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Prospective clinical study on cardiotoxicity induced by anthracycline on a sample of 29 patients with breast cancer

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Abstract. Objective: This study is focused on the evaluation of the early and late cardiotoxic effects of chemotherapy with anthracyclines based on conventional electrocardiography, echocardiography transtoracic, and determination of the markers of myocardic, harming and invasive evaluation by endomyocardial punction-biopsy. Material and methods: The sample was formed by female patients with breast cancer, homogenous, the majority of them without preexisting cardiac pathology and without risk factors to develop this. Results and discussion: It was observed that the standard EKG examination is unspecific to detect the first signs of cardio toxicity, modifications appearing tardy to those with certain echocardiography signs or being possible the appearance of some EKG modifications. Concerning the echocardiographic and Doppler examination, the first suggestive modifications for cardiotoxicity were ascertained to the level of diastolic function of LV (left ventricle), but these appeared to a large number of patients and were slightly specific. The decline of the EF (ejection fraction) is the most specific sight of anthracyclines cardiotoxicity, resulting in a dilated cardiomyopathy, with the classic symptoms of cardiac failure. RT, generally with small doses, was associated CT in the majority of cases and did not determined modifications of the parameters of cardiac function.
Key Words: early and late cardiotoxicity, anthracycline, breast cancer.

Rezumat. Obiectiv : Studiul de faţă a avut drept obiectiv evaluarea efectelor cardiotoxice precoce şi tardive, secundare chimioterapiei (CT) cu antraciclină, bazându-ne pe electrocardiografia clasică (EKG), ecocardiografia transtoracică (ETT), determinarea markerilor de necroză miocardică şi evaluarea invazivă prin puncţia–biopsie endomiocardică (BEM). Material şi metodă : Lotul de studiu a fost omogen, format din femei cu neoplasm mamar, cu vârsta cuprinsă între 31 şi 58 de ani, majoritatea dintre ele fiind fără patologie cardiovasculară preexistentă şi fără factori de risc cardiovascular, precum şi cu o funcţie sistolică ventriculară stângă normală la debutul studiului. Rezultate şi discuţii : S-a constat că examenul EKG standard a fost nespecific pentru detectarea primelor semne de cardiotoxicitate, modificările apărând tardiv la cele cu semne ecocardiografice certe de cardiotoxicitate. Referitor la examenul ecocardiografic, primele modificări sugestive pentru efectele secundare toxice ale adriamicinei au fost la nivelul funcţiei diastolice (FD) a ventriculului stâng (VS), însă modificări ale FD au apărut la un număr mare de paciente şi au fost puţin specifice. Modificările fracţiei de ejecţie (FE) au fost cele mai specifice pentru detectarea cardiotoxicităţii şi au fost semnificative statistic atât la 6 luni postCT ($p=0,0018$), cât şi la 24 de luni postCT ($p=0,0035$). Modificările FE nu s-au corelat semnificativ cu doza totală de adriamicină/m^2 ($p>>0,05$). Radioterapia în doze relativ mici a fost asociată CT, însă nu a determinat modificări semnificative ale parametrilor funcţiei sistolice sau diastolice a VS. Confirmarea diagnostică în cazul suspiciunii de cardiotoxicitate a fost făcută pe baza examenului anatomopatologic efectuat din BEM recoltată din ventriculul drept.
Cuvinte cheie: cardiotoxicitate timpurie şi latentă, antraciclină, cancer de sân.

Introduction. The treatment with cytostatics has many side effects and cardio toxicity is already well known. Anthracyclines, represented first by Doxorubicin and Daunorubicine, are very efficient agents in many solid tumors and malign blood disease, but has the most important toxic cardiac effects (Yeh et al 2004; Floyd et al 2005). It is described an acute cardiotoxicity (Steinberg et al 1987), but especially a chronic/backward one (Praga et al 1979).

Cardiotoxicity mechanisms induced by anthracycline are represented by the harm of myocytes caused by oxygen reactive species, malfunction of the adrenergic system and release of proinflammatory cytokines (Praga et al 1979; Steinberz et al 1991; Bates et al 2006). Known risk factors are: cumulative dose, age of the patients, radiotherapy

and chemotherapy or the alternative one (Hitchock-Bryan et al 1986; Steinberz et al 1991; Nysom et al 1998; Sigal et al 1998; Swaim et al 2003).

In order to reduce the risk, different methods were tested: modification of the way of administration (Lipshultz et al 2002), structural modification of the anthracycline molecule with the appearance of new representatives, such as Epirubicine and Mitoxantrone (Henderson et al 1989; Kaklamani et al 2003; Minoti et al 2004; Young et al 2004), encapsulation in liposome (Young et al 2004) and use of cardioprotector agents, iron chelators, the most efficient being Dexrazoxane (Seifert et al 1994) or antioxidative, the studies with Probucol being promising (Li et al 2000). Monitorization during treatment with anthracycline is made by well known noninvasive methods: echocardiography (Force et al 2008; Cheillin et al 2003), radionuclide angiocardiography (Gottdiener et al 1981; Palmeri et al 1986), nuclear magnetic resonance (Oberholzer et al 2004), Holter monitorisation of electrocardiogram (Hrushesky et al 1991), measurement of myocardic necrosis markers (Force et al 2008; Herman et al 1999). Invasive exploration, like end-myocardial puncture-biopsy, is recognized as "golden standard" (Force et al 2008; Isner et al 1983).

Treatment of cardiomyopathy induced by anthracycline is the same as the therapy for heart failure, and it contains drugs like with angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists (sartans), βblockers, diuretics, cardiotonics (Force et al 2008; Silber et al 2004), and, in general, is followed by clinical improvement. Cardiac transplantation remains the extreme option, but a valuable one (Wigo et al 1995).

Aim. The objectives of this study were the evaluation of early and late cardio toxic effects of chemotherapy with anthracyclines, by the use of conventional electrocardiography (EKG), transchest echocardiography (ETT), determination of the markers of myocardic injury and invasive evaluation by endomyocardial punction-biopsy (BEM).

Material and Method. We surveyed a sample of female patients with breast cancer, between December 2004 - September 2008, which had started chemotherapy (CT) with anthracyclines in association with other cytostatics or in combination with radiotherapy (RT). The sample was formed by 34 female patients with breast cancer, generally homogenous, aged between 31 and 58 years old, the majority of them without preexisting cardiac pathology and without risk factors for the onset of the disease. Clinical characteristics of patients can be seen in Table 1. Five of them were lost from the study for various reasons (2 deaths, 3 were not came back for check-ups). In the end only 29 patients remained. Standard EKG exam was performed at the beginning of the treatment and with the occasion of upcoming visits at 6 months, 1 year, and 2 years, and then yearly. A Siemens, Sicard 460, device was used.

Transchest echocardiography (TTE) was performed in the same time sequence, respectively at the beginning, at 6 months, at 1 year and 2 years, then yearly but the check-ups were even more often for female patients with cardio toxicity, presumably that these patients were able to be present for visits. Initially, we used a Vingmed CFM 800 device (Sonotron, Horton, Norway) equipped with a transducer of 3.25 MHz, and later, a device VIVID 4 CE Medical System, with a transducer of 3.5 MHz.

We used the following sections: parasternal long and short axes, apical four chambers and apical two chambers. The end-systolic diameter (normal values (n.v.).: 21-40 mm) and end-diastolic diameter (n.v.: 35-60 mm) were measured based on known standards, by calculating due volumes too with the Simpson rule: end-systolic volume (n.v.: 18-65 ml) and end-diastolic volume (n.v.: 59-147 ml). After that, we calculated the ejection fraction (EF) of the left ventricle with the known formula. To analyze the diastolic function of the left ventricle was used the pulsed Doppler exam (PW), with the sample of volume placed between mitral sheets. The maximal velocity of the E wave, E/A wave was measured the ratio E/A, the time of deceleration of the E wave (TDE) and the time of isovolumetric relaxation (TRIV), with known normal values (Table 2).

Table 1

Clinical characteristics, therapeutic protocols and evolution of echocardiographic parameters for systolic and diastolic function of the left ventricle during screening

No.	Age	Scheme CT	Doze A	Asoc. RT (Gy)	Pathology cardiovascular pre-existent	Cardio vascular Risk factors	ETT1 (debut)		ETT2 (la 6+/-2 months)		ETT3 (la 24+/-3 months)	
							EF (%)	*DF*	*EF (%)*	*DF*	*EF (%)*	*DF*
1.	37	A+C	600 mg (330mg/m^2)	-	HTA		72	N	69	N	58	D
2.	41	A+C+Txf	600 mg (350mg/m^2)	-	-		59	N	55	D	52	D
3.	49	A+C+M	720 mg (350mg/m^2)	L/50	-	smoking	64	N	60	D	58	D
4.	53	A+C	820 mg (430 mg/m^2)	R/50	HTA	dyslipidemia	58	D	52	D	42	D
5.	40	A+C+T	540 mg (320 mg/m^2)	L/66	-		70	N	67	D	60	N
6.	43	A+C	480 mg (300mg/m^2)	-	-		74	N	64	N	58	D
7.	48	A+C	440 mg (270mg/m^2)	-	-		67	N	63	D	57	N
8.	34	A+C	300 mg (200mg/m^2)	L/50	-	smoking	76	N	72	N	65	N
9.	52	A+C+T	500 mg (350mg/m^2)	R/50	HTA	dyslipidemia	56	D	52	D	41	D
10.	39	A+C+T	500 mg (320mg/m^2)	L/50	-		70	N	62	D	54	D
11.	31	A+C+T	400 mg (290mg/m^2)	R/40L/40	-		75	N	68	N	64	N
12.	58	A+C+T	440 mg (220mg/m^2)	R/50	HTA	dyslipidemia	58	D	46	D	40	D
13.	45	A+C+Txf	600 mg (320mg/m^2)	L/50	-	dyslipidemia	62	N	56	D	50	D
14.	38	A+C	600 mg (350mg/m^2)	-	-		76	N	72	N	62	N
15.	32	A+C+T	440 mg (250mg/m^2)	-	-	smoking	72	N	68	N	65	N
16.	55	A+C	480 mg (280mg/m^2)	R/50	-	DZ	56	D	52	D	45	D
17.	36	A+C+T	550 mg (330mg/m^2)	-	-		68	N	56	D	54	D
18.	47	A+C+Txf	600 mg (300mg/m^2)	-	-	dyslipidemia	62	N	57	D	55	D
19.	40	A+C	440 mg (260mg/m^2)	L/50	-	smoking	65	N	62	N	54	D
20.	37	A+C+T	600 mg (360mg/m^2)	R/50	-		72	N	67	N	60	N
21.	52	A+C	480 mg (260mg/m^2)	-	HTA	dyslipidemia	54	D	45	D	43	D
22.	43	A+C+T	550 mg (270mg/m^2)	-	-		65	N	57	D	55	D
23.	39	A+C+T	600 mg (320mg/m^2)	L/50	-		72	N	68	N	56	D
24.	37	A+C+M	550 mg (300mg/m^2)	-	-		70	N	56	D	54	N
25.	51	A+C+Txf	480 mg (260mg/m^2)	R/50	HTA		56	D	52	D	50	D
26.	54	A+M+T	500 mg (280mg/m^2)	-	-	dyslipidemia	58	D	47	D	42	D
27.	39	A+C+T	660 mg (380mg/m^2)	L/50	-		68	N	60	N	52	D
28.	46	A+C+T	440 mg (250mg/m^2)	-	-		59	N	55	D	45	D
29.	42	A+C	600 mg (330mg/m^2)	-	-		73	N	64	D	58	N

CT - chemotherapy; A - Adriamicine; C - Cyclophosphamide; T - Taxol; Txf - Tamoxifen; M - Metrotexat; RT-radiotherapy; Gy - grey; ETT - trans chest echocardiography; EF - ejection fraction; DF - diastolic function; N -normal; D – dysfunctional; DZ - diabetes mellitus; HTA - arterial hypertension

Table 2

Normal values of the parameters of the diastolic function for the left ventricle (Ginghină et al 2005)

Parameters of Transmitral Flow	Normal Values
Maximal velocity of the precocious diastolic filling (E)	0.72 (0.44-1.00) m/s
Maximal velocity of the tardy diastolic filling through atrial contraction (A)	0.40 (0.20-0.60) m/s
Ratio E /A	1.9 (0.7-3.1)
Time of decelation of the wave E (TDE)	179 (139-219) ms
Time of relaxation isovolumetric (TRIV)	76 (54-98) ms

Results

Clinical Aspects. All patients were clinically evaluated by a physical general-historic examination of anterior illnesses, focused on the presence of cardiovascular preexistent pathology (arterial hypertension, ischemic heart disease, valvular heart diseases or cardiomyopathy, peripheral artery disease) and of the presence of the known cardiovascular risk factors: dyslipidemia, smoking, diabetes mellitus, obesity, chronic kidney disease (Force et al 2008). In the beginning of the study, we did not observed significant modifications at physical examination. Clinical aspect did not changed significantly during monitorization and it was not relevant for detection of those which developed cardio toxicity to anthracycline.

ECG Exams were normal for 27 of 29 female patients included in study, however for one patient we found a major right bundle branch block (RBBB) of unspecified duration, and, for another patient, we detected unspecified modifications in terminal phase ST-T, respectively oblate T wave and ST segment under level 0.5 mm in anterior derivations V_2-V_6 asymptotic. During observation period, some modifications appeared in the ECG aspect of some patients, initially for 3 patients, then for 2 patients. We observed zoomorphic ventricular premature beats, and, for one patient (34 years) modifications of terminal phase ST, T suggestive for myocardic ischemia, which were accompanied by chest pain. The modifications appeared three months after CT initiation with Adriamicine and Cyclophosphamide. The histopathologic examination performed in this case revealed early modifications of cardio toxicity that were induced by anthracycline, respectively by cytoplasmatic vacuolization and the spacing out of the myofibrillation structure. There were not significant stenosis on epicardial coronaries, just a slower flow, which raised the problem of an endothelial dysfunction, or of a pathology of small vessels, intramyocardic ones. This case falls into the second type of cardio toxicity to anthracycline, respectively the acute type.

Echocardiographic Examination was also performed at the beginning and subsequent at 6 months, 1 year, 2 years and respectively 3 years. Only at the check-ups at 6 and 24 months all patients were present. All echocardiographic parameters, related to the dimensions and systolic function, were found between normal limits at the beginning of the study. The diastolic function was slightly depreciated (decayed relaxation) at 7 patients aged over 50 years, probably in the context of physiological modifications specific for this age (Force et al 2008).

After 6 months from the completion of chemotherapy, we ascertained modifications statistically significant, basically of diastolic function of left ventricle, as evaluated by maximal velocity of E and A waves, the E/A ratio, TDE and TRIV. The E/A ratio decreased significantly at 6 months, especially because of the decreasing of maximal velocity of the E wave. In 19 cases this percent become under unit ($p=0.002$).

Regarding the level of systolic function of the left ventricle, as evaluated by EF, were found modifications statistically significant in both situations, with the occasion of the first evaluation at 6 months ($p=0.0018$), and also at 2 years ($p=0.0035$). For the examination after 24 months we determined that the EF decreased below the inferior

limit of the normal, namely under 50%, for 7 patients, but not under 40%, so it was a slightly systolic dysfunction. None of them had presented symptoms of congestive heart failure.

Modifications of EF and LV were not correlated with the total dose of Doxorubicin ($p>0.05$) which was small in all cases and it was far from the "threshold" known value (Praga et al 1979; Nysom et al 1998; Bates et al 2006), namely 550 mg/m^2. Association of Doxorubicin was made in all 7 cases with Cyclophosphamide, being known that it does not determine late modifications of EF and LV, being eventually implicated into an acute cardiotoxicity (Yeh et al 2004; Floyd et al 2005; Force et al 2008,). In the case of 4 patients, Taxol was associated, being known for the significant incensement of cardiotoxicity induced by anthracycline, this effect being possible to appear for larger doses than those considered as "threshold" (Praga et al 1979; Yeh et al 2004; Floyd et al 2005). Also, for the 7 patients for whom it was found the decrease of EF after 2 years after finishing CT, a slightly mitral regurgitation was found due to the increase of the dimensions of the secondary mitral ring and increase of LV dimensions.

For one patient, aged 34, with very good systolic function at the beginning of the chemoterapic treatment (EF of 76%), the decrease of EF with 5% after 3 months from the beginning of CT was accompanied by chest pains and modifications of the segment ST, T (Fig. 1), without segment kinetic turmoil at the level LV. CT ascertained in this case from the association of A with C, total doze of A being small, respectively 200 mg/m^2, and was completely stopped when chest pains and EKG modifications appeared. It was considered as adequate to perform the control coronarography and the endomyocardic punction biopsy. There were not found significant modifications, respectively stenosis on epicardial coronaries, just a lower flow, taking into account a possible endothelial dysfunction and of pathology of small vessels, intramyocardial. But, to the biopsy examination, specific modifications appeared of light anthracycline cardiotoxicity, respectively cytoplasmatic vacuolization, spacing out of the myofibrilative structure (Fig. 2). This aspect falls into the second type of cardio toxicity, but of under acute anthracycline. After CT interruption, the aspect of EKG was still the same for several months, but pains gave up after few days under treatment with beta blockers, trimetazidine and nitrites. Echocardiography observed even an improvement of EF and LV after 6 months. The patient refused mastectomy, in this case sectorectomy was performed. She also refused any other type of CT, and after one year breast cancer backslides. She does not checked in to subsequent examinations.

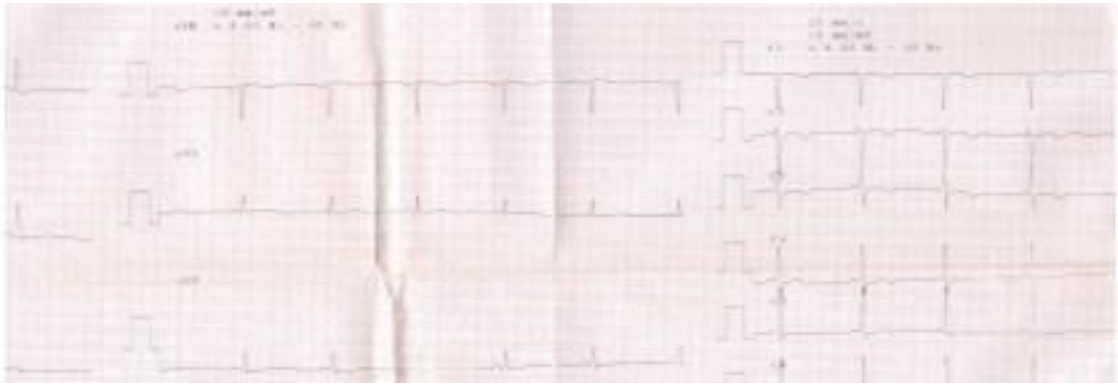

Figure 1. The aspect of EKG route reflecting diffuse modifications in terminal phase at 3 months after beginning CT with Adriamicine and Cyclophosphamide for a patient of 34 years with breast cancer, in the context of chest pains suggestive for myocardial ischemia.

Concerning bioumoral determination, we considered as useful dosing troponin T(TnT) and creatinkinase fraction MB (CK-MB), which has values slightly raised over superior limit of the normal, in this case it suggested an incipient lesion of cardiomyocites.

Under the treatment with beta blockers, nitrites and trimetazidine an obvious symptomatic amelioration was succeeded, a slight correction of the ECG aspect and reversion of EF to the initial value after 6 months. For this patient, the parameters of diastolic function had a slight decrease of maximal velocity of the E wave with equalization of the two vertex velocities, respectively of the E and A wave, which appeared with the occasion of the examination at 3 months. The ratio E/A became over unit again in the moment of examination at 6 months. Subsequent they have not came back to examination.

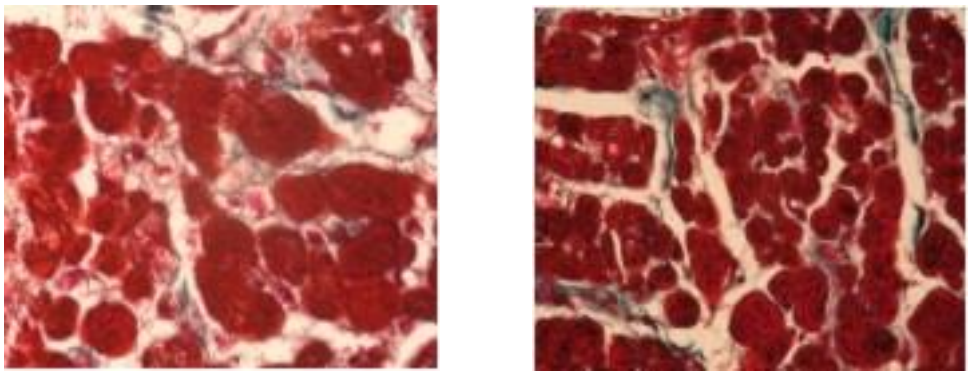

Figure 2. Endomyocardial biopsy from VD effectuated to the anterior patient, which points out cytoplasmatic vacuolisations and rarefaction myofibrilant structure without fibrosis elements.

The lowest value of EF was 40% and it was registered at 18 months from the beginning CT treatment in a patient of 53 years old with hypertension and dyslipidemia. Clinically speaking, the patient described the decrease of the effort tolerance and she does not presented objective signs of heart failure. Adriamicine, in total dose of 220 mg/m^2, was associated with Taxol and Ciclophosphamide. After 6 months of treatment with angiotensin II receptor antagonist (Irbesartan), small doses of beta blocker (Betaxolulum) and diuretic (Furosemid with Spironolactone) was found an increase of 7% of EF. The patient refused endomyocardial biopsy for diagnosis purpose. We did not found a statistically significant correlation in regard to presence of cardiovascular risk factors and appearance of the objective signs of cardiotoxicity, respectively modification of EF and of parameters of diastolic function of LV.

Supplementary, the echocardiographic aspects of the first examination were small or average pericardial collections in 5 asymptomatic patients, all of them having RT associated, being known the possibility of pericardial affection in this context (Shapiro et al 1998). In time, the pericardial collections have persisted under treatment with non-steroidian anti-inflammatory, that were instituted for a period of 3 or 4 weeks. Due to the absence of the symptoms and due to the small dimensions of collections, we did not considered as opportune the pericardial punction for diagnostic and therapeutic purpose. There were no radiological or echocardiographic signs of evolution towards pericardial constriction during monitorization of maximum four years, respectively thickness of the pericardia, appearance of pericardial calcification and Doppler modifications characteristics of the transtricuspidian flow, transmitral and from the VCI level. Although, it cannot be excluded this type of evolution and we recommended echocardiography and tomographic examinations aimed on pericardia, yearly, to all patients which have effectuated RT too.

Discussion. We found a large prevalence of the modifications of the diastolic function of LV during monitorization, although EF and LV have remained in normal limits. This suggests that diastolic dysfunction antecedes systolic dysfunction, accordingly with anterior reports (Force et al 2008). Therefore, surgery for diastolic function of LV, with help from echocardiography and especially with radioisotropic ventriculography, which has a superior sensitivity (Force et al 2008; Palmeri et al 1986), could provide proof of

cardiotoxicity in early stage. All patients that presented depreciation of systolic function, respectively decreasing in LVEF, had also modifications of the diastolic functions of LV.

ECG modifications were slightly sensitive to determine cardio toxicity induced by anthracic lines, these being, generally speaking, unspecific. It could be of high importance the analysis of the variability of the cardiac frequency, to Holter monitorization, considered to be the first under clinic marker of cardiac touching in the CT context (Hrushesky et al 1991). This examination was not available in our service at the date of the effectuation of the study.

Bioumoral dosing of CK-MB were also slightly sensitive and cannot be done to each control due to the momentary missing of the necessary biochemical reactive.

The most specific were the histopathology modifications distinguished by endomyocardial punction biopsy from RV, which were found in two patients with clinical and echocardiographic signs of cardiotoxicity. One patient refused the effectuation of this invasive exploration. There were also two anatomopathological examinations with normal aspect, effectuated for two patients with suggestive pains for chest angina and ischemic-injuries modifications on ECG of spell appeared during treatment, to which was considered as opportune effectuation of coronarography, but there was not found significant stenosis on epicardial vessels, just atherosclerotic plates, in the context of dyslipidemia and smoking. It was taken into account the possibility of convulsion over added or of some endothelial dysfunction for which a special treatment was set up.

As limitation of the study I could mention the following:

1. The reduced dimension of the studied sample.
2. Insufficient number of examinations for some patients with obvious elements of cardiotoxicity, generally from objective reasons depending on patient, so only two examinations could be found to which the entire sample had participated, respectively to 6 +/- 2 months and 24 +/- 3 months.
3. The loss from the study of five patients from various reasons: 3 were not present to further examinations and two deceased.
4. The absence of complex biochemical study as markers of harming myocytes (troponines T and E, creatinkinaze MB) or for heart failure (BNP, pro-BNP), generally speaking due to the absence of the necessary reactive at the specific moment.
5. The impossibility of effectuation of some studies of cardio protection due to the absence of those drugs (Dexrazoxane).

As clinical implications I tried to elaborate a toxicity score after analyzing all parameters implied in the appearance of cardio toxicity. The importance would be in the following order:

1. Total doze of anthracycline / m^2.
2. Preexistent cardiovascular pathology.
3. Association with other cardiotoxic chemotherapics (taxol, cyclophosphamide).

Even so, for any of these parameters we did not found a statistically significant correlation. This fact could be related to the age relatively young of the patients, risk factors with reduced prevalence and magnitude and small doses of anthracycline used in this therapeutically protocols, much under the value considered as "threshold" of 550 mg/m^2.

Conclusions

1. To perform a rigorous cardiologic survey of patients with CT with anthracycline, the rhythm of the examinations should be the following: in the first year at 3 months, in the second year at 6 months and then yearly for at least 10 years.
2. It was observed that the standard ECG examination is unspecific in detecting the first signs of cardiotoxicity, modifications appearing tardy to those with certain echocardiographic signs or being possible the appearance of some ECG modifications which are important for other reasons: electrolytic imbalance, anemia, myocardial ischemia due to coronary stenosis. It would be very useful Holter ECG monitorization during 24 hours to evaluate RR variability, which was

recently imposed as precocious marker of cardio toxicity for anthracyclines (modifications appears before echocardiographic ones and Doppler).

3. Concerning the echocardiographic and Doppler examination, the first suggestive modifications for cardio toxicity were ascertained to the level of diastolic function of LV, but these appeared to a large number of patients and were slightly specific. Later, modifications of systolic function of LV had appeared, much more specific, being checked by anatomopathological examination in four cases (27%) or appeared in the absence of other etiological conditions which to explain the decrease of EF of LV. It would be ideal the monitorization EF of LV by ventriculography radioisotopic (MUGA technique) according to actual guides, but this is very expensive and for the moment disposable in few centers.
4. RT, generally with small doses, was associated CT in the majority of cases and did not determined modifications of the parameters of cardiac function. Eventually, it was implicated in the etiology of pericardial collections appeared during monitorization of the patients.

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