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

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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/m² epirubicin is cardiotoxic. Studies have documented that even in lower doses such as 300 mg/m², 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-
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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/m² 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/m² epirubicin and 500 mg/m² 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 anulus (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.
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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 ± 6.48 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...
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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/m². If cyclophosphamide, trastuzumab, 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. Radiouclide 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


JBUON 2013; 18(4): 1057