authors found that FUFA chemotherapy prolonged the QT dispersion in ECG analysis, so that, they advocated that this regimen may be a predictive factor for malignant arrhythmias but they did not investigate the RV functions by echocardiography. In another study Tanrıverdi et al, investigated the long-term effect of trastuzumab on QT dispersion and also they found that patients with breast cancer treated with trastuzumab after an anthracycline-based regimen had significantly higher QT dispersion compared to the non-treated patients (0.064 ± 0.023 sec vs. 0.051 ± 0.016 sec, respectively)¹⁰. In a recent study anthracycline-based chemotherapy did not change significantly the QT dispersion, but prolonged P dispersion, in a pediatric population¹¹. In our study also, we didn't find any deterioration in LVEF by echocardiography but we found a significant prolongation of QT dispersion as Oztop et al; however, in our study there was no clinical arrhythmia in the ECG analyses.

To our knowledge, there are no studies investigating the RV functions changes especially with TAPSE and Tei index, following the administration of FUFA regimen. The cardiac toxicity of 5-FU is well known but we are not aware of its possible clinical or subclinical effects on RV. RV dysfunction is associated with an adverse outcome in patients with left ventricular dysfunction¹². Determining of RV function by echocardiography has some limitations, inability to represent the complex shape of the RV. Based on the observation that the contraction pattern of the RV, unlike the left ventricle, begins at the RV sinus and ends at the infundibulum and RV outflow tract, and that the RV free wall consists predominantly of longitudinal myocardial fibers, the TAPSE has been shown to correlate with RV ejection fraction^{13,14}. In addition TAPSE

is an independent predictor for survival, doubling of the value of TAPSE is associated with a 26% reduction in mortality, so assessing the RV functions by TAPSE is a reliable method¹⁴. In our study, TAPSE did not increase by the treatment with FUFA regimen, meaning that this regimen did not cause negative side effects to RV in acute term of chemotherapy.

In addition to the TAPSE, Tei index is a valuable method to measure of systolic and diastolic function and it is well correlated, compared with invasive methods¹⁵. It has been shown that higher values of Tei index has worse prognosis for assessing the RV function¹⁶. Specifically relating to anthracyclines, the Tei index has been used to evaluate their effect on cardiac function in the pediatric population¹⁷. Eidem et al, have found that there were no significant changes in Tei index in patients under treatment with anthracycline chemotherapy¹⁸. To our knowledge, this is the first study to demonstrate a differential effect on RV function associated with the use of FUFA regimen in the adult cancer patients and we didn't find any deterioration in RV functions assessed by Tei index.

This study also has some limitations; limited number of patients and short term of follow up period been the major limitations.

Conclusion

This is the first study investigating the relationship of RV functions, assessed with TAPSE, and bolus FUFA regimen, which is one of the most common chemotherapy regimens. It is well known that 5-FU can cause cardiac side effects especially in patients with underlying cardiac pathology. In this study basal cardiac examinations were normal in all patients and we did not find any deterioration in right and left ventricular functions following by the FUFA regimen.

Conflict of interest

Authors report no conflict of interest.

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