CorSalud 2014 Jul-Sep;6(3):229-234

Cuban Society of Cardiology

Brief Article

Early detection of anthracycline-induced cardiotoxicity

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ARTICLE INFORMATION

Received: November 21, 2013
Accepted: January 7, 2014

Competing interests
The authors declare no competing interests

Acronyms
DTI: Doppler tissue imaging
Ɛ: *strain*
LAP: left atrial pressure
LVEF: left ventricle ejection fraction
SR: *strain rate*

On-Line Versions:
Spanish - English

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ABSTRACT

Introduction: Cancer is the most dreaded disease known to mankind. Cardiotoxicity is a complication of antineoplastic treatment, which can be detected early by echocardiogram.

Objective: To identify echocardiographic variables related to the occurrence of cardiotoxicity by anthracycline.

Method: A descriptive, prospective and longitudinal study was conducted with all patients admitted to the Hematology Department of Hermanos Ameijeiras Surgical Clinical Hospital, from January 2010 to January 2012. 28 patients who received chemotherapy with anthracyclines were studied. The general information of each patient, as well as the information concerning the transthoracic echocardiogram, was obtained during hospitalization, at one, 6 and 12 months.

Results: 69.3% of patients who developed cardiotoxicity were older than 45 years and there was a predominance of males (76.9%). 56.8% had cardiotoxicity at a dose lower than 550 mg/m2 ($p = 0.032$). Strain rate/Ɛ values in patients who developed cardiotoxicity were significantly reduced at one month [0.8638/0.2 ($p = 0.043$) and 13.77/4.1 ($p = 0.031$)]; while LVEF remained normal [54.6 ± 4 ($p = 0.036$)]. Regarding volume/pressure of the left atrium, there was an increase in the reference values (21.13 ± 5.08 ml and 10.91 ± 0.57 mmHg), although without statistical significance ($p = 0.217$ and $p = 0.728$).

Conclusions: Strain rate/Ɛ technique has been helpful for early diagnosis of cardiotoxicity.

Key words: Cardiotoxicity, Anthracyclines, Echocardiography, Strain rate

Detección precoz de cardiotoxicidad inducida por antraciclinas

RESUMEN

Introducción: El cáncer es la enfermedad más temible conocida por la humanidad. La cardiotoxicidad, es una complicación del tratamiento antineoplásico, la cual puede ser detectada precozmente mediante ecocardiograma.

Objetivo: Identificar las variables ecocardiográficas relacionadas con la aparición de cardiotoxicidad por antraciclinas.

Método: Se realizó un estudio descriptivo, prospectivo, de corte longitudinal con todos los pacientes que ingresaron en el servicio de Hematología del Hospital Clínico-Quirúrgico "Hermanos Ameijeiras", durante el período comprendido entre enero de 2010 hasta enero de 2012. Fueron estudiados 28 pacientes, los cuales recibieron quimioterapia con antraciclinas. La información general de cada paciente, así como la inherente al ecocardiograma transtorácico, fue obtenida durante el ingreso hospitalario, al mes, a los 6 y a los 12 meses.

Resultados: El 69,3 % de los pacientes que desarrollaron cardiotoxicidad eran mayores de 45 años y existió un predominio del sexo masculino (76,9 %). El 56,8 % presentó cardiotoxicidad a dosis menor de 550 mg/m^2 (p=0.032). Los valores del *strain rate*/Ɛ* en los pacientes que presentaron cardiotoxicidad, se redujeron significativamente al mes [0.8638/0.2 (p= 0.043) y 13.77/4.1 (p=0.031)]; mientras que la FEVI, permaneció normal [54,6±4 (p=0.036)]. En relación al volumen/presión de la aurícula izquierda, existió un incremento en los valores de referencia (21,13 ± 5,08 ml y 10,91 ± 0,57 mmHg), aunque sin significación estadística (p=0.217 y p=0.728).

Conclusiones: Para el diagnóstico precoz de cardiotoxicidad la técnica de *strain rate*/Ɛ ha sido útil.

Palabras clave: Cardiotoxicidad, Antraciclinas, Ecocardiograma, *Strain rate*

INTRODUCTION

Cancer is the most dreaded disease known to mankind. Some complications arise more due to therapy than due to the disease *per se*. However, there should be no doubt as to the risk/benefit ratio in the antineoplastic treatment of cancer[1]. Among the antineoplastic therapies, anthracyclines are the best studied and the most used in the treatment of many hematologic malignancies[2]. The major factor limiting the use of these drugs is cardiotoxicity, which is defined as the reduction of left ventricle ejection fraction (LVEF) greater than 10% of its normal limit of 55%. This definition is used as a strict criterion for stopping treatment[3].

Cardiotoxicity can be acute (during drug administration or immediately after), early (from days to 12 months after administration) or late (more than 12 months)[4]. The acute form occurs in less than 1% of patients and is generally identified by the presence of hypotension, tachycardia, arrhythmia, pericarditis and decreased myocardial contractility. No cardiac monitoring is required during this stage, as it is usually transient and reversible[5]. Other authors have agreed that early toxicity is clearly dose dependent[6,7]; however, there are other risk factors such as intravenous administration, single high dose, prior radiotherapy on the mediastinum, concomitant use of other cardiotoxic drugs, female sex, extreme ages of life and preexisting subclinical myocardial damage[8-10].

This study was designed based on the great usefulness provided by echocardiography, with the aim to assess, by echocardiography, the cardiovascular changes that occur with the use of anthracyclinesin our hospital; and determine the relationship between the cumulative dose of chemotherapy and the appearance of cardiotoxicity caused by these drugs.

METHOD

A descriptive, prospective andlongitudinal study was conducted with all patients admitted to the Hematology Department of Hermanos Ameijeiras Surgical Clinical Hospital, from January 2010 to January 2012. All were requested to sign written informed consent. Inclusion criteria were age over 18 years, diagnosis of lymphoma (Hodgkin and non-Hodgkin) or acute myeloid leukemia, and treatment with antineoplastic drugs of the Adriamycin or Rubidomycin type, exclusively.

The general information of each patient, as well as the information concerning the transthoracic echocardiogram, was obtained during hospitalization, at one, 6 and 12 months.

All patients underwent transthoracic echocardiography with a Philips iE33 unit; their hearts were examined from conventional views (long and short parasternal axis and apical views on 2, 4 and 5 chambers). LVEF was measured from the apical views with the use of area-length method. The left atrial volume was obtained by the area-length method modified at the end of ventricular systole just before the opening of the mitral valve from two orthogonal apical views (2 and 4 chambers, respectively). Pulsed Doppler in apical view (4-chambers) was used to record mitral flow chart and obtain peak velocity of E wave. The mitral spectral recording was obtained at a scanning speed of 100mm/s. From the same projection, Doppler tissue imaging (DTI) was activated, and at the medial mitral annulus the E' was obtained. Subsequently, we proceeded to estimate the left atrial pressure (LAP) using the LAP formula = [1.24 (E/E ') + 1.91]. For the strain (Ɛ) and strain rate (SR), DTI color remained activated with the sample volume placed in the mid-apical septum after acquiring at least 3 cycles (with optimal ECG signal), a virtual M line was placed in the thickness of the wall, and its width was adjusted to prevent the registration of blood pool and thereby optimize the noise-signal ratio.

To meet the objectives, the information was summarized and placed in a database created in SPSS version 16.0, for this purpose the percent was used as summary measure for qualitative data, and the average and standard deviation forquantitative variables. Fisher's exact test was used to assess the association among qualitative variables in relation to the presence of cardiotoxicity. Considering the sample size, the Mann Whitney test was used for comparison of averages. The level of statistical significance was taken into account and the 95% of associated probability was established as significant, i.e., $p < 0.05$.

The results, which were compared with national and foreign authors, are shown in tables and graphs.

Table 1. Relation between age, sex and cardiotoxicity by anthracycline.

Age groups (years) and sex	No Cardiotoxicity		With Cardiotoxicity	
	Nº	%	Nº	%
Under de 45	5	33,3	4	30,7
Over de 45	10	66,7	9	69,3
Female	7	46,7	3	23,1
Male	8	53,3	10	76,9
Total	15	100	13	100

Source: Data Collection Sheet.

Table 2. Relationship between dose of anthracyclines and cardiotoxicity.

Cumulative dose	No Cardiotoxicity		With Cardiotoxicity		p
	Nº	%	Nº	%	
Less than 550 mg/m^2	2	13,3	7	53,8	0.032
Greater than 550 mg/m^2	13	86,7	6	46,2	0.716
Total	15	100	13	100	

Source: Data Collection Sheet.
$p<0.05$

Table 3. Relation between echocardiographic variables and cardiotoxicity.

Variables	Cardiotoxicity		p
	No	Yes	
	Mean ± SD	Mean ± SD	
Strain rate			
Baseline	1,2567 ± 0,7	1,1933 ± 0,6	0.140
1 month	1,4193 ± 0,9	0,8638 ± 0,2	0.043
6 months	1,1933 ± 0,6	0,8792 ± 0,3	0.132
12 months	1,3087 ± 0,71	0,7400 ± 0,24	0.260
Ɛ			
Baseline	24,73 ± 13,1	22,92 ± 3,0	0.500
1 month	21,13 ± 20,2	13,77 ± 4,1	0.031
6 months	20,33 ± 17,7	14,88 ± 3,2	0.119
12 months	22,48 ± 12,6	14,24 ± 3,2	0.979
LVEF			
Baseline	55 ± 4	50 ± 8	0.150
1 month	52,5 ± 5	54,6 ± 4	0.036
6 months	53,4 ± 5	53,8 ± 6	0.413
12 months	56,8 ± 5	52,7 ± 6	0.715

Source: Data Collection Sheet
$p < 0.05$

RESULTS

Table 1 shows that 69.3% of patients who developed cardiotoxicity (9/13) were older than 45, and 10 (76.9%) were male.

53.8% of these showed cardiotoxicity at a dose lower than 550 mg/m^2 (**Table 2**).

In **Table 3** the relationship of SR, Ɛ and LVEF, in relation to cardiotoxicity is observed. It can be noted that after administration of an anthracycline cycle, the mean values of SR and Ɛ decreased significantly at one month [0.8638 ± 0.2 (p = 0.043) and 13.77 ± 4.1 (p =

0.031), respectively] whereas LVEF remained within normal limits [54.6 ± 4 (p = 0.036)].

In patients who developed cardiotoxicity (**Table 4**), there was a slight increase in volume (21.13 ± 8.0 ml) and pressure values (10.91 ± 2.0 mmHg) of LA. Although no significant differences between both groups were evident.

Table 4. Volume/pressure ratio of the left atrium.

Left Atrium	Cardiotoxicity No Mean ± SD	Cardiotoxicity Yes Mean ± SD	p
Volume			
Baseline	19,97 ± 6,7	21,13 ± 8,0	0.601
1 month	22,51 ± 6,2	25,45 ± 7,4	0.165
6 months	23,65 ± 5,3	25,56 ± 6,6	0.095
12 months	23,71 ± 5,0	26,21 ± 6,8	0.217
Pressure			
Baseline	10,67 ± 1,7	10,91 ± 2,0	0.438
1 month	11,27 ± 3,1	12,66 ± 2,7	0.940
6 months	11,43 ± 1,8	12,01 ± 1,2	0.735
12 months	11,30 ± 1,0	11,48 ± 1,6	0.728

Source: Data Collection Sheet
p > 0.05

DISCUSSION

This research found that the most susceptible patients to develop cardiotoxicity were males over 45 years. This result contrasts with that found by Grenier *et al.*[11], where patients under 18 were more likely to develop this complication. However, another author[12] states that in extreme ages (under 18 and over 65), there is more vulnerability to develop cardiotoxicity, since they consider that myocytes from young patients are more susceptible to antineoplastic drugs, as well as in the case of adult patients, to preexisting subclinical myocardial damage.

The risk of clinical cardiotoxicity increases with cumulative doses of anthracyclines. Studies[13] have recorded its appearance with cumulative dose lower than 400 mg/m^2, and another report[14] states that the incidence of cardiotoxicity approaches 30% with cumulative dose of 500 mg/m^2. Our results agree with the literature reviewed, although the high percentage of cases (53.8%) that developed this complication is noteworthy, which probably could have been influenced by the sample size, the higher number of patients who received cumulative doses lower than 500 mg/m^2, in addition to individual variability.

Some authors suggest that left ventricular longitudinal mechanics depends predominantly on the subendocardium, which is more vulnerable and sensitive to the presence of myocardial disease[6,15,16]. In addition, the decreased compliance leads to alterations in the longitudinal relaxation, which causes a progressive delay of ventricular torsion, altering diastolic function and raising the ventricular filling pressures, in a phase in which LVEF remains normal[6]. This situation promotes the use of other echocardiographic techniques to early identify the onset of cardiotoxicity[6,15,16]. Based on this, other authors have shown that there is a significant reduction in the SR and Ɛ, with very low cumulative doses of antineoplastic drugs, while other echocardiographic variables such as LVEF and mitral Doppler remain unchanged[17]. Our results are consistent with the literature reviewed, where there was a reduction in the SR/Ɛ, being very significant after the end of a cycle ofanthracyclines. Based on the above mentioned it should be noted, that SR/Ɛ techniques could warn us about the presence of an underlying ventricular dysfunction associated with chemotherapy, despite a preserved LVEF[18].

The modest increase (not significant) in the volume and pressure of the LA occurs because when the atrium empties into a rigid ventricle (by increasing its diastolic pressure), both parameters are increased to maintain an adequate ejection volume, and considering that during ventricular diastole the LA is directly exposed to the pressures of the left ventricle, these parameters are indicators of the duration and severity of diastolic dysfunction[19].

It is believed that stopping chemotherapy after diagnosis of cardiotoxicity, along with medical treatment, could have influenced the lack of relationship between LA volume and the presence of cardiotoxicity. Similarly, the pressure values in the left atrium were not significant.The therapeutic manipulations performed in some patients, once cardiotoxicity was diagnosed, may have influenced this,which may have resulted in significant reduction in preload and filling pressures in general[20].

CONCLUSIONS

SR/Ɛ techniques were useful for early diagnosis of cardiotoxicity.

RECOMMENDATION

Further studies with more patients are needed. It is considered that the criterion for early detection of cardiotoxicity should not be limited only to reduced LVEF (greater than 10%), but the use of other echocardiographic tools (Ɛ/SR) should be taken into account, in order to promote a comprehensive assessment of the patient.

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