RESEARCH ARTICLE / *Araştırma Makalesi*

The Effect of Anthracycline Chemotherapy on Arterial Stiffness

Antrasiklin Kemoterapisinin Arteriyel Sertlik Üzerine Etkisi

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Geliş Tarihi / Received : **12.01.2020** Kabul Tarihi / Accepted : **21.04.2020**

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(Sakarya Tıp Dergisi / ***Sakarya Med J*** **2020, 10(2):191-196) DOI: 10.31832. 673754**

Abstract

Objective	Anthracycline-derived chemotherapy for cancer treatment may cause dose-dependent irreversible heart failure. Arterial stifness is a predictor of cardiovascular events. We aimed to investigate the relationship between chemotherapy and arterial stiffness.
Materials and Methods	Patients diagnosed non-Hodgkin's lymphoma, agreed to recieve anthracycline chemotherapy, were included in the study. Arterial stiffness was evaluated with applanation tonometer before, first and sixth cycles of chemotherapy.
Results	There was a tendency to increase first and sixth cycles pulse wave velocity values before anthracycline chemotherapy [9.08 (8.12-9.76), 10.31 (8.22-12.62), 9.64 (8.22-12.62) m/s, p = 0.053] but those changes were not reach statistically significance. Augmentation index change did not significantly change between anthracycline chemotherapy cycles (p = 0.810). There was also a tendency to decrease first and sixth cycle subendocardial viabilty ratio values before 151.60 (122.20-188.70) and after 124.30 (94.50-154.10), p = 0.058 chemotherapy.
Conclusion	Anthracycline chemotherapy tends to impaire arterial stiffness parameters.
Keywords	Chemotherapy; arterial stiffness; anthracycline

Öz

Amaç	*Kanser tedavisinde kullanılan antrasiklin türevli kemoterapi doz bağımlı olarak geri dönüşümsüz kalp yetersizliğine sebep olabilmektedir. Arteriyel sertlik kardiyovasküler olayların öngördürücüsüdür. Kemoterapi ile arteriyel sertlik arasındaki ilişkiyi araştırmak amaçlandı.*
Gereç ve Yöntemler	*Çalışmamıza, Hodgkin dışı lenfoma tanısı alan ve antrasiklin kemoterapisi alacak olan hastalar dahil edildi. Hastaların kemoterapi öncesi, ilk ve altıncı kür kemoterapi sonrası arteryel sertlik parametreleri aplanasyon tonometri ile değerlendirildi.*
Bulgular	*Antrasiklin kemoterapi sonrası 1.kür ve 6.kür nabız dalga hızı değerlerinde bazale göre artış eğilimi vardı [9.08 (8.12-9.76), 10.31 (8.22-12.62), 9.64 (8.22-12.62) m/s, p = 0.053]. Antrasiklin kemoterapisiyle augmentasyon indeksinde anlamlı değişim olmadı (p=0.810). Tedavi öncesi bazal ve altıncı kür kemoterapi sonrası subendokardiyal viabilite oranı değerlerinde azalma eğilimi vardı. [151.60 (122.20-188.70) and 124.30 (94.50-154.10), p = 0.058].*
Sonuç	*Antrasiklin kemoterapisi arteriyel sertlik parametlerini bozma eğilimi göstermektedir.*
Anahtar Kelimeler	*Kemoterapi; arteriyel sertlik; antrasiklin*

INTRODUCTION

Chemotherapy plays a major role in the management of cancer patients. Anthracycline based chemotherapy developed important improvement in the management of solid and hematologic malignancies.[1] Despite this success, anthracyclines also have undesirable effects. Cardiotoxicity is the best known and may be the most important one. It can occur weeks or months after exposure of anthracyclines.[2-4] Toxicity causes myocardial injury and subsequently reduction of left ventricular ejection fraction (LVEF) can lead to congestive heart failure (HF). It is important to define patient at risk and predict before HF develops.

Arterial stiffening generally occurs as a consequence of multiple factors such as individual properities (e.g.biological aging) and chronic diseases (e.g hypertension, diabetes, coronary artery disease).[5] Stiffening in the larger central arterial system significantly associated with systolic hypertension, coronary artery disease, stroke and heart failure.[6-8] Also stiffining large arteries increase left ventricular (LV) afterload thus causes LV hypertrophy. As a consequence of these pathological processes HF can be developed. It has been shown that anthracyclines could impaire arterial stiffness in cancer patients at the mid and long term.[9,10] In this study we aim to compare arterial stiffness parameter differentiations between chemotherapy cycles in non-Hodgkin's lymphoma patients.

MATERIAL and METHODS

This study was approved by Karadeniz Technical University Ethic committee (Approved number: 2012/170 and date:12.02.2013), all participants provided informed consent. This study was prognostic cohort study. The study consisted of 10 newly diagnosed non-Hodgkin's lymphoma patients who agreed to recieve 6 cycle anthracycline based chomethrapy. Patients were enrolled the study between march 2013 to december 2013. Patients with history of coronary artery disease, heart failure, chronic kidney disease, carotid sinus syndrome and/or unable to measure arterial stiffness parameters because of local infection were excluded.

Measurement of Arterial Stiffness

SphygmoCor system (AtCor Medical, Sydney, Australia) was used to assess the arterial wall properties with the foot-to-foot method for aortic pulse wave velocity (PWV).[11]Aortic PWV was calculated with the time shift between the appearance of both waves at the first and the second sites. The distance between the carotid to femoral side was measured on the body surface to determine aortic PWV. The average of measurements gained from calculation over 9-10 cardiac cycles of a period after the exclusion of extreme values. Radial artery pressure waveforms were recorded at the wrist, using applanation tonometry with a high-fidelity micromanometer (Millar Instruments, Houston, Texas). After 20 sequential waveforms had been acquired and averaged, a validated generalized mathematical transfer function was used to synthesize the corresponding central aortic pressure waveform.[12] Augmentation index (AIx) and augmentation pressure (AP) were derived from this with the technique of pressure waveform analysis.[11] The AIx was defined as the AP divided by pulse pressure and expressed as a percentage. AIx is dependent upon the elastic properties of the entire arterial tree (elastic and muscular arteries). In addition, because AIx is influenced by heart rate, an index normalized for heart rate of 75 bpm (AIx@75) was used which described before.[13] Only high-quality recordings, defined as an in-device quality index of > 80% were included in the analysis. All measurements were performed with the patient in the supine position in a quiet temperature-controlled room after a brief rest period of at least 5 minute by an experienced cardiologist. All parameters were measured for each patient within 24 hours at baseline, after first and sixth cycle of chemotherapy.

Echocardiography

All patients were evaluated in the echocardiography laboratory using a Vivid 7 system (GE Vingmed Ultrasound, Horten, Norway). Echocardiographic examination was

performed in the left lateral outward position in all subjects on standard parasternal and apical images. Left ventricular end systolic and diastolic diameters and volumes and diastolic function parameters were measured within 24 hours after basal and final chemoteraphy cycles. Ejection fraction was measured with modified Simpson's method.

Statistical analysis

Statistical analyses were performed by using the SPSS software (Version 23.0, SPSS, Inc., Chicago, IL). Variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they were normally distributed. All variables were non-normally distributed and they were represented using median, minimum and maximum values. For continuous dependent variables Freidman test was used to compare the differences. After Bonferroni correction p-values less than 0.017 were considered statistically significant. After the significance determined Wilcoxon test was used to compare binary groups. A p-value less than 0.05 were considered statistically significant to this subanalysis.

RESULTS

The median age of the patients was 52 years old and 80% were female. Other characteristics of the patients are given in Table 1. The mean total cumulative dose of doxorubicin treatment was 436 ± 94 mg /m2 of all patients. Before and after chemotherapy LV end-systolic diameter (LVSD) (27 and 29 mm, p = 0.010 respectively) was significantly increased and LVEF was significantly decreased (65.50 to 62 %, p <0.05). The Tei index was found to be similar with at the baseline and after sixth chemotherapy cycles. Table 2 shows echocardiographic data of the study patients before and after chemotherapy.

Table 1.Baseline demographic and laboratory parameters of the study patients (n=10)

Variables	Values
Age (years)	52 (36-68)
Female gender, n %	8 (80%)
Hypertension, n (%)	2 (20%)
Dyslipidemia, n (%)	2 (20 %)
Smoking, n (%)	1 (10 %)
ACE inh., n (%)	2 (20%)
Beta blocker, n (%)	2 (20 %)
Statin, n (%)	2 (20 %)
BMI (kg/m2)	25 (22-29.50)
BSA (m2)	1.80 (1.60-1.90)
Systolic blood pressure, mmHg	124.50 (111.50-133.50)
Diastolic blood pressure, mmHg	75 (67-82)
Glucose (mg/dl)	90 (77-101)
Creatinine (mg/dl)	0.82 (0.66-1.01)
Hemoglobin (g/dl)	12.30 (11.70-12.90)
Platelet (103/mm3)	259 (188-302)

All continuous variables represented as median (min-max). Categorical variables represented as number and precentages.
Abbreviations: SD: Standart deviation, ACE: Angiotensinogen converting enzyme, BMI: Body mass index, BSA: Body surface area

Table 2. Echocardiographic data of the study patients before and after chemotherapy

Variables	Before chemotherapy	After chemotherapy	p value
LVSD (mm)	27 (23.50-31)	29 (26.50-31.50)	**0.010**
LVDD (mm)	44.50 (42-49.50)	47 (44-50.50)	0.060
LVSV (ml)	31 (23.50-38)	33.50 (25-41)	0.400
LVDV (ml)	90.40±23.20	83±10.20	0.240
EF (%)	65.50 (63-68.50)	62 (59-65.50)	**0.010**
LA (mm)	34.50 (31.50-36-50)	35 (32-38)	0.320
E/A	1.24 (1-1.55)	1.1 (0.90-1.30)	0.220
DT (ms)	238.90 (155.40-291.50)	196.70 (145.60-233.80)	0.180
Tei index	0.34 (0.26-0.45)	0.32 (0.23-0.42)	0.130

All continuous variables represented as median (min-max). Categorical variables represented as number and precentages. Wilcoxon test was used to compare the groups.
Abbreviations: SD: Standart deviation,LVSD: Left ventricule systolic diameter, LVDD: Left ventricule diastolic diameter, LVSV: Left ventricule systolic volume, LVDV: Left ventricule diastolic volume, EF: Ejection fraction, LA: Left atrium, DT: Deceleration time

A statistically significant difference was not found between all groups PWV values [9.08 (8.12-9.76) vs 10.31 (8.22-12.62) and 9.64 (8.22-12.62); baseline, first and sixth cycles of chemotherapy, respectively p = 0.053] (Figure 1A)

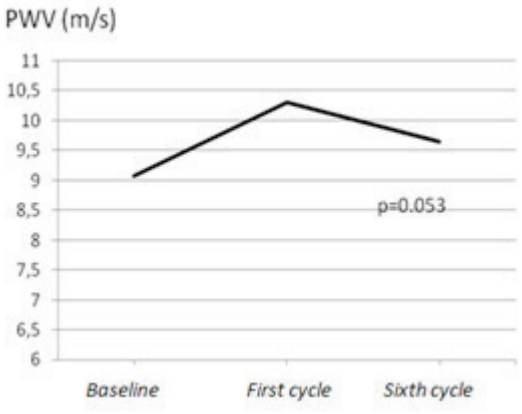
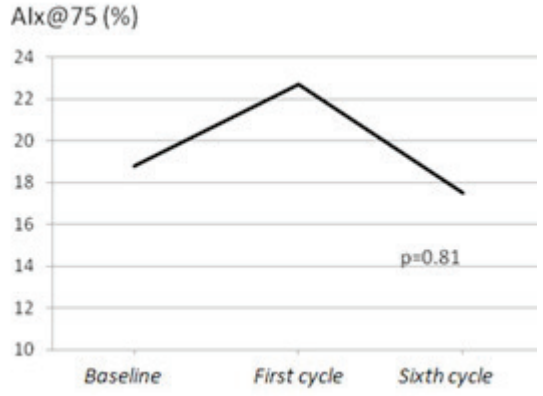


Figure 1. Arterial stifness parameters changes between baseline and after chemotherapy cycles. A (upper): PWV, B (lower): AIx@75 (%), C (right): SEVR (%)

Also AIx @ 75 % values were not found to be statistically different between baseline and anthracycline chemotherapy cycles (p=0.400) (Figure 1B)



The median basal subendocardial viability (SEVR %) rate was 151.60. The SEVR % decreased to 130.60 after first cycle but not statistical signifcantly (p=0.060). However SEVR % was significantly decreased after sixth cyle of chemotherapy compared to baseline [151.60 (122.20-188.70) vs 124.30 (94.50-154.10), p=0.047] (Figure 1C).

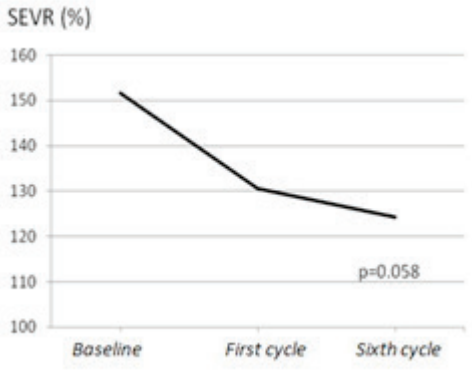


Table 3 presents the median values of baseline, first and sixth cycle chemotherapies arterial stiffness parameters.

Table 3. Arterial stiffness parameters between all chemotherapy cycles

Variables	Baseline	First cycle	Sixth cycle	p value
PWV, m/s	9.08 (8.12-9.76)	10.31 (8.22-12.62)	9.64 (8.22-12.62)	0.053
AP, mmhg	8.60 (2-15.50)	9.40 (2.80-14.40)	8 (2-12.40)	0.547
AIx@75, %	18.80 (7-27.80)	22.70 (9-33.60)	17.50 (4-33.70)	0.810
SEVR, %	151.60 (122.20-188.70)	130.60 (98-160.60)	124.30 (94.50-154.10)	0.058
Heart rate, bpm	69 (58-71)	72 (60-84)	77 (69-86)	0.121

All continuous variables represented as median (min-max). Categorical variables represented as number and precentages. Freidman test was used to compare the differences between all gropus. After the significance determined Wilcoxon test was used to compare binary groups
Abbreviations: SD: Standart deviation, PWV: Pulse wave velocity, AP: Aortic augmentation pressure, AIx@75: Augmentation index normalized with 75 bpm heart rate, SEVR: Subendocardial viability rate

DISCUSSION

Our study results revealed between anthracycline chemotherapy cycles PWV increased, SEVR decreased, AIx not changed. But all those changes did not reach statistically significance. Those findings have some contributions to the management of cancer survival patients.

Patient and therapy related risk factors play important role in chemotherapy induced HF.[14] Patient related risk factors

were advanced age, hypertension, diabetes mellitus and coronary artery disease.[15] In our study 20% of patients had hypertension and they were at the mid ages. Therapy related risk factors mainly related to total cumulative dosage of anthracyclines. Also combination of cancer therapy with other chemotherapeutic agents and mediastinal irradiation increase the risk. The total cumulative dosage exceed 400–600 mg/m2 HF risk increased.[15] Our study patients were consisted of non-Hodgkin lymphoma with same therapy cycle protocole and they did not recieve mediastinal irradiation but recieved 436 ± 94 mg /m2 total cumulative dosage which potantially had a risk of HF developing. In the literature anthracycline cardiotoxicity is defined as 20% and more decrease in LVEF when baseline LVEF is normal (≥50%), or 10% or more decrease when baseline LVEF is not normal.[16] There were significantly LVEF reduction determined in our study but those levels were not met the systolic dysfunction level. Also the Tei index, which shows global (systolic and diastolic) function of LV, was not affected by the exposure of anthracycline chemotherapy. Between anthracycline therapy cycles arterial stiffnes tent to impaire in our study. Thus could be an early marker of subclinical changes.

The mechanism of anthracycline-induced cardiotoxicity remains unclear, though it is likely to be reactive oxygen species related DNA damage.[17] Anthracyclines cause nitric oxide (NO) synthesis corruption in vascular endothelium and thus cause endothelial dysfunction.[18,19] It has been shown that decreased nitric oxide production was associated with arterial stiffnes.[20] In addition, a decrease in total antioxidant capacity levels also has been shown to be associated with arterial stiffness.[21] These effects of anthracyclines may lead to an increase arterial stiffness parameters in the first encounter and after-treatment. Recently a magnetic resonance imaging modality used arterial stiffness measurements study showed within 4 months of exposure to an anthracycline results a significant increase in aortic stiffness.[10] This study consisted of 53 solid and hematologic malignency patients. They found aortic distensibility and PWV were related aortic stifness that is an independent predictors of cardiovascular diseases. We used an another arterial stiffness measurement method which was well established and had an at the border changes PWV and other aortic stiffness parameters.

Our study has some limitations. First is the small number of patients. Second we did not follow patients' HF symptoms and thus prevented to compare the relation between subclinical ejection fraction impairment with clinical symptoms.

In conclusion, arterial stiffness parameters might be use for a marker of subclinical myocardial dysfunction of anthracycline chemotherapy patients. Needs for further clinical follow up trials to show also arterial stiffness parameters could be a potential marker in the long term.

This study was approved by Karadeniz Technical University Ethic committee (Approved number: 2012/170 and date:12.02.2013), all participants provided informed consent

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