JBUON 2013; 18(4): 1052-1057
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Can the epirubicin cardiotoxicity in cancer patients be prevented by angiotensin converting enzyme inhibitors?

D. Radulescu[1], E. Buzdugan[1], T. E. Ciuleanu[2], N. Todor[2], L. Stoicescu[1]

[1]University of Medicine and Pharmacy "Iuliu Hatieganu", 5th Medical Hospital, Department of Cardiology, Cluj-Napoca; [2]Oncology Institute "Prof. Dr. I. Chiricuta", Department of Chemotherapy, Cluj-Napoca, Romania

Summary

Purpose: *The aim of this study was to assess whether treatment with angiotensin converting enzyme inhibitors (ACEI) can prevent the alteration of left ventricular systolic and diastolic performance in cancer patients treated with different chemotherapy regimens containing epirubicin.*

Methods: *In this prospective study , 68 patients with different malignant tumors treated with epirubicin and perindopril in different chemotherapy protocols (study group), and a gender- and age-matched group of 68 patients with different malignant tumors treated with epirubicin without perindopril in different chemotherapy protocols (control group), were assessed by Doppler echocardiography. Left ventricular systolic function was assessed by measuring left ventricular ejection fraction (EF). Left ventricular diastolic function was assessed by Doppler ultrasound by evaluating the transmitral flow. We also assessed the QTc on the 12 lead electrocardiograms.*

Results: *At the end of chemotherapy the left ventricular systolic function was less altered in the study group compared to the control group and was superior in the study group (epirubicin+ACEI) compared to the control group (epirubicin alone). We documented a significantly deteriorated left ventricular diastolic function in both groups at the completion of chemotherapy. QTc time in both arms was also significantly prolonged.*

Conclusion: *In the present echo–Doppler study we documented a preserved left ventricular systolic performance in patients with various malignancies treated with epirubicin plus perindopril. Although co-treatment with ACEI prevented the alteration of systolic performance, it failed to prevent the deterioration of the left ventricular diastolic performance impairment due to poor left ventricular compliance.*

Key words: *angiotensin converting enzyme inhibitors, anthracyclines, chemotherapy, echocardiography, left ventricular function*

Introduction

Anthracycline antibiotics and topoisomerase II inhibitors are very efficient antineoplastic drugs administered to a wide variety of malignancies. These drugs need close cardiac follow up during and after treatment because they are cardiotoxic. The pathogenesis of cardiotoxicity is still not very well documented. Doxorubicinol, a metabolite of doxorubicin, inhibits the mitochondrial iron-pumping proteins inducing chronic cardiomyopathy [1,2]. High baseline superoxide dismutase activity predicts doxorubicin-induced cardiotoxicity in humans, mainly because recruitment of antioxidant defense mechanisms may be limited [3,4]. In doses over 900 mg/m^2 epirubicin is cardiotoxic. Studies have documented that even in lower doses such as 300 mg/m^2, in childhood cancer survivors, may be cardiotoxic, in time [5]. Endomyocardial biopsy represents the technique of election in documenting cardiotoxicity, but echocardiography is a noninvasive, quite sensitive and specific method, easy to perform. Anthracyclines generate a depreciation of the ventricular diastolic and systolic function, with a secondary decreased EF.

The aim of the present study was to assess whether treatment with ACEI can prevent the left ventricular diastolic and systolic performance dysfunction in cancer patients treated with dif-

Correspondence to: Dan Radulescu, MD, PhD. 5th Medical Hospital, Department of Cardiology, Tabacarilor Street, No. 11, Cluj-Napoca 400139, Romania. Tel: + 40 264 437050, Fax: + 40 264 438256, E-mail: dan_rad31@yahoo.com
Received: 14/04/2013; Accepted: 28/05/2013

ferent chemotherapy regimens containing epirubicin, using Doppler echocardiography.

Methods

This study started after the University Ethics Committee has given its approval.

Patients and treatment

The group of epirubicin and ACEI treated patients (study group) consisted of 68 patients (36 males and 32 females), with an average age of 53.88 ± 10.01 years, mainly from our outpatient clinic who had different malignant tumors with a definite diagnosis of malignancy established with standard criteria. All the patients were admitted in our clinic in the last 5 years (2007-2012) and all were treated with epirubicin in total doses up to 550 mg/m^2 and in association with ACEI. Patients who had undergone other chemotherapies prior to admission were ruled out. The control group consisted of 68 gender-and age-matched subjects (38 males and 30 females, average age 46.28±14.42 years) diagnosed with malignancies, who had no history of cardiovascular disease and had undergone chemotherapy with epirubicin in different chemotherapy protocols, but no ACEI. The patients from both groups were treated for the following tumor localizations: lung, lymphoma, nasopharynx, breast, urinary bladder, and stomach. Patients with hypertension, myocardial ischemia, diabetes mellitus, valvular heart disease, and other diseases affecting the left ventricular diastolic function were excluded from both groups.

Chemotherapy

Epirubicin was administered in the following regimens: CEV (cyclophosphamide, epirubicin, vincristine in lung cancer), CEOP/EBVD (cyclophosphamide, epirubicin, vincristine, prednisone/ epirubicin, bleomycin, vinblastine, dacarbazine in lymphomas), BEC (bleomycin, epirubicin, cisplatin in cancer of the nasopharynx), CISCE (cisplatin, epirubicin, cyclophosphamide in urinary bladder cancer), FE (5-fluorouracil, epirubicin in gastric cancer), FEC (5-fluorouracil, epirubicin, cyclophosphamide in breast cancer).

EC chemotherapy consisted of 90 mg/m^2 epirubicin and 500 mg/m^2 cyclophosphamide on day 1, repeated every 21 days, for 5 cycles.

Therapy with ACEI

Perindopril was administered at a dose of 10 mg daily. Patients in the study group started ACEI therapy at the beginning of chemotherapy and continued it 1 year after completing chemotherapy.

Cardiac function assessment

Cardiac assessment included history, physical examination, echocardiography, and ECG. It was performed before starting chemotherapy, before each cycle, after finishing and at 6 months up to 1 year after the end of chemotherapy.

Echocardiography

An Aloka echocardiograph with a 3.5 MHz transducer and Doppler mode was used, the examination being performed in conformity with the guidelines of the American Society of Echocardiography. The left ventricular systolic performance was assessed by measuring the global EF. The left ventricular diastolic function was assessed, before starting, before each cycle, at the end chemotherapy, and at 6 months and 1 year after chemotherapy. We measured the transmitral flow, the Doppler being parallel with the mitral flow with the cursor placed at the level of the mitral anulus in order to detect the early peak wave velocity (Emax) and the atrial peak flow velocity (Amax). The ratio of Emax/Amax (normal >1), the pressure half time (PHT) of the E wave, the deceleration time of the E wave (normal <220 msec) and the isovolumic relaxation time (IVRT; normal <100 msec) were also calculated. We assessed the diastolic performance also by tissue Doppler imaging by measuring Ea velocity at lateral mitral annulus (apical view). We considered a value <8 cm/s to indicate altered ventricular relaxation (helpful in differentiating a pseudonormal from a normal transmitral flow) [6].

Electrocardiogram

On the standard 12-lead ECG, the QT time was corrected for heart rate (QTc) using the Bazett's equation (QTc =QT/√RR), the normal value being <440 msec.

Statistics

MS EXCEL version 2003 and SPSS version 16 were used for computer-aided analysis and figure generation. Unpaired t-test for normally distributed variables (respectively the Wilcoxon two sample test for skewed distributions) for comparison between 2 groups and the F test for comparison between more than 2 groups were used. Normally distributed variables were reported as mean ± standard deviation (SD), and the skewed distributed ones as median and range. Pearson's coefficient test was used to assess correlations between variables. In all analyses statistical significance was set at $p<0.05$.

Results

Cardiac assessment

During the 1 year assessment, we did not document cases with overt congestive heart failure, or with major heart rhythm problems. The mean systolic and diastolic pressures in both groups were within normal limits at the beginning of treatment.

Table 1. Echocardiographic parameters in the control group (mean ± standard deviation) before and after completion of chemotherapy

Parameter	*Control group before chemotherapy*	*Control group after chemotherapy*	*p-value*
Age (years)	48.24 ± 12.2	48.24 ± 12.2	
BP systole	136 ± 24	137 ± 20	NS
BP diastole	81± 20	82 ± 18	NS
V rate	76 ± 12	78 ± 16	NS
C index	4.40 ± 1.20	4.56 ± 1.22	NS
EF	59.46 ± 7.12	50.09 ± 6.48	<0.05
Emax	69.35 ± 10.86	48.12% ± 4.44	<0.001
Amax	36.64 ± 8.28	57.88 ± 5.68	<0.001
PHT	52.62 ± 12.54	66.64 ± 12.64	<0.001
IVRT	85.50 ± 12.22	98.22 ± 11.33	<0.05
DT (msec)	169 ± 37	204 ± 38	<0.05
QTc time (msec)	360 ± 12	436 ± 12	<0.05

BP: blood pressure, V rate: ventricular rate, C index: cardiac index, EF: ejection fraction (%), Emax: maximal velocity of the E wave (cm/sec), Amax: maximal velocity of the A wave (cm/sec), PHT: pressure half time (msec), IVRT: isovolumic relaxation time (msec), DT: E wave deceleration time, QTc: corrected QT interval, NS: non significant

Table 2. Echocardiographic parameters in the study group (mean ± standard deviation) before and after chemotherapy

Parameter	*Study group (+ACEI) before chemotherapy*	*Study group after chemotherapy*	*p-value*
Age (years)	49.66 ± 9.02	49.66 ± 9.02	
BP systole	140 ± 24	118 ± 20	<0.05
BP diastole	82 ± 22	71 ± 18	<0.05
V rate	77 ± 12	80 ± 10	NS
C index	4.52 ± 1.20	4.58 ± 1.10	NS
EF	58.48 ± 6.12	57.09 ± 6.48	NS
Emax	68.34 ± 10.44	49.08% ± 3.54	<0.001
Amax	37.22 ± 6.28	56.66 ± 4.44	<0.001
PHT	54.22 ± 10.22	64.44 ± 11.22	<0.001
IVRT	86.40 ± 10.44	96.14 ± 12.20	<0.05
DT (msec)	166 ± 66	200 ± 33	<0.05
QTc time (msec)	366 ± 10	434 ± 14	<0.05

For abbreviations see footnote of Table 1

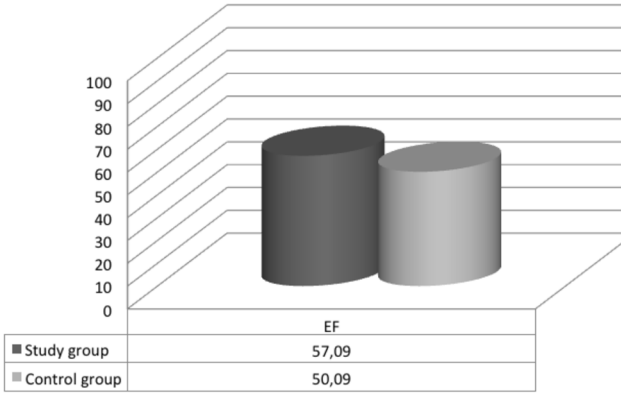

Figure 1. Ejection fraction (EF) in the study and control group, after chemotherapy (p<0.01).

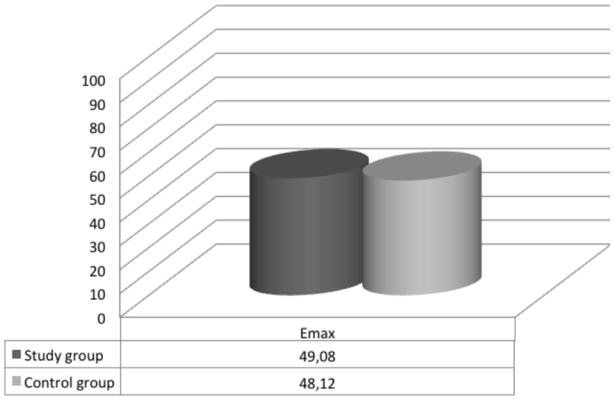

Figure 2. Emax in the study and control group, after chemotherapy (p>0.05).

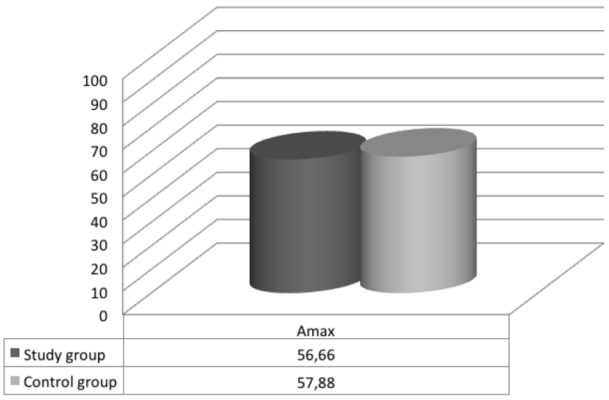

Figure 3. Amax in the study and control group, after chemotherapy (p>0.05).

Echocardiography

The left ventricular systolic performance was significantly altered at the end of chemotherapy in the control group, but remained preserved in the study group (from 59.46% ± 7.12 to 50.09% ± 6.48 in the control group and from 58.48 % ± 6.12 to 57.09 % ± 6.48 in the study group ; p<0.05).

We documented an altered left ventricular diastolic performance in both groups at the end of chemotherapy (Tables 1 and 2). Emax decreased significantly in the control group (69.35 ± 10.86 to 48.12% ± 4.44 cm/s p<0.001) with an increase of Amax (36.64 ± 8.28 to 57.88± 5.68 cm/s p<0.001). In the study group Emax also decreased significantly (68.34 ± 10.44 to 49.08% ± 3.54 cm/s p<0.001) with an increase of Amax (37.22 ± 6.28 to 56.66± 4.44 cm/s p<0.001). The mitral E/A ratio became subunitary in both groups. The diastolic performance was also assessed by TDI, by measuring Ea velocity

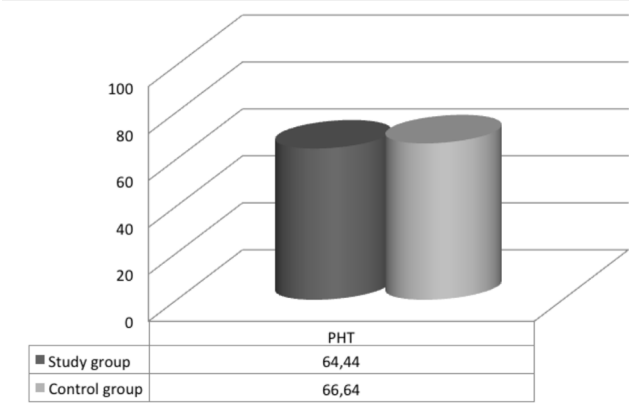

Figure 4. PHT in the study and control group, after chemotherapy (p>0.05).

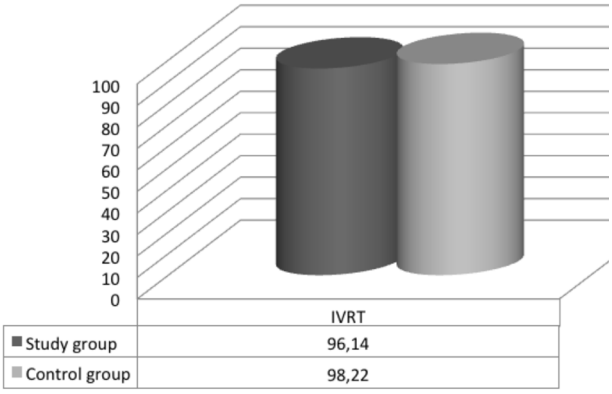

Figure 5. IVRT in the study and control group, after chemotherapy (p>0.05).

at lateral mitral annulus (apical view). A value <8 cm/s was considered to indicate altered ventricular relaxation (helpful in differentiating a pseudonormal from a normal transmitral flow). The decrement of Emax and increment of Amax at the end of chemotherapy presented no significant statistical difference between the control and the study group (Figure 1). The PHT of E wave was significantly prolonged in both groups at the end of chemotherapy (from 52.62 ± 12.54 to 66.64 ± 12.64 msec in the control group, and from 54.22 ± 10.22 to 64.44 ± 11.22 msec in the study group ; p<0.001). The E wave deceleration time was significantly prolonged in both arms at the end of chemotherapy (from 169 ± 37 to 204 ± 38 msec in the control group, and from 166 ± 66 to 200 ± 33 msec in the study group; p<0.05). Also the IVRT was significantly prolonged in both groups at the completion of chemotherapy (from 85.50 ± 12.22 to 98.22 ± 11.33 msec in the control group, and from 86.40 ± 10.44 to 96.14 ± 12.20 msec in the study group; p<0.05). There were no significant statistical differences concerning the prolongation of either PHT, or E wave deceleration, or IVRT between the control and the study group at the end of chemotherapy (Figures 2-6).

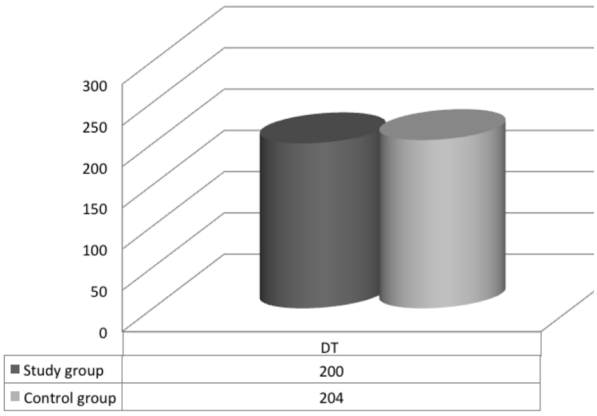

Figure 6. DT of E wave the study and control group, after chemotherapy (p>0.05).

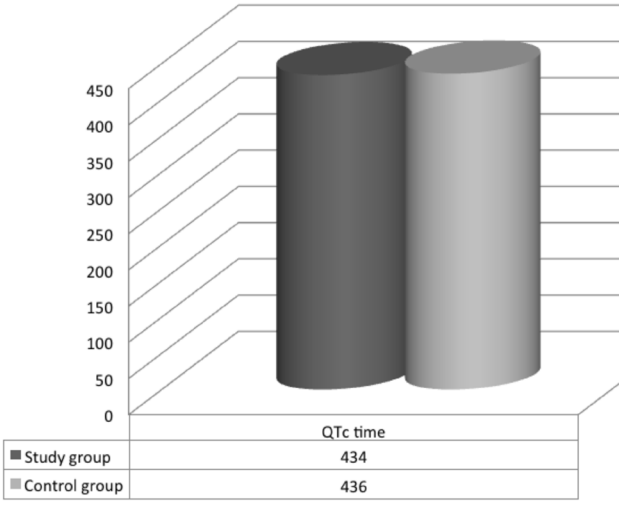

Figure 7. QTc time in the study and control group, after chemotherapy (p>0.05).

Electrocardiograms

The QTc time was prolonged in both groups at the end of therapy (from 360 ± 12 msec to 436± 12 msec in the control group, and from 366 ± 10 msec to 434± 14 msec in the study group; p<0.05). There was no significant statistical difference concerning this prolongation between the control and the study group at the end of chemotherapy (Figure 7).

Discussion

The mechanism of action of anthracyclines is by insertion into DNA pairs, with DNA rupture, and decreased DNA, RNA and protein synthesis. Heart fibers mitochondria possess an enzyme which converts anthracyclines to metabolites that generate oxidative stress, damage to mitochondrial DNA , and apoptosis of muscular myocardial fibers [7-10]. The anthracyclines' metabolites alter the intracellular iron handling. Risk factors for

cadiotoxicity are individual susceptibility, gender and age of the patient, the cumulative drug dose, prior irradiation, associated administration of other chemotherapeutic drugs, and existence of heart disease [11-15]. Epirubicin is much less cardiotoxic than doxorubicin. In order to prevent cardiomyopathy, the maximal total epirubicin dose is up to 900 mg/m^2. If cyclophosphamide, transtuzumab, or paclitaxel or radiotherapy are administered concomitantly with epirubicin, cardiotoxicity is even higher [16-23]. Associated therapy with trastuzumab and, to a lesser extent, alemtuzumab may induce heart failure or asymptomatic left ventricular dysfunction in 1-10% of the patients.

Tyrosine kinase inhibitors may produce left ventricular dysfunction. In some patients treated with imatinib mesylate, but also in a proportion of those receiving sunitinib or erlotinib, lapatinib and dasatinib, left ventricular dysfunction was documented [20].

Myocardial biopsy is considered by some the best and most certain method in documenting anthracycline cardiotoxicity, but it has the disadvantage of being invasive and since biopsies only involve the right ventricle, they may be irrelevant. A noninvasive method is the serial determination of serum troponin, released from destroyed myocytes; the serum concentration of troponins is in a direct proportion with the quantity of anthracyclines administered and also with the degree of cardiotoxicity [24,25].

Doppler echocardiography is a noninvasive technique, helpful in evaluating the ventricular diastolic and systolic performance in patients treated with chemotherapy [26]. It has some limits (moderate sensitivity, low reproducibility between different laboratories, not the most accurate method in evaluating precisely ventricular performance). Ultrasound monitoring of cardiac damage during chemotherapy only seldom documents major cardiac function alterations that may modify significantly the treatment strategies. Radionuclide angiography, if performed with exercise test to measure the ventricular functional reserve and deterioration of diastolic performance which precedes the alteration of systolic function, may be the best noninvasive method for monitoring cardiotoxicity. New methods in detecting cardiotoxicity are: indium-111 antimyosin scintigraphy for the detection of myocardial injury, and iodine-123 meta-iodobenzylguanidine scintigraphy to assess cardiac adrenergic innervation, that is affected by anthracyclines Magnetic resonance spectroscopy and positron emission tomography scanning are also being investigated to evaluate anthracycline cardiac damage. In patients with no risk factors, ultrasound or multigated acquisition scanning may be sufficient in preventing toxicity. In patients with risk factors, ventricular biopsy may also be needed. Serum troponin and brain natriuretic peptide measurements may help in detecting and preventing cardiotoxicity.

Methods helpful in diminishing cardiotoxicity of chemotherapeutic drugs are : new and less cardiotoxic chemotherapeutic drugs (epirubicin is less cardiotoxic than doxorubicin, nonliposomal doxorubicin is also less cardiotoxic than liposomal one), longer infusions, periodic myocardial biopsy and noninvasive monitoring of ventricular performance, and use of adjunctive agents. The best known agent is dexrazoxane, which chelates iron released from intracellular storage as a consequence of lipid peroxidation. As this agent induces myelosuppression, it may interfere with cancer therapy, and because it is not known if it protects against late cardiovascular effects, new agents are being developed : coenzyme Q10, carvedilol, statins, enalapril. Some studies in children treated with chemotherapy documented that enalapril may have some effects in preventing cardiotoxicity [27,28].

The aim of the present study was to assess whether treatment with angiotensin converting enzyme inhibitors (ACEI) can prevent the left ventricular systolic and diastolic performance dysfunction in cancer patients treated with different chemotherapy regimens containing epirubicin, using Doppler echocardiography. The left ventricular systolic performance was significantly altered at the end of chemotherapy in the control group, but remained preserved in the study group. We documented an altered left ventricular diastolic performance in both groups at the end of chemotherapy. There was no significant statistical difference concerning the alteration of left ventricular diastolic performance between the control and the study group at the end of chemotherapy.

The QTc time was prolonged in both groups at the end of therapy. There was no significant statistical difference concerning this prolongation between the control and the study group at the end of chemotherapy. A prolonged QTc (alteration in repolarization of myocardium) is a sign of cardiotoxicity.

Conclusion

In the present echo–Doppler study a preserved left ventricular systolic performance was documented in patients with various malignancies treated with epirubicin and perindopril. At

the end of chemotherapy, left ventricular systolic function was superior in the study group (anthracycline+ACEI) compared to the control group (anthracycline alone). Although anthracycline plus ACEI prevented the alteration of systolic performance, it failed in preventing the deterioration of left ventricular diastolic performance, impairment due to poor left ventricular compliance.

References

1. Minotti G, Recalcati S, Mordente A et al. The secondary alcohol metabolite of doxorubicin irreversibly inactivates aconitase/iron regulatory protein-1 in cytosolic fractions from human myocardium. FASEB J 1998;12:541-552.
2. Minotti G, Ronchi R, Salvatorelli E, Menna P, Cairo G. Doxorubicin irreversibly inactivates iron regulatory proteins 1 and 2 in cardiomyocytes:evidence for distinct metabolic pathways and implications for iron-mediated cardiotoxicity of antitumor therapy. Cancer Res 2001;61:8422-8428.
3. Pereira RP, Fleck JF, Rohde LE et al. Superoxide dismutase activity in doxorubicin-induced cardiotoxicity in humans:A novel tool for risk stratification. Proc Am Soc Clin Oncol 2004;22:738s (abstr 8036).
4. Zhang S, Liu X, Bawa-Khalfe T et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012;18:1639-1642.
5. Hudson MM, Rai SN, Deng H et al. Non-invasive evaluation of late cardiac toxicity in childhood cancer survivors. Proc Am Soc Clin Oncol 2004;22:530s (abstr 6047).
6. Ho CY, Solomon SD. A Clinician's Guide to Tissue Doppler Imaging. Circulation 2006;113:e396-e398.
7. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 1973;32:302–314.
8. Bristow MR. Clinical spectrum of anthracycline cardiotoxicity. Cancer Treat Rep 1978;62:873-879.
9. Kantrowitz NE. Cardiotoxicite des agents antitumoraux. Acquis Nouv Pathol Cardiovasc 1985;27:285-291.
10. Cittadini A. Subclinical cardiotoxicity by doxorubicin. Eur Heart J 1991;12:1000-1005.
11. Ferrari E. Repercussions cardiaques de la chimiotherapie. Medicorama 1982;295:5-19.
12. Gustafsson F, Torp- Pedersen C, Burchardt H et al. Female sex is associated with a better long term survival in patients hospitalized with congestive heart failure. Eur Heart J 2004;25:129 -135.
13. Swain MM, Whaley FS, Ewer MS. Congestive heart failure of patients treated with doxorubicin. A retrospective analysis of three trials. Cancer 2003;97:2869 – 2879.
14. Massie BM, Shah NB. The heart failure epidemic. Curr Opin Cardiol 1996;11:221–226.
15. Schwartz K, Mercadier JJ. Molecular and cellular biology of heart failure. Curr Opin Cardiol 1996;11:227-236.
16. Valero V, Gill E, Paton V et al. Normal cardiac biopsy results following co-administration of doxorubicin (A), cyclophosphamide (C) and trastuzumab (H) to women with HER2 positive metastatic breast cancer. Proc Am Soc Clin Oncol 2004;22:20s (abstr 572).
17. Keefe DL. Tratuzumab- associated cardiotoxicity.Cancer 2002 ;95:1592–1600.
18. Romond EH, Perez EA, Bryant J et al. Transtuzumab plus adjuvant chemotherapy for operable HER 2 positive breast cancer. N Engl J Med 2005;353:1673–1684.
19. Piccart-Gebhart MJ, Proctor M, Leyland – Jones B et al.Transtuzumab after adjuvant chemotherapy in HER 2 positive breast cancer. N Engl J Med 2005;353:1659 –1672.
20. Monsuez JJ, Charniot JC, Vignat N, Artigou JY. Cardiac side-effects of cancer chemotherapy. Int J Cardiol 2010;144:315.
21. Giordano SH, Booser DJ, Murray JL et al. A detailed evaluation of cardiac toxicity :A phase II study of study of doxorubicin and one- or three- hour infusion paclitaxel in patients with metastatic breast cancer. Clin Cancer Res 2002;8:3360–3368.
22. Lee PJ, Mallik R. Cardiovascular effects of radiation therapy:Practical approach to radiation therapy – induced heart disease. Cardiol in Rev 2005;13:80-86.
23. Meinardi MT, Van Veldhuisen DJ, Gietema JA et al. Prospective evaluation of early cardiac damage induced by epirubicin – containing adjuvant chemotherapy and locoregional radiotherapy in breast cancer patients. J Clin Oncol 2001;19:2746-2753.
24. Cardinale D, Sandri MT, Martinoni A et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol 2000;36:517-524.
25. Kilickap S, Barista I, Akgul E et al. Increased troponin-T level is associated with anthracyclines-induced diastolic dysfunction of the left ventricle. Proc Am Soc Clin Oncol 2004. J Clin Oncol 2004, 22 (14S) :890s (abstr 9722).
26. Tjeerdsma G, Meinardi MT, van der Graaf WTA et al. Early detection of anthracyclines induced cardiotoxicity in asymptomatic patients with normal left ventricular systolic function:autonomic versus echocardiographic variables. Heart 1999;81:419-423.
27. Iarussi D, Indolfi P, Casale F, Martino V, Di Tullio MT, Calabrò R. Anthracycline-induced cardiotoxicity in children with cancer:strategies for prevention and management. Paediatr Drugs 2005;7:67-76.
28. Cardinale D, Colombo A, Sandri MT et al. Prevention of High-Dose Chemotherapy–Induced Cardiotoxicity in High-Risk Patients by Angiotensin-Converting Enzyme Inhibition. Circulation 2006;114:2474-2481.