Assessment of left ventricular systolic and diastolic function with conventional and tissue Doppler echocardiography imaging techniques in patients administered tyrosine kinase inhibitor

Tirozin kinaz inhibitörü kullanılan hastalarda sol ventrikül sistolik ve diyastolik işlevlerinin geleneksel ve doku Doppler ekokardiyografik görüntüleme teknikleri ile değerlendirilmesi

Yusuf İzzettin Alihanoğlu, M.D., Zeynettin Kaya, M.D.,[#] Hatem Arı, M.D.,[*] Şükrü Karaarslan, M.D.,[†] Bekir Serhat Yıldız, M.D., Mustafa Karanfil, M.D.,[‡] Mehmet Yazıcı, M.D.,[‡] Melih Cem Börüban, M.D.,[§] Kurtuluş Özdemir, M.D.,[‡] Mehmet Sıddık Ülgen, M.D.[¶]

Department of Cardiology, Denizli State Hospital, Denizli; [#]Department of Cardiology, Numune State Hospital, Konya; [*]Department of Cardiology, Beyhekim State Hospital, Konya; [†]Department of Cardiology, Nigde State Hospital, Nigde; Departments of [‡]Cardiology, [§]Oncology, Selcuk University, Meram Faculty of Medicine, Konya; [¶]Department of Cardiology, Dicle University Faculty of Medicine, Diyarbakir

ABSTRACT

Objectives: The aim of this study was to use echocardiographic techniques to determine the possible cardiotoxic effects of low molecular weight tyrosine-kinase inhibitors (TKI) in patients receiving the therapy for the first time.

Study design: Thirty patients (17 females; 13 males; mean age 49±16; range 22 to 76 years) who met the exclusion criteria and were diagnosed as having malignancy were enrolled. All patients underwent conventional echocardiography and tissue Doppler imaging (TDI) prior to the treatment. The conventional echocardiogram was repeated 2 months later as the patients were concurrently receiving therapy. Myocardial Performance Index was obtained by conventional echocardiography and by TDI techniques to evaluate left ventricular systolic and diastolic function.

Results: Statistically significant increase occurred in mean left ventricle (LV) end-systolic volume. However, there was significant decrease in both mean LV ejection fraction and LV stroke volume values (64±3, 62±4, p=0.000 and 67±13, 61±13, p=0.000, respectively). Anterior wall Em/Am ratio measured by using the TDI technique was significantly decreased at the end of two months (0.99±0.49, 0.90±0.41, p=0.03). In addition, decreases were determined in Sm values obtained from all of four LV walls and also in mean Sm value, but this decrease was significant only for the lateral wall Sm measurement (12.8±2.9, 11.6±2.3, p=0.004).

Conclusion: Tyrosine-kinase inhibitors therapy can be administered safely to patients without predisposing factors for cardiotoxicity in short treatment intervals, and low molecular TKIs may cause subtle or clinically significant cardiotoxicity following the treatment period even in patients without predisposing factors for cardiotoxicity, so clinicians should consider this possibility.

ÖZET

Amaç: İlk kez küçük moleküllü tirozin kinaz inhibitörü (TKİ) tedavisi uygulanacak hastalarda geleneksel ekokardiyografi ve doku Doppler ekokardiyografik incelemesiyle, bu sınıftaki ilaçlara bağlı olarak gelişebilecek kardiyotoksik bozuklukları erken dönemde belirlemektir.

Çalışma planı: Çalışmaya, dışlanma ölçütlerini karşılayan ve kötü huylu tümör tanısı alan 30 hasta (17 kadın, 13 erkek; ort. yaş 49±16; dağılım 22-76 yıl) alındı. Bütün hastalara tedaviye başlamadan hemen önce ve tedavi başlangıcından 2 ay sonra, hem geleneksel ekokardiyografi hem de doku Doppler görüntüleme tekniği kullanılarak ekokardiyografik değerlendirmeler yapıldı. Ventrikülün sistolik ve diyastolik işlevlerini değerlendirme amacıyla, her iki yöntemle de miyokart performans indeksi ölçümleri yapıldı.

Bulgular: Sol ventrikül (SV) sistol sonu hacmi ort. değerinde anlamlı artış, SV ejeksiyon fraksiyonu ort. değerinde ve SV atım hacminde ise anlamlı azalma saptandı (sırasıyla, 64±3, 62±4, p=0.000 ve 67±13, 61±13, p=0.000). İki ay sonunda doku Doppler görüntülemede ön duvar Em/Am değerinde anlamlı düşme saptandı (0.99±0.49, 0.90±0.41, p=0.03). Ayrıca Sm ölçümlerinde gerek SV'nin dört duvarında ayrı ayrı ölçülen değerler, gerekse bunların ortalamalarını yansıtan Sm ort. değerinde düşme saptanırken, bu düşüş sadece lateral duvar Sm değeri için istatistiksel anlamlılığa ulaştı (12.8±2.9, 11.6±2.3, p=0.004).

Sonuç: Tirozin kinaz inhibitörleri kardiyotoksik bozuklukların gelişmesine yatkınlık yaratan etmenlere sahip olmayan hastalarda kısa tedavi aralıklarında güvenle kullanılabilir. Risk faktörlerinin dışlandığı hastalarda bile her şeye rağmen TKİ ile ilişkili olarak ileride klinik veya subklinik kardiyotoksik olay gelişebilir, tüm tedavi sürecinde dikkatli olunmalıdır.

Received: April 01, 2012 *Accepted:* July 16, 2012

Correspondence: Dr. Yusuf İzzettin Alihanoğlu. Gerzele Mah., 508/1 Sok., Çamlıköşk Apt. Kat 5 Daire 16, Servergazi, Denizli, Turkey. Tel: +90 258 - 265 34 30 e-mail: aliizyu@mynet.com

Tyrosine-kinases (TK) play a role in the transfer of phosphate atoms from ATP to the tyrosine residues of polypeptides. They paticipate in cellular proliferation, differentiation, movement, and cellular viability. Although the principal mechanism of tyrosine-kinase inhibitors (TKIs) is generally competitive inhibition of ATP at the catalytic region of TK, the kinase spectrum that they affect, their pharmacokinetics, and their side effect profiles differ.[1] Besides the common dermatologic, hematopoietic, and extrahematopoietic side effects (nausea, diarrhea, edema, weakness, hypothyroidism, etc.), recent research has shown that some TKIs have particularly cardiotoxic side effects, ranging from asymptomatic cases to congestive heart failure (CHF). Because TKIs are generally well-tolerated drugs, the prediction is that this cardiotoxicity is mainly dependent on patient selection.[2]

Tyrosin-kinase inhibitors are divided into two main groups: low molecular TKIs (LMTKIs) and humanized antibody TKI (AbTKI). Humanized antibody TKI have increased ability to bind to receptors of TK and its ligands.[3] AbTKIs are specifically designed to bind to cancer cell antigens, typically, they bind to extracellular growth factor receptors.[4] LMTKIs directly inhibit kinase's catabolic activity by interfering with ATP and its substrate's binding region.[5] Low molecular TKIs can also inhibit both receptor and nonreceptor TKIs. They can inhibit phosphorylation of kinase areas directly, and they can phosphorylate the substrate of signal cascades as well. As the ATP gaps of more than 500 kinases of the human genome are subsequently similar, the LMTKIs are less selective than the AbTKIs, and they can inhibit more than one kinase, of which we know little.[4]

When the treatment TKIs was first designed, the drug was expected to only inhibit mutated and/or overexpressed kinase pathways. Some of the earliest data acquired indicated that the inhibition of vascular endothelial growth factor does not only inhibit tumoral angiogenesis but also causes hypertension and vascular thickening.[6] Cardiotoxicity can only occur when the significant kinase pathways for cardiomyocytes and vascular endothelial cells are inhibited by TKIs. Therefore, the larger spectrums of the chosen kinases for treatment have been related to a greater likelihood of cardiotoxicity.[7]

Our aim in this study was to investigate whether it was possible to diagnose early clinical or subclinical cardiotoxicity from TKI therapy by performing conventional and tissue Doppler imaging (TDI) echocardiography, just prior to treatment and at the end of the second month of TKI treatment, in patients who were receiving this therapy for the first time and who do not have previously known cardiac pathology or comorbidity. There are no studies in the literature which have used conventional and TDI echocardiography to evaluate early and subclinical cardiotoxicity related to these agents.

Abbreviations:

AbTKI	*Antibody TKI*
CHF	*Congestive heart failure*
EDD	*End diastolic diameters*
EDV	*End diastolic volumes*
EF	*Ejection fraction*
ESD	*End systolic diameters*
ESV	*End systolic volume*
ICT	*Isovolumetric contraction time*
IRT	*Isovolumetric relaxation time*
LMTKIs	*Low molecular TKIs*
LV	*Left ventricle*
MPI	*Myocardial performance index*
SV	*Stroke volumes*
TDI	*Tissue Doppler imaging*
TK	*Tyrosine-kinases*
TKIs	*Tyrosine-kinase inhibitors*

PATIENTS AND METHODS

Patient population

After taking the medical faculty local Ethic committee approval with the number of 2008/328 on 28 November 2008, the study was started with the informed consent of the patients. Thirty patients with a diagnosis of malignant disease who planned to be given LMTKIs for the first time in the hematology and oncology departments, between December 2008 and December 2009, constituted our study population. Echocardiography was performed at the beginning of the therapy and two months after the start of therapy. Systolic and diastolic functional parameters were measured with conventional and pulsed-wave tissue Doppler (PWTDI) echocardiography.

Exclusion criteria

Patients with known CHF or signs and symptoms of CHF, history of coronary artery disease, diabetes, hypertension, severe valvular heart disease, history of radiotherapy, or prior history of cardiotoxic chemotherapy and those who were receiving medical treatment which affected cardiac function (β-blockers, ACE inhibitors, etc.) were excluded from this study.

Echocardiography

ATL HDI-500 (Advanced Technology Laboratories, Bethel, WA; 2-4 MHz phased array) and Philips En-

visor-C echocardiography machines were used for the measurements. Electrocardiogram (ECG) recordings were taken simultaneously. Conventional and PWT-DI echocardiographic measurements were taken in the left lateral decubitus position by using the parasternal long and short axes and also apical four- and two-chamber views. Recordings were taken while the patients held their breath at expirium. The measurements were registered as the mean of the values of three consecutive beats. The arterial blood pressure and beat per minute values of all the patients were recorded as basal and control measurements while echocardiography was being performed.

Conventional echocardiography

According to the American Society of Echocardiography's guidelines,[8] we calculated fractional shortening by measuring left ventricle (LV) end-systolic and end-diastolic diameters (LVESD, LVEDD) by M-mod imaging in the parasternal long-axis view. By using the modified Simpson method, from apical two- and four-chamber view LV end-systolic and end-diastolic volumes (LVESV, LVEDV) were measured and then left ventricle ejection fraction (LVEF) and LV stroke volumes (LVSV) were calculated through these volumes.

The American Society of Echocardiography's 16-segment model was used while evaluating regional systolic functions. A transmitral flow sample was recorded by placing a pulse-wave Doppler sample volume to the tips of mitral valve. Mitral E, A velocity, and mitral E wave deceleration time values were measured, and the E/A ratio was calculated. The time between the end of the A wave and the beginning of the E wave (a) was calculated. LV ejection time (b) was calculated by placing a pulse-wave Doppler sample volume parallel to LV outflow tract in the apical long-axis view. The conventional myocardial performance index (MPI) was calculated through the a-b/b formula, with the acquired a and b values.

Isovolumetric contraction time (ICT) and isovolumetric relaxation time (IRT) values were calculated by placing a sample volume in the middle of the mitral and aortic valves in the apical five-chamber view. A sample volume was placed 1 cm inside of the best-viewed pulmonary vein at the apical four-chamber view; pulmonary vein flow velocities (Ps and Pd) were acquired, and the Ps/Pd ratio was calculated. Also, the time difference between atrial A wave and pulmonary vein reverse flow time (Ra) was calculated.

Tissue Doppler imaging

Apical two- and four-chamber views were used for the measurements. PWTDI views were acquired by placing the sample volume to the mitral annulus of the septum, lateral, anterior, and inferior walls. The Sm, Em, and Am velocities of all the segments were measured. The Em/Am and mitral E/Em ratios for all walls were calculated. ICT, IRT, and ejection time (ET) values of all walls were calculated. Left ventricular mean Sm, mean Em/Am, and mean mitral E/Em values were calculated using all the acquired data. A tissue Doppler MPI (TDMPI) value for all walls was calculated by using the (ICT+IRT)/ET formula. Basal and control echocardiography recordings were taken

Table 1. Demographic characteristics, clinical diagnoses and the chemotherapeutic agents used for the patients

	n	%	Mean±SD
Demographic characteristics			
Gender			
Male	17	57	
Female	13	43	
Age (year)			49±16
Time for control			
echocardiography (day)			62±1
Known malignity duration (day)			116±19
Number of smokers	3	3	
Type of malignancy			
Chronic myeloid leukemia	7	23.3	
Lung cancer	6	20	
Hepatocellular cancer	6	20	
Chronic lymphoid leukemia	4	13.3	
Renal cell cancer	3	10	
Acute lymphoid leukemia	2	6.7	
Gastrointestinal stromal cancer	1	3.3	
Pancreatic cancer	1	3.3	
Chemotherapeutic agent			
Imatinib	14	46.7	
Erlotinib	7	23.3	
Sorafenib	6	20	
Sunitinib	3	10	

by two different echocardiographers without knowing the prior values.

Statistical analyses

All of the data analyses in this study was performed with the SPSS 15.0 computer program (SPSS Inc. Chicago, IL, USA). The data was analyzed to ensure normal distribution. Definitive findings are shown as mean ± standard deviation. A paired-sample t test was used for the analyses of basal data and for changes after the treatment. The results with a *p* value less than 0.05 were accepted as statistically significant, and results are shown in tables.

RESULTS

Thirty patients with malignancies who had not received prior LMTKI treatment were enrolled in our study. Seventeen (57%) of the patients were female and 13 of them were male (43%). The average age of the patients was 49±16 (median 52, minimum 22 and maximum 76). Three (10%) of the patients were active smokers. The duration of known diagnosed malignancy was 116±19 days (median 72, minimum 15 and maximum 350). The administered chemotherapeutic agents were imatinib (46.7%, 600 mg OD), erlotinib (23.3%, 150 mg OD), sorafenib (20%, 800 mg OD), sunitinib (10%, 50 mg OD). All of the patients were reevaluated with echocardiogram in the planned control period (mean 62±1 days). The main characteristics of the study are shown in Table 1. There were no clinically noticeable cardiac complications that developed during the treatment period.

Conventional echocardiography

The basal echocardiographic findings of all the patients enrolled in the study were normal. The increases in LVEDD and LVESD at the end of the treatment were not statistically significant. There were increases in the mean values of LVESV and LVEDV at the end of the second month, compared to the basal values.

Table 2. Parameters obtained by conventional echocardiography before and after the treatment

	Basal Mean±SD	After treatment Mean±SD	*p*
Left ventricle end diastolic diameter (cm)	4.5±0.4	4.6±0.4	NS
Left ventricle end systolic diameter (cm)	2.6±0.4	2.7±0.4	NS
Fractionel shortening	43.1±5.9	43±6	NS
Systolic pulmonary arterial pressure (mmHg)	28±5.7	29±6.7	NS
Systolic blood pressure (mmHg)	126±7	127±6	NS
Diastolic blood pressure (mmHg)	81±6.6	82±6	NS
Heart rate (bpm)	88±13	87±12	NS
LV end-systolic volume (ml)	34.5±9	37±11	**0.007**
LV end-diastolic volumes (ml)	98±25	98±25	NS
LV ejection fraction	64±3	62±4	**0.000**
E velocity (cm/sec)	70±13	71±13	NS
A velocity (cm/sec)	81±18	82±20	NS
E/A ratio	0.95±0.36	0.96±0.35	NS
E deceleration time (msec)	181±33	182±32	NS
Isovolumetric relaxation time (msec)	73±16	76±16	**0.03**
Isovolumetric contraction time (msec)	60±9	63±12	NS
Stroke volume	67±13	61±13	**0.000**
A-Ra (time difference of the velocities)	19±13	18±11	NS
Ps/Pd ratio	1.19±0.42	1.13±0.37	NS
Myocardial performance index	52±8	54±10	NS

SD: Standard deviation, NS: Statistically not significant; Ra: Pulmonary vein reverse flow; Ps/Pd: Pulmonary vein flow velocities. p<0.05: Statistically significant.

Table 3. The comparisons of Doppler parameters obtained from four walls of left ventricle

	Basal Mean±SD	After treatment Mean±SD	*p*
Septal Sm (cm/sec)	10.6±2.3	10.1±2.1	NS
Septal Em (cm/sec)	9.4±2.7	9.1±2.9	NS
Septal Am (cm/sec)	10.8±2.5	11.6±2.8	NS
Septal Em/Am ratio	0.92±0.41	0.84±0.42	NS
Septal E/Em ratio	7.9±1.9	8.5±2.6	NS
Lateral Sm (cm/sec)	12.8±2.9	11.6±2.3	**0.004**
Lateral Em (cm/sec)	11.9±4.1	11.2±3.5	NS
Lateral Am (cm/sec)	13.2±2.7	13±2.9	NS
Lateral Em/Am ratio	0.96±0.51	0.91±0.45	NS
Lateral E/Em ratio	6.2±2.1	6.7±2.9	NS
Anterior Sm (cm/sec)	11.2±2.8	10.8±2.6	NS
Anterior Em (cm/sec)	10.5±4	9.9±3.2	NS
Anterior Am (cm/sec)	11.3±2.5	11.5±2.3	NS
Anterior Em/Am ratio	0.99±0.49	0.90± 0.41	**0.03**
Anterior E/Em ratio	7.5±2.3	7.9±3.2	NS
Inferior Sm (cm/sec)	11.7±2.2	11.1±2.3	NS
Inferior Em (cm/sec)	10.6±3.6	10.4±3.4	NS
Inferior Am (cm/sec)	13.9±3.1	13.3±2.9	NS
Inferior Em/Am ratio	0.79±0.33	0.79±0.31	NS
Inferior E/Em ratio	7.3±2.4	7.5±2.8	NS

Sm: Systolic myocardial motion velocity; Em, Am: Diastolic myocardial motion velocities (early and late phase); p<0.05: Statistically significant; SD: Standard deviation; NS: Statistically not significant.

While the increase of the LVESV mean value was statistically significant, the increase of the LVEDV mean value was not. There was statistically significant reduction in the mean values of LVSV and SVEF which were calculated by Simpson's method, howerever, at the end of the second month, the values obtained were within normal limits.

When the diastolic dysfunction indicators were evaluated, there was a statistically significant prolongation only in the value of IRT measured by Doppler. There was a slight increase in the MPI value calculated by the conventional method; however, this increase was not statistically significant. Parameters obtained by conventional echocardiography before and after the treatment are shown in Table 2.

There was a decrease in the Sm values of all four walls at the end of the second month, compared to the basal values, but only the decrease in the Sm of the lateral wall was statistically significant. In addition, there was a slight decrease in the values of the Em of all four walls compared to the basal values, but none of these were statistically significant. There was a statistically significant decrease in the value of the Em/Am ratio of the anterior wall; however, no statistically significant difference was detected in the other three walls for this ratio. The comparisons of Doppler parameters obtained from the four walls for LV are shown in Table 3.

There was no statistically significant difference in the LV lateral, interventricular septum, anterior, or inferior TDMPI values at the end of the two months of the treatment, compared to the basal values. The TDMPI values of the LV walls are shown in Table 4. There were decreases in the values of the Sm mean and Em-mean at the end of two months, but they were not statistically significant. While there were increases in the values of the E/Em mean and TDMPI mean, Em/Am mean value was decreased at the end of the two months of the treatment. They were not statistically significant as well. A comparison of these average tissue Doppler parameters of LV is shown in Table 5.

Table 4. The comparisons of tissue Doppler myocardial performance index values of left ventricle walls

	Basal Mean±SD	After treatment Mean±SD	*p*
Septal TDMPI	54.8±8.4	55.8 ±8.5	NS
Lateral TDMPI	52.8±7.1	54.9± 7.2	NS
Anterior TDMPI	55.2 ±8.1	55.4 ±7.6	NS
Inferior TDMPI	53.7±7.4	54.4 ± 7.7	NS

TDMPI: Tissue Doppler myocardial performance index; p<0.05: Statistically significant; SD: Standard deviation, NS: Statistically not significant.

Table 5. The comparison of mean tissue Doppler parameters of left ventricle

	Basal Mean±SD	After treatment Mean±SD	*p*
Sm-mean (cm/sec)	11.4±2.2	10.9±2.1	NS
Em-mean (cm/sec)	10.4±3.2	10±2.9	NS
Em/Am ratio-mean	0.95±0.39	0.91±0.97	NS
E/Em ratio-mean	7.4±1.8	7.8±2.6	NS
TDMPI-mean	53.3± 6.5	54±6.8	NS

Sm: Systolic myocardial motion velocity; Em/Am: Diastolic myocardial motion velocities (early and late phase); TDMPI: Tissue Doppler myocardial performance index; SD: Standard deviation; NS: Statistically not significant.

DISCUSSION

In our study, statistically significant increase occured in mean LVESV value. However, there was significant decrease in both mean LVEF and LVSV values obtained by conventional echocardiography. As for TDI technique, anterior wall Em/Am ratio was significantly decreased. In additiıon Sm values obtained from all of four LV walls and also mean Sm value were decreased, but this decrease was significant only for the lateral wall Sm measurement.

Cardiotoxicity caused by TKIs is classified as "target- or mechanism-dependent toxicity" and "target- or mechanism-independent toxicity." If the pathway targeted by the TKI is necessary for cardiomyocytes as well, then the myocardial dysfunction caused by this agent is called "target- or mechanism-dependent toxicity".[9] Conversely, target- or mechanism-independent toxicity is the toxicity caused by the inhibition of a kinase that is not the primary target of the drug; this situation is generally caused because these drug are not structurally selective.[4]

Cardiotoxicity caused by TKIs occurs across a wide spectrum, from an asymptomatic QT prolongation, hypertension, and left ventricular (LV) dysfunction to symptomatic heart failure, acute coronary syndrome, and sudden death. The data about the systolic dysfunction and heart failure caused by these agents are relatively new. In contrast to several other chemotherapeutic agents (antracyclins, 5-flourouracyl, etc.), which are known to be cardiotoxic, the FDA does not recommend SV monitoring for these agents. Therefore, the cardiac data are very limited in this regard. In addition, most patients with metastatic malignancies have heart failure consisting of the classic triad of shortness of breath, fatigue, and edema.[10] Consequently, if these symptoms are thought to be caused by the progression of malignancy then the underlying cardiac problems may be overlooked if a detailed cardiac evaluation is not performed.

In a study consisting of 10 patients with known predisposing factors, such as coronary artery disease, hypertension, or diabetes, Kerkela et al. found that severe heart failure and LV systolic dysfunction occurred after the first dose of LMTKI treatment.[11] In another study, Midgley et al.[12] observed at least a 20% decrease in the value of LVEF in roughly 1.3% of the patients. They also found that this fall occurred in the first nine weeks of treatment in 68% of the patients and that it was generally asymptomatic, nonprogressive, and reversible. In a prospective study by Chu et al., which included patients with gastrointestinal stromal tumors who were treated with LMTKIs, the value of LVEF was found to be lower than 50% in approximately 20% of the patients. They also observed that the decrease in LVEF value was greater than 20% in 2% of the patients and that symptomatic CHF developed in 8% of these patients.[10]

In a retrospective study, Khakoo et al.[13] found that CHF developed immediately after treatment (mean 22 days) in 2.7% of patients receiving LMTKIs. They observed that it was related to the hypertension occurring secondary to LMTKI treatment. Despite termination of the treatment, complete resolution of cardiotoxicity was not obtained. In another study, Telli et al.[14] found that CHF was seen in 15% of the patients receiving LMTKI treatment, and the mean occurrence time of CHF was between 22 and 435 days. In a six month follow up study with patients who received LMTKIs, Motzer et al.[15] found that systolic dysfunction developed in 10% of the patients and that EF values fell to less than 40% in 2% of the patients, but none of the patients developed symptomatic CHF.

Cardiotoxicity was evaluated by conventional echocardiography or radionuclide imaging modalities in all of these studies. The authors explained the relatively high incidence of cardiotoxicity in these studies by the non-selective identification of the patient group, the presence of previously known cardiac risk factors, and previous treatment of the patients with other cardiotoxic chemotherapies.

In our study, a statistically significant decrease in the values of the LVEF mean and LVSV was found at the end of approximately eight weeks of treatment (mean 62±1 days), this decrease was 3.5% for the LVEF mean and 11% for LVSV. These values were still within normal limits at the end of the second month of treatment, and no clinical or hemodynamic disturbances were identified. Systolic functional disturbance was rare at the end of the two months of treatment; this result was probably a result of eliminating the predisposing cardiotoxic factors prior to the start of the study.

Given the small number of patients included in our study, the results may be considered to be coincidental. Additionally, in previous studies, the average

follow-up period for evaluating LV dysfunction was between one and 16 months, but in our study, that period was almost two months, which could be considered a short time period. We still believe that a more prominent risk of developing cardiotoxicity resulting in both clinical and hemodynamic disturbances should be taken into consideration.

Tissue Doppler imaging is an echocardiographic diagnostic method that is used for the evaluation of regional or global systolic and diastolic functions of the ventricles. There has been no research in the literature that investigates cardiotoxicity in patients receiving LMTKIs by tissue Doppler technique. In our study, we found the diastolic functional parameters by tissue Doppler technique as follows: a non-significant increase in the value of the E/Em mean, an insignificant decrease in the value of the Em/Am mean, but a statistically significant decrease in the value of the anterior wall Em/Am value by segmental analysis. Non significant decreases in the Em values obtained from all four walls and the LV Em mean value were detected. A decrease in the Em ratio, which reflects LV relaxation, is one of the earliest markers of diastolic dysfunction.[16]

In the previous studies, it was shown that an increase in the value of the E/Em ratio is correlated with an increase in the filling pressure of the LV;[17] conversely, the value of Em/Am decreases progressively in accordance with the disturbances of LV diastolic functions.[18] The Sm value recorded in the systole reflects the LVEF. It is the best marker of slightly impaired LV systolic function[19] regardless of normal LVEF. In a study evaluating the early (one to three months) and late phases (3.5 years) of cardiac function after treatment with antracyclin, a cardiotoxic chemotherapeutic agent, it was found that the Sm and Em ratios of both the posterior and lateral walls decreased significantly in the early and late phases.[20] In our study, although a decrease compared to the basal values was found in the Sm and Sm mean values obtained from all four walls at the end of two months by segmental analysis, a statistically significant decrease was found only in the Sm value of the lateral wall.

Conventional MPI is a parameter that shows both LV systolic and diastolic function. It has been shown that MPI is well correlated with measures of invasive and noninvasive methods of LV function.[21] There are data that MPI can be used to determine the prognosis of cardiopulmonary diseases, such as dilated cardiomyopathy and pulmonary hypertension.[22,23] Authors have indicated that MPI is a more sensitive parameter than standard echocardiographic measurements in detecting subclinical cardiotoxicity. In addition, TDMPI, calculated by the tissue Doppler method, is less affected by changes in heart rate when compared with conventional MPI.[24] Conventional MPI and TDMPI are equivalent determining cardiotoxicity in ill and healthy individuals.[25]

In the previous studies, conventional MPI was used for the determination of antracyclin cardiotoxicity. Eidem et al.[26] found that there was an increase in the conventional MPI value after an average of two years of treatment with doxorubicin. They also found a correlation between the increasing dose of antracyclin and the conventional MPI value. In another study consisting of adult patients, it was shown that there was a correlation between the change in conventional MPI value after doxorubicin treatment and the increasing dose of antracyclin.[27] However, there are no current data showing a connection between TKI and MPI.

Our study is the first one that uses conventional and TDMPI for demonstrating cardiotoxicity after LMTKI treatment. After two months of treatment, there was an insignificant increase in both the conventional and TDMPI mean values calculated by average measurements of the four walls of the LV. Because the prognostic significance of early detected subclinical myocardial damage in patients given LMTKI treatment has not been fully understood yet, this increase in MPI values can be considered an indicator of developing cardiotoxicity during the ongoing process of treatment. In particular for asymptomatic patients for whom EF values, which are the routine markers of LV function, have not been affected yet, the need for new monitoring techniques to determine early cardiac damage and future treatment, new echocardiographic techniques, such as MPI and tissue Doppler parameters, are increasingly important.

Currently, LVEF parameters obtained through the radionucleotide and/or echocardiography are often used to evaluate cardiac damage. However, it is difficult to determine cardiac damage in the early phase, because there is not significant LVEF disturbance. This is largely because there is no change in the value of the LVEF until cardiac damage reaches a critical level.

Limitations of the study

The main limitations of the study were the lack of a control group, the small number of patients, and the short follow-up period. Therefore, it should be considered that the obtained results may be coincidental. Furthermore, in addition to the class effects of these drugs, if each LMTK molecule were separately evaluated in light of the different molecular targets affected by these molecules, the significance of the study would increase. No subgroup analysis could be performed because the number of the patients included in the study was small. In addition, the other new methodologies such as strain-strain rate and spackle tracking which evaluate LV functions might contribute some additional data.

Conclusion

Our study's findings indicate that LMTKIs can be used safely for patients who do not have predisposing factors for cardiotoxicity for short treatment intervals. However, the data obtained by the echocardiographic evaluations made by both conventional and tissue Doppler techniques indicate that there is still an LMTKI-related clinical or subclinical cardiotoxicity risk during ongoing treatment, even for patients who do not have any risk factors. Therefore, caution should be exercised during the treatment period.

In the event of a prolonged treatment period, significant disturbances in LV systolic and diastolic function in the early phase can be markers of possible cardiotoxicity induced by TKIs, which may arise in the later stages of the treatment. Our study is the only one in the literature in which the tissue Doppler technique was used to evaluate patients receiving LMTKIs. Clinical studies with longer follow-up periods and larger sample size are needed to support our conclusions.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell 2000;103:211-25.
2. Hartmann JT, Haap M, Kopp HG, Lipp HP. Tyrosine kinase inhibitors - a review on pharmacology, metabolism and side effects. Curr Drug Metab 2009;10:470-81.
3. Zhang J, Yang PL, Gray NS. Targeting cancer with small molecule kinase inhibitors. Nat Rev Cancer 2009;9:28-39.
4. Chen MH, Kerkelä R, Force T. Mechanisms of cardiac dysfunction associated with tyrosine kinase inhibitor cancer therapeutics. Circulation 2008;118:84-95.
5. Kwak EL, Sordella R, Bell DW, Godin-Heymann N, Okimoto RA, Brannigan BW, et al. Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib. Proc Natl Acad Sci U S A 2005;102:7665-70.
6. Veronese ML, Mosenkis A, Flaherty KT, Gallagher M, Stevenson JP, Townsend RR, et al. Mechanisms of hypertension associated with BAY 43-9006. J Clin Oncol 2006;24:1363-9.
7. Sica DA. Angiogenesis inhibitors and hypertension: an emerging issue. J Clin Oncol 2006;24:1329-31.
8. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). Circulation 2003;108:1146-62.
9. Maitland ML. Cardiovascular toxicity of new agents. Clin Adv Hematol Oncol 2008;6:657-9.
10. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet 2007;370:2011-9.
11. Kerkelä R, Grazette L, Yacobi R, Iliescu C, Patten R, Beahm C, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med 2006;12:908-16.
12. Midgley RS, Kerr DJ, Flaherty KT, Stevenson JP, Pratap SE, Koch KM, et al. A phase I and pharmacokinetic study of lapatinib in combination with infusional 5-fluorouracil, leucovorin and irinotecan. Ann Oncol 2007;18:2025-9.
13. Khakoo AY, Kassiotis CM, Tannir N, Plana JC, Halushka M, Bickford C, et al. Heart failure associated with sunitinib malate: a multitargeted receptor tyrosine kinase inhibitor. Cancer 2008;112:2500-8.
14. Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. Ann Oncol 2008;19:1613-8.
15. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007;356:115-24.
16. Wang M, Yip GW, Wang AY, Zhang Y, Ho PY, Tse MK, et al. Peak early diastolic mitral annulus velocity by tissue Doppler imaging adds independent and incremental prognostic value. J Am Coll Cardiol 2003;41:820-6.
17. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788-94.

18. Rodriguez L, Garcia M, Ares M, Griffin BP, Nakatani S, Thomas JD. Assessment of mitral annular dynamics during diastole by Doppler tissue imaging: comparison with mitral Doppler inflow in subjects without heart disease and in patients with left ventricular hypertrophy. Am Heart J 1996;131:982-7.
19. Alam M, Wardell J, Andersson E, Samad BA, Nordlander R. Effects of first myocardial infarction on left ventricular systolic and diastolic function with the use of mitral annular velocity determined by pulsed wave doppler tissue imaging. J Am Soc Echocardiogr 2000;13:343-52.
20. Tassan-Mangina S, Codorean D, Metivier M, Costa B, Himberlin C, Jouannaud C, et al. Tissue Doppler imaging and conventional echocardiography after anthracycline treatment in adults: early and late alterations of left ventricular function during a prospective study. Eur J Echocardiogr 2006;7:141-6.
21. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. J Am Soc Echocardiogr 1997;10:169-78.
22. Dujardin KS, Tei C, Yeo TC, Hodge DO, Rossi A, Seward JB. Prognostic value of a Doppler index combining systolic and diastolic performance in idiopathic-dilated cardiomyopathy. Am J Cardiol 1998;82:1071-6.
23. Yeo TC, Dujardin KS, Tei C, Mahoney DW, McGoon MD, Seward JB. Value of a Doppler-derived index combining systolic and diastolic time intervals in predicting outcome in primary pulmonary hypertension. Am J Cardiol 1998;81:1157-61.
24. Schaefer A, Meyer GP, Hilfiker-Kleiner D, Brand B, Drexler H, Klein G. Evaluation of Tissue Doppler Tei index for global left ventricular function in mice after myocardial infarction: comparison with Pulsed Doppler Tei index. Eur J Echocardiogr 2005;6:367-75.
25. Gaibazzi N, Petrucci N, Ziacchi V. Left ventricle myocardial performance index derived either by conventional method or mitral annulus tissue-Doppler: a comparison study in healthy subjects and subjects with heart failure. J Am Soc Echocardiogr 2005;18:1270-6.
26. Eidem BW, Sapp BG, Suarez CR, Cetta F. Usefulness of the myocardial performance index for early detection of anthracycline-induced cardiotoxicity in children. Am J Cardiol 2001;87:1120-2, A9.
27. Senju N, Ikeda S, Koga S, Miyahara Y, Tsukasaki K, Tomonaga M, et al. The echocardiographic Tei-index reflects early myocardial damage induced by anthracyclines in patients with hematological malignancies. Heart Vessels 2007;22:393-7.

Key words: Cardiotoxicity; echocardiography, Doppler; elasticity imaging techniques; heart failure/chemically induced; drug interactions; neoplasms/drug therapy; protein-tyrosine kinases/antagonists & inhibitors; ventricular function, left.

Anahtar sözcükler: Kardiyotoksisite; ekokardiyografi, Doppler; esneklik görüntüleme teknikleri; kalp yetersizliği/kimyasal nedenlerle oluşmuş; ilaç etkileşimi; neoplazi/ilaç tedavisi; protein tirozin kinaz/antagonist ve inhibitörleri; ventrikül fonksiyonu, sol.