İstanbul Med J 2019; 20(6): 528-34
DOI: 10.4274/imj.galenos.2019.09734

Investigation of Subclinical Cardiotoxicity in Chronic Leukemia Patients with Non-invasive Tests

Kronik Lösemi Hastalarında Subklinik Kardiyotoksisitenin Non-invazif Testler ile Araştırılması

Timor Omar[1], Rasim Enar[2], Barış İkitimur[2], Burçak Kılıçkıran Avcı[2]

[1]Kars Harakani State Hospital, Clinic of Cardiology, Kars, Turkey
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Cardiology, İstanbul, Turkey

ABSTRACT

Introduction: This study aimed to investigate the left ventricular function and electrocardiographic findings in patients with chronic leukemia receiving and not receiving chemotherapy during a one-year follow-up.

Methods: A total of 111 patients with chronic leukemia were included in the study. Electrocardiographic and mechanical findings of the heart were evaluated by surface 12-lead electrocardiogram and 2-dimensional transthoracic echocardiography, and cardiac troponin (cTn) was evaluated for myocyte damage and B-type natriuretic peptide marker for heart failure at baseline, 6th month and 12th month.

Results: During the study, a total of six patients reached the endpoint, including two patients to primary endpoint (atrial fibrillation) and four patients to secondary endpoint (non-cardiac death). However, asymptomatic hemodynamic and electrocardiographic changes were observed in all patients who did not reach the endpoint. There was a quantitative decrease in left ventricular ejection fraction and an increase in the rate of diastolic dysfunction. Increased incidence of fragmented QRS, and prolongation of QT interval and QT dispersion, which are important indicators of possible cardiac events, were detected. cTn levels were observed to be at the upper limit of the normal range. All these findings show that myocardial damage has begun in the study patients, even if it is asymptomatic.

Conclusion: In order to prevent future cardiac events in this patient group, these changes need to be taken into consideration and closely monitored.

Keywords: Chronic leukemia, heart failure, cardiotoxicity

ÖZ

Amaç: Kemoterapi alan ve almayan kronik lösemi tanılı hastalarda 1 yıllık izlemde sol ventrikül fonksiyonunun ve elektrokardiyografik bulgularının araştırılması amaçlanmıştır.

Yöntemler: Kronik lösemi tanılı 111 hasta çalışmaya alındı. Başlangıçta, 6. ve 12. aylarda kalbin elektrokardiyografik ve mekanik bulgularına yüzeyel 12-derivasyonlu elektrokardiyogram ve 2-boyutlu transtorasik ekokardiyografi ile, bunun yanında miyosit hasarının önemli belirteci olan kardiyak troponin (cTn) ve kalp yetersizliğinin belirteci B-tipi natriüretik peptid düzeyleri bakılıp karşlaştırıldı.

Bulgular: Çalışma süresince 2 hasta birinci (atriyal fibrilasyon), 4 hasta ikinci sonlanım noktası (kardiyak olmayan ölüm) olmak üzere toplam 6 hasta sonlanım noktasına ulaştı. Ancak asıl önemli olan sonlanım noktasına ulaşmayan hastaların tamamında, asemptomatik olmak ile beraber, takipte hemodinamik ve elektrokardiyografik değişiklikler gözlendi. Sol ventrikül ejeksiyon fraksiyonunda kantitatif olarak düşme görülürken diyastolik disfonksiyon görülme oranında da artış görüldü. Olası kardiyak olayların önemli göstergeleri olan fragmante QRS görülme oranında artış, QT intervali ve QT dispersiyonunda uzama olduğu tespit edildi. cTn düzeyinin normal aralığın üst sınırında seyrettiği görüldü. Bunların hepsi çalışma hastalarında, asemptomatik olsa bile, miyokard hasarının başladığını, ancak daha başlangıç aşamasında olduğunu göstermektedir.

Sonuç: Bu hasta grubunda gelecekteki olası kardiyak olayların önlenebilmesi için bahsi geçen değişikliklerin daha başta dikkate alınması ve yakın takip gerekmektedir.

Anahtar Kelimeler: Kronik lösemi, kalp yetersizliği, kardiyotoksisite

Address for Correspondence/Yazışma Adresi: Timor Omar MD, Kars Harakani State Hospital, Clinic of Cardiology, Kars, Turkey
Phone: +90 531 910 95 30 **E-mail:** tbigmurad@gmail.com **ORCID ID:** orcid.org/0000-0002-2481-0505

Cite this article as/Atıf: Omar T, Enar R, İkitimur B, Kılıçkıran Avcı B. Investigation of Subclinical Cardiotoxicity in Chronic Leukemia Patients with Non-invasive Tests. İstanbul Med J 2019; 20(6): 528-34.

Received/Geliş Tarihi: 27.12.2018
Accepted/Kabul Tarihi: 04.09.2019

©Copyright 2019 by the İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.
©Telif Hakkı 2019 İstanbul Eğitim ve Araştırma Hastanesi/İstanbul Tıp Dergisi, Galenos Yayınevi tarafından basılmıştır.

Introduction

Despite all the advances in medicine, cardiovascular diseases (CVD) and malignancies are the leading causes of death in the world (1). Although there is enough information about diagnosis and treatment when CVD and malignancies are evaluated separately, there is not enough information about how a treatment strategy if both diseases occur in the same individual.

Although it has been shown in many studies that agents used in chemotherapy (CT) adversely affect left ventricular (LV) function, there are not many studies in the literature showing the effect of malignant blood diseases on LV function (2-4). For this purpose, in this study, the effects of the primary effects of the disease on the mechanical and electrocardiographic functions of the heart were investigated.

Lymphoproliferative diseases such as leukemia and lymphoma are diseases that have effects on many organs through inflammation and mediators such as cytokines, hormones, etc. (5). It is also possible to think that it may negatively affect heart function using various mediators released into the environment. Myocardial injury may result in cardiomyopathy (CMP) and heart failure (HF). HF can be in the form of a decrease in LV ejection fraction (LVEF), or EF can be preserved. In recent studies, HF with preserved EF accounts for 50% of HF (6-8).

Tests and markers used in the diagnosis and prognosis of myocardial injury or developing HF in cancer patients include a surface 12-lead electrocardiogram (ECG), 2-dimensional transthoracic echocardiography (TTE), cardiac troponin (cTn), B-type natriuretic peptide (BNP), and some other blood markers (9-11).

High sensitivity cTn has been suggested to be used in the diagnosis of diseases other than non-myocardial infarction. An increase in cTn levels in the early and late post-CT period is associated with an increased incidence of cardiac events (12). Abnormal ECG findings are observed in the majority of patients with HF that developed as a result of myocardial injury (13,14). Again, TTE is an excellent method for demonstrating cardiac function. While it is a good test to show the size of the cardiac cavities and LVEF, it also helps to show HF with preserved EF (15,16).

Fifty percent of the asymptomatic patients with normal LVEF after CT have diastolic dysfunction (16). Significant echocardiographic changes after CT can be observed in most cases, while no signs and clinical symptoms of cardiotoxicity are present (17). The abovementioned biomarkers may help detect structural damage due to cardiotoxicity at an early stage.

The specific treatment of HF caused by CT has not been widely studied. Angiotensin-converting enzyme (ACE) inhibitors (ACEi) increased LVEF in breast cancer patients treated with epirubicin; therefore, ACEi should be part of the treatment of LV dysfunction in cancer patients. It has been shown that the addition of β-blockers (Bb) to ACEi in LV dysfunction following doxorubicin and imatinib treatment improves LVEF more significantly than those receiving ACEi alone. LVEF was significantly improved with the combined treatment of ACEi and Bb in CT-induced CMP (18,19).

This study aimed to investigate the LV function and electrocardiographic findings in patients with chronic leukemia receiving and not receiving CT during a one-year follow-up.

Methods

Between March 2014 and April 2015, 111 chronic myeloid leukemia (CML) and chronic lymphocytic leukemia (CLL) patients who were followed in the hematology outpatient clinic of Cerrahpaşa Medical Faculty were included in the study.

Each patient was informed about the scope of the study, and written consent was obtained for participation in the study. The study was evaluated by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee, and ethical approval was obtained (decision no: 83045809/604.01/02-14160).

At the beginning of the study, the patient's history was taken, and the risk factors (RF) were questioned. Initial physical examinations were performed, blood samples were analyzed, resting ECG and TTEs were recorded, and the same procedures were repeated at 6 and 12 months. The analyzed data were compared in all of the patients, as well as between age (median age of 55) and gender subgroups.

Inclusion Criteria

Patients over 18 years of age (with or without CT) with a diagnosis of CML and CLL were included. Patients with a history of CVD, HF, and CMP, signs of LV hypertrophy on ECG, stroke, atrial fibrillation (AF), and malignant arrhythmia were not included in the study.

Endpoints

The primary endpoints were hemodynamic impairment, symptomatic or asymptomatic LV systolic dysfunction (5-10% decrease in LVEF in TTE) or diastolic dysfunction of stage 2 and above, malignant arrhythmia (ventricular tachycardia, AF with rapid ventricular response), atrioventricular and interventricular blocks, cardiovascular mortality, and increase in cTn level 20% above 99. percentil of standard value. The secondary endpoints were death due to non-cardiac causes.

Electrocardiographic Parameters and Their Definitions

The ECGs of the patients were recorded in the supine position (Schiller AT-2 Plus, 9.025000C, Baar, Switzerland).

P Wave Dispersion: The difference between the longest p wave and the shortest p wave duration in the ECG.

QT dispersion: The difference between the longest QT interval and the shortest QT interval in the ECG.

Fragmented QRS (fQRS): The presence of r'- R'- s' - S' wave in any lead in the ECG (Figure 1).

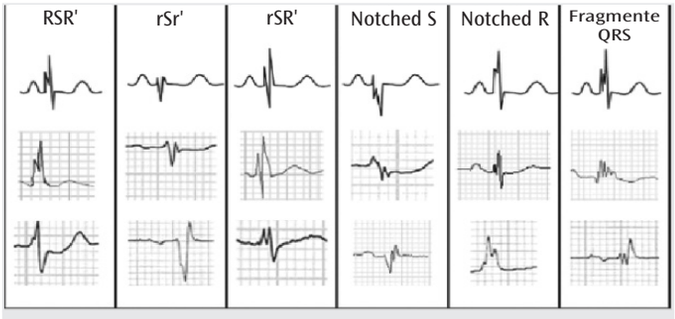

Figure 1. Fragmented QRS examples

Echocardiographic Evaluation

Two-dimensional images from apical 4th, 3rd and 2nd chambers, parasternal short and long axis in accordance with the recommendation of the AHA 2015 echocardiography guide using GE Vingmed System Five (GE Vingmed Ultrasound, Horten, Norway) and 2.5 MHz probe (70-80 frame) were obtained with standard methods in TTE, and cardiac cavities and wall thickness, systolic and diastolic ventricular functions of the patient were examined and calculated (20).

LVEF: After the mean systolic and end-diastolic volume measurements were obtained from three repeated measurements of apical four chambers and parasternal short-axis during consecutive heart cycles using the classical two-dimensional and modified Simpson rule method, the mean EF values obtained for each cycle were recorded.

Pulmonary Hypertension: Tricuspid regurgitation (TR) jet velocity was measured from apical four chambers, right ventricular entrance or parasternal short axis windows as much parallel as to continuous-wave Doppler insufficiency jet at the end of the diastole while the patient exhaled as much as possible and held the breath. The pulmonary artery systolic pressure (PASP) was calculated by excluding pulmonary stenosis, assuming right ventricular systolic pressure to be equal to PASP, using the Bernoulli equation from the TR rate and adding estimated right atrial pressure. PASP above 25mmHg was accepted as pulmonary hypertension (PH).

Diastolic Dysfunction: It was calculated by measuring e' by tissue Doppler, and E, A, E/A waves by checking transmitral jet velocities by PW Doppler.

Heart Failure: It was accepted as having an LVEF of 45% or less or diastolic dysfunction of stage 2 or more in TTE.

Statistical Analysis

In our study, we compared the findings of the patients in each of the three follow-up examinations, and gender subgroups and age subgroups (55 years of age was accepted as RF for CVD) were also compared among themselves. Statistical analysis was performed with SPSS v21.0. The statistical significance level was accepted as $p<0.05$. Normality assessments were made by Kolmogorov-Smirnov and Shapiro-Wilk tests. A chi-square test was used to compare categorical data, and the Mann-Whitney U test was used to compare continuous data. For repeated measures, ANOVA was used for continuous variables, and Cochran Q was used for categorical variables obtained during follow-up examinations. ANOVA test results were evaluated with Pillai's Trace. Post-hoc evaluations were performed with Bonferroni. When comparing the changes between groups, the model was evaluated by a single group. Significance in the Cochran Q test was assessed using the McNemar test as a post-hoc binary comparison test.

Results

Of the 111 patients in our study group, 67 were male, and 44 were female. The percentages of specific malignant diseases in our study group were similar: CML was 52.3%, and CLL was 47.7% (Table 1). In the age subgroup, CML and CLL rates were 72.2% and 27.8%, respectively, at <55 years of age, whereas it was 33.3% and 66.7% at >55 years of age. Accordingly, CML was significantly higher at <55 years, and CLL significantly higher at >55 years ($p<0.001$).

During the study, a total of six patients reached the endpoint, including two patients to primary endpoint (AF) and four patients to secondary endpoint (non-cardiac death). AF developed in two patients in the third and fifth months. Both were male, and one had CML, and the other had CLL. One of them had asymptomatic LV dysfunction (LVEF: 55% at baseline; 35% and 40% at follow-up). Four patients died in the second half of the study due to non-cardiac causes. Three of them were CLL, one was CML, and two were male, and two were female. All patients reaching the endpoint were above the median age of 55 years.

The Use of CT in Our Patients: As expected, it was significantly higher in CML patients than in patients with CLL (91.4% vs. 32.1%, $p=0.001$). Proportional to this, PR dispersion, f(QRS) and diastolic dysfunction were higher in the CML group ($p=0.01$; $p=0.05$; $p=0.03$, respectively, at baseline, first and second follow-up) (Table 2).

Table 1. Demographic features

Age (mean ± SD)	53.18±13.05	
Height (mean ± SD)	168.19±7.75	
Risk factors		
Smoking (n, %)	22	19.8
HT (n, %)	35	31.5
DM (n, %)	23	20.7
CRF (n, %)	0	0
Alcohol (n, %)	0	0
Hyperlipidemia (n, %)	18	16.2
Gender		
Male (n, %)	67	60.4
Female (n, %)	44	39.6
	111	100
Disease		
CML (n, %)	58	52.3
CLL (n, %)	53	47.7
Median age		
<55 (n, %)	54	48.6
≥55 (n, %)	57	51.4

SD: standard deviation, HT: hypertension, DM: diabetes mellitus, CRF: chronic renal failure, CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia

Table 2. Comparison of electrocardiographic and dynamic changes in CML and CLL patients

	CML	CLL	p
Number (n)	58	53	-
CT rate (%)	91.4	32.1	0.001
PR dispersion (ms)	2.57±5.24	1.95±5.15	0.014
QT dispersion (ms)	27.45±13.71	24.83±15.72	0.036
fQRS (%)	63.7	47.1	0.05
Diastolic dysfunction (%)	65.5	47.1	0.039

CML: chronic myeloid leukemia, CLL: chronic lymphocytic leukemia, CT: chemotherapy, fQRS: fragmented QRS complex

When TTE findings were evaluated, EF was 62.0% at baseline, and 61.8% and 61.1% in the first and second follow-up, respectively. Even if there was only 0.2 and 0.9 decrease (<1.0) in the absolute value at follow-up compared to the baseline EF value (relative decrease of 1.45%), it was statistically significant (p=0.018). The mean PASP values were 22.48 mmHg at baseline and 22.94 mmHg and 24.06 mmHg, respectively, at follow-up. Although PASP did not meet the diagnostic criteria for PH, it was significantly increased in the second follow-up when compared to the baseline (p=0.001). The incidence of diastolic dysfunction was found in 35.2% of the patients at the beginning and in 36.2% and 47.6% of the patients, respectively. At the end of the follow-up, the diastolic dysfunction rate increased significantly in the second half of the follow-up period (p<0.001). The incidence of PH was 17.9% at baseline and 22.9% and 31.4%, respectively (p<0.001) (Table 3).

In our study, the mean value of PR dispersion calculated on ECG was 0 at baseline and then measured as 1.19±4.07 ms and 2.57±5.10 ms at the follow-up, respectively. It was found to increase significantly at the follow-up (p<0.001). The incidence of fQRS was 7.2% at baseline, and 20% and 46.7% at follow-up, respectively, and it increased significantly (p<0.001). The mean QT dispersion was 23.24±13.37 ms at baseline, while it was measured 25.14±15.48 ms and 26.48±14.44 ms during follow-up. It was increased significantly (p=0.004). Again, this increase was higher in men than in women (p=0.03) (Table 4).

The mean cTn value was measured as 0.0047±0.0028, 0.0053±0.0032 and 0.0067±0.0012, respectively, at baseline and at follow-up (p=0.012). cTN increase was continuous during follow-up (baseline vs. first follow-up: p<0.001; baseline vs. second follow-up: p=0.001; first follow-up vs. second follow-up: p=0.001) (Table 5).

Table 3. Transthoracic echocardiography findings

	Baseline	First follow-up	Second follow-up	p
EF (%)				
Total	62	61.8	61.1	0.018
Male	61.4	61.3	60.4	0.48
Female	63	62.7	62.3	0.48
<55 years	62.7	62.6	62.3	0.59
≥55 years	61.2	61.02	59.9	0.59
PASP (mmHg)				
Total	22.48	22.94	24.06	0.001
Male	22.34	22.67	24.27	0.001
Female	22.68	23.37	23.73	0.03
<55 years	22.58	23.4	23.8	0.045
≥55 years	22.38	22.49	24.3	0.001
DD (%)				
Total	35.2*	36.2	47.6*	<0.001*
Male	32.8	35.9	46.8	0.002
Female	34	36.5	73.1	0.03
<55 years	28.8	30.7	34.6	0.24
≥55 years	41.5	45.5	60.3	<0.001
PH (%)				
Total	17	22.9	31.9	<0.001
Male	14	20.3	34.3	<0.001
Female	21.9	26.8	26.8	0.44
<55 years	19.2	26.9	25	0.039
≥55 years	15	18.8	37.7	<0.001

*Difference between baseline and second follow-up, EF: ejection fraction, PASP: pulmonary artery systolic pressure, DD (%): diastolic dysfunction rate, PH (%): pulmonary hypertension rate

Discussion

The cytotoxic and cardiotoxic effects of CT agents used in the treatment of cancers are known to adversely affect the prognosis of the disease.

Table 4. Electrocardiographic parameter changes

	Baseline	First follow-up	Second follow-up	p
PR Dispersion (ms)				
Total	0	1.19±4.07	2.57±5.10	0.001
Male	0	1.95±5.08	3.52±5.95	<0.001
Female	0	0	1.10±2.85	<0.001
<55 years	0	0.48±2.47	2.60±5.85	0.11
≥55 years	0	1.89±5.11	2.55±4.23	0.11
f(QRS) (%)				
Total	7.2	20	46.7	<0.001
Male	10.9	26.5	48.4	<0.001
Female	2.4	9.7	43.9	<0.001
<55 years	7.6	11.5	34.6	<0.001
≥55 years	7.5	28.3	58.4	<0.001
QT Dispersion (ms)				
Total	23.24±13.37*	25.14±15.48	26.48±14.44*	0.004*
Male**	24.38±12.98	24.61±12.64	27.50±13.62	0.035**
Female**	21.46±13.93	25.98±19.24	24.88±15.67	
<55 years***	23.85±14.19	25.96±18.41	26.06±14.49	0.41***
≥55 years***	22.64±12.61	24.34±12.05	26.89±14.51	

*Difference between baseline and second follow-up, **Difference between genders ***Difference between age groups, f(QRS) (%) Fragmented QRS complex rate

Table 5. Changes in troponin level

Troponin (ng/dL)	Baseline	First follow-up	Second follow-up	p
Total	0.0047±0.0028	0.0053±0.0032	0.0067±0.012	0.012
Male*	0.0049±0.003	0.0058±0.0034	0.0076±0.014	0.22*
Female*	0.0043±0.0024	0.0044±0.0026	0.0054±0.009	
<55 years**	0.0040±0.0022	0.0040±0.0022	0.0041±0.0023	0.011**
≥55 years**	0.0054±0.0031	0.0066±0.0035	0.0093±0.017	

*Difference between genders, **Difference between age groups

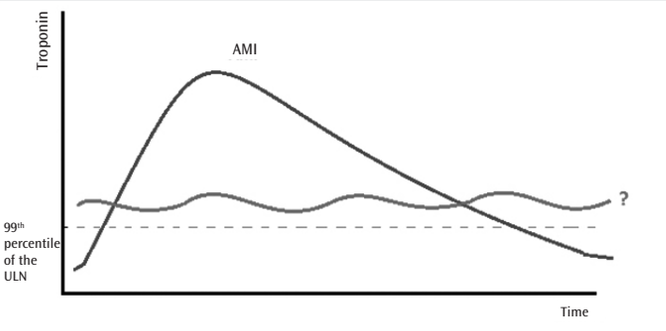

Figure 2. Troponin: course of troponin levels in AMI and non-ischemic conditions (a marker of cardiotoxicity during cancer treatment)

ULN: upper limit of normal, AMI: acute myocardial infarction, the course of troponin levels in non-ischemic conditions

However, the direct effect of the malignant disease itself in the chronic process on cardiac histopathology and functions is not known, and the number of studies to be attributed to the subject in the literature is limited (21,22). Therefore, in order to shed light on this issue, the effects of chronic leukemia disease (primary malignant disease of circulating blood) on the functions of the heart were investigated in patients without primary (documented) heart disease in this study. For this purpose, in our study, patients with a history of coronary atherosclerotic heart disease that is the major cause of the high prevalence of heart disease in adults were excluded. However, about half of the randomly selected cases had no major RFs. Also, the mean age of our patient group was lower than the level of atherosclerosis defined as a conventional RF (55 years for men, 65 years for women). Atherosclerosis, which occurs in younger than the expected age in the general population and is usually manifested by clinical manifestations, can be seen by the presence of several RFs (diabetes + 1 RF, 3 RFs without diabetes, and the presence of early cardio- and non-cardiovascular manifestations in hereditary first-degree relatives) and can be defined as "premature". In conclusion, the effect of atherosclerosis on the cardiovascular outcomes of the study in the medium and long-term follow-up was eliminated to some extent due to these demographic characteristics of the study group.

In our prospective study, we investigated cardiac involvement in chronic leukemia patients, and functional, electrocardiographic, and chemical concrete evidence of myocardial involvement was determined during the 1-year follow-up period in patients with or without CT treatment. According to this:

1. Echocardiographic findings showed that mechanical contractile functions (systolic and diastolic) of LV were impaired,

2. The increase in the frequency of f(QRS), reflecting changes in the depolarization and repolarization of the heart, and especially the calculated QT dispersion time in the ECG compared to baseline values were the electrocardiographic findings of myocardial damage and specifically developing LV remodeling,

3. cTn, which is the marker and/or product of the cytological physiopathological process underlying these findings, increased to the upper level of the standard (99th percentile of the reference level) and continued elevated cTn levels with fluctuations without showing the classic "delta pattern" for acute myocardial infarction (AMI) during follow-up was observed (Figure 2),

4. BNP, which is the sensitive and specific hemodynamic marker of elevated LV filling pressures proportional to the magnitude of myocardial damage, did not increase significantly in our asymptomatic patient group as expected.

In the literature, in studies in which the effects of CT are mostly examined and questioned in cancer patients, LV dysfunction in cancer patients was found to be non-homogeneous (asymptomatic, subclinical, manifested by signs and symptoms of prominent HF, and sudden cardiac death).

EF, which is the quantitative indicator of LV systolic function independent of CT in cancer patients, is a crucial marker even in asymptomatic patients with EF, and a decrease was found in our study compared to baseline values. However, since it cannot show microscopic myocyte damage, it may be insensitive to measure EF for early detection of global heart damage, and no correlation could be detected between clinical HF symptoms and signs and EF changes (9).

After CT, diastolic dysfunction was found in approximately 50% of asymptomatic patients with preserved LV systolic function in TTE, especially in early (<1 month) and mid-term (<3 months) (7). In the absence of clinical signs and symptoms of cardiotoxicity, structural pathologies in the myocardium (such as cardiomyocyte damage without cell death, hydropic degeneration, and interstitial edema) are the main pathological changes that impair myocardial compliance and relaxation function. In parallel to this, in our study, the incidence of diastolic dysfunction increased at the end of one year compared to baseline.

Systolic functional impairment occurs as a result of acute mass or persistent and minor loss of myocytes and LV remodeling. It may emerge with clinical, echocardiographic pump insufficiency, and severe clinical systolic dysfunction very early (with toxicity) or mostly late (with low flow syndrome). EF is an important prognostic marker in these patients (23).

Diastolic dysfunction may occur (be expected) before or at the beginning of a decrease in EF, as in acute myocardial ischemia or acute myocarditis, in light of the above physiopathological process. Therefore, early detection of cardiotoxicity (in the acute phase) is essential in terms of treatment and preventive measures in asymptomatic patients, as in our study (8).

Serial monitoring of cardiac bio- and/or electro-markers may be helpful in early detection of cardiotoxicity in the asymptomatic and subclinical stage during follow-up:

- The process leading to CMP caused by CT begins primarily with massive damage to cardiomyocytes (such as cTn elevation; 2X standard upper limit) and acute/subacute and chronic microscopic myocyte damage (≥standard upper limit) in the chronic period, and increasing mass loss of functional myocardium (elevation of BNP) leads to asymptomatic LV dysfunction.

- Diastolic dysfunction is often expected to occur earlier, probably due to edema formation as a result of inflammation reaction in myocardium due to CT and disruption of LV wall compliance (as in AMI and myocarditis) (24).

- In our study, the absolute but not significant decrease of EF in the follow-up and the significant increase in the frequency of diastolic dysfunction implied acute-subacute myocardial injury and involvement of the myocardium.

- Despite the myocardial functional and electrocardiographic changes observed in almost all of our patients (95%) after one year of clinical follow-up, almost all of them remained asymptomatic (clinically silent, subclinical). In these, the findings mentioned above pointing to acute and subacute myocardial damage were noted ("myocarditis-like" condition).

- In summary, LV dysfunction developed as a result of disruption of compliance due to initial acute-subacute interstitial edema causing in particular diastolic and relatively less systolic dysfunction.

The levels of cTn, which is the specific marker of myocardial damage and myocyte loss, were higher according to baseline and slightly above the upper limit of the standard reference value. Three findings reflecting myocardial physiopathology were: 1) myocardial damage is not massive as in AMI (transmural or subendocardial, myocardial infarction with or without ST-segment elevation), but microscopic, 2) the absence of a "delta pattern" during follow-up and continuous fluctuations above the upper limit of normal were a distinctive feature of chronic myocardial damage pathology rather than acute myocardial ischemia, 3) continuous fluctuating cTn levels could be the sign of smoldering fire. The clinical messages of this physiopathological process are a) "the best" is the ability to prevent or even regress the progression of LV remodeling with combined renin-angiotensin-aldosterone system (RAAS) inhibitor and Bb agents (19), b) "the worst" is that asymptomatic myocardial and electrocardiographic pathological changes, which can often be overlooked or ignored, may adversely affect prognosis by symptomatic HF (stage C HF), increased risk of sudden cardiac death in the long-term (>1 year, mean 19 months) and inhibiting and restricting the treatment of malignant disease.

In our study, because of the higher rate of CT in CML patients, PR dispersion, QT dispersion, f QRS, and diastolic dysfunction were higher in this group than in the CLL group. This may be due to the high rate of CT in patients with CML.

Conclusion

The subclinical diagnosis of cardiac dysfunction during CT is complicated, with the most important reason being that most of the patients are asymptomatic initially and during the short-to-medium period despite significant changes in noninvasive tests. Therefore, in order to prevent possible future cardiac events (with early RAAS inhibition and regulation of the CT program), these changes should be taken into consideration and monitored closely.

Ethics Committee Approval: The study was evaluated by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee, and ethical approval was obtained (decision no: 83045809/604.01/02-14160).

Informed Consent: Each patient was informed about the scope of the study, and written consent was obtained for participation in the study.

Peer-review: Internal peer-reviewed.

Authorship Contributions: Concept - T.O., R.E.; Design - R.E.; Supervision - R.E.; Resources - T.O.; Materials - T.O.; Data Collection and/or Processing - T.O.; Analysis and/or Interpretation - T.O., R.E.; Literature Search - R.E.; Writing Manuscript - T.O.; Critical Review - R.E., B.İ., B.K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006; 3: e442.
2. Jones RL, Swanton C, Ewer MS. Anthracycline cardiotoxicity. Exp Opin Drug Saf 2006; 5: 791-809.
3. Yeh ET1, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, et al. Cardiovascular complications of cancertherapy: diagnosis, pathogenesis, and management. Circulation 2004; 109: 3122-31.
4. Gradishar WJ, Vokes EE. 5-Fluorouracil cardiotoxicity: a critical review. Ann Oncol 1990; 1: 409-14.
5. David C. Stolinsky, MD. Paraneoplastic Syndromes , West J Med 1980; 132: 189-208.
6. Oliveira GH, Qattan MY, Al-Kindi S, Park SJ. Advanced heart failure therapies for patients with chemotherapy-induced cardiomyopathy. Circ Heart Fail 2014; 7: 1050-8.
7. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation 2003; 108: 977-82.
8. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol 2005; 23: 2900-2.
9. Rihal CS, Davıs KB, Kennedy JW, Gersh BJ. The utility of clinical,electrocardiographic and roentgenographic variables in the prediction of leftventricular function. Am J Cardinol 1994; 75: 220-3.

10. Cheng JM, Akkerhuis KM, Battes LC, van Vark LC, Hillege HL, Paulus WJ, et al. Biomarkers of heart failure with normal ejectionfraction: a systematic review. Eur J Heart Fail 2013; 15: 1350-62.

11. Daniels LB, Maisel AS. Natriuretic peptides. J Am Coll Cardiol 2007; 50: 2357-68.

12. Cardinale D1, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I incardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation 2004; 109: 2749-54.

13. Jose F, Krishnan M. Fragmented QRS Electrocardiogram-the hidden talisman? Indian Pacing Electrophysiol J 2009; 9: 238-40.

14. Pietrasik G, Goldenberg I, Zdzienicka J, Moss AJ, Zareba W. Prognostic significance of fragmented QRS complex for predicting the risk of recurrent cardiac events in patients with Q-wave myocardial infarction. Am J Cardiol 2007; 100: 583-6.

15. Dokainish H. Left ventricular diastolic function and dysfunction: Central role of echocardiography. Glob Cardiol Sci Pract 2015; 2015: 3.

16. Kovács SJ. Diastolic function in heart failure. Clin Med Insights Cardiol 2015; 9(Suppl 1): 49-55.

17. Tjeerdsma G1, Meinardi MT, van Der Graaf WT, van Den Berg MP, Mulder NH, Crijns HJ, et al. Early detection of anthracycline induced cardiotoxicity in asymptomatic patients with normal left ventricular systolic function: autonomic versus echocardiografphic variables. Heart 1999; 81: 419-23.

18. Yeh ET, Tong AT, Lenihan DJ, Yusuf SW, Swafford J, Champion C, et al. Cardiovascular complications of cancertherapy: diagnosis, pathogenesis, and management. Circulation 2004; 109: 3122-31.

19. Ahl R, Matthiessen P, Fang X, Cao Y, Sjolin G, Lindgren R, et al. Effect of beta-blocker therapy on early mortality after emergency colonic cancer surgery. Br J Surg 2019; 106: 477-83.

20. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging Roberto M. J Am Soc Echocardiogr 2015; 28: 1-39.e14.

21. Pavo N, Raderer M, Hülsmann M, Neuhold S, Adlbrecht C, Strunk G, et al. Cardiovascular biomarkers in patients with cancer and their association with all-cause mortality. Heart 2015; 101: 1874-80.

22. Rasim Enar, Kanıta Dayalı Kalp Yetersizliği Kitabi, Nobel Tıp Kitabevleri 2010 s.21-62.

23. Seidman A, Hudis C, Pierri MK, Shak S, Paton V, Ashby M, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. J Clin Oncol 2002; 20: 1215-21.

24. Dow E, Schulman H, Agura E. Cyclophosphamide cardiac injury mimicking acutemyocardial infarction. Bone Marrow Transplant 1993; 12: 169-72.