THESISES

Anthracycline induced cardiomyopathy and endothelin-1

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1. INTRODUCTION

Adriamycine is widely used in monotherapy and in combination since the 1960s, as an anticancer drug. The therapeutic use of adriamycine is limited by its dose-dependent cardiotoxicity.

According to the latest estimation of WHO, in the year 2000 more than 340,000 patients suffered from Hodgkin and non-Hodgkin lymphoma. CHOP is the most frequently used therapeutic combination against non-Hodgkin lymphoma. It consists of cyclophosphamide, hydroxidaunorubicin, vincristine and prednisone. For Hodgkin’s disease the similarly popular treatment is ABVD, containing doxorubicine, bleomycin, vinblastine and dacarbasine.

In consequence of the cardiotoxic effect of anthracyclines, heart failure can develop one or even 4-20 years after the treatment. 4% of patients receiving 500-550 mg/m² adriamycine will have heart failure. This ratio is 18% and 36 % with the doses 550-600 mg/m² and
over 600 mg/m², respectively. Evaluation of the risk of cardiomyopathy before and after administration of adriamycine has great significance for the further treatment of patients.

Pathomechanism of adriamycine-induced cardiomyopathy is multifactorial. Besides direct DNA destroying effect of the drug, free radicals may play important role in this. The oxidative stress can inhibit the intracellular molecular processes and can cause structural destruction, too. Circulating proinflammatory citokines could also have role in the development of cardiotoxicity.

Vessels are covered by endothelium. Its function is to support the vascular tone and structure. Endothelium reacts to stimuli by secretion of vasoactive substances and signal transduction molecules. The imbalance of the reversely acting molecules presents as endothel dysfunction. Oxidative stress causes endothel dysfunction. Endothel dysfunction is a complex process, which can be investigated in different ways. Part of the methods target the circulating vasoactive substances, as
endothelin-1 (ET-1), von Willebrand factor, adhesion molecules. Most important of them is ET-1. The cardiac endothelial cells regulate the functions of the cardiomyocytes by a paracrine manner, and ET-1 plays an important role in this. Increase in plasma ET-1 level and ET(A) receptor number were observed in heart failure patients with NYHA III-IV functional stage.

2. OBJECTIVES

1. Investigation of cardiotoxic effect of anthracyclines and the subsequent upon developing cardiomyopathy by echocardiography.

2. Investigation of anthracycline induced endothel dysfunction by measurement of the plasma level of the most important mediator, ET-1.

3. Revealing relationship between plasma ET-1 level and citostatics-induced left ventricular dysfunction.
4. Assessment of echocardiographic parameters, which are suitable for early detection of cardiotoxicity, simple, can quickly carried out, and convenient for long term follow-up of patients.

We desired to investigate the long term effects of anthracyclines, therefore the assessments occurred after cessation of anthracycline treatment and one year later.

3. PATIENTS AND METHODS

3.1 Patients

We included patients with Hodgkin or non-Hodgkin lymphoma receiving anthracycline containing chemotherapy without known cardiac abnormalities.

The cumulative dose of anthracycline was maximum 450 mg/m².
Our study was conducted according the principles of the Helsinki Declaration and with the permission of the Ethics Committee of Semmelweis University. All patients undesignated a written informed consent before the study.

3.1.1 Data of patients investigated after cessation of anthracycline treatment

At the first processing of our data we used the data of 31 patients (13 male, 18 female; age 19-70, average: 38,93 years). 24 patients had Hodgkin lymphoma and received ABVD therapy. The 7 non-Hodgkin lymphoma patients were treated with CHOP. We processed the results of examinations before and after the anthracycline treatment.

3.1.2 Data of patients investigated after cessation of anthracycline treatment and one year later
Patients were followed-up and examinations were repeated one year later. Follow-up was completed in 20 patients (20-68, average: 36,1 years, 7 male and 13 female). Fourteen patients had Hodgkin, and 6 non-Hodgkin lymphomas.

3.2 Methods

The left ventricular systolic and diastolic performance were assessed by echocardiography (Hewlett-Packard Sonos 2500), and blood samples were taken for plasma ET-1 assay before, 2-4 weeks after the anthracyline treatment and one year later.

Patients were examined in standard settings according the recommendation of the American Society of Echocardiography.

Results were averaged from 5 different measurements, done by the same sonographer.
3.2.1 Left ventricular systolic function

The left ventricular systolic function was characterized with the ejection fraction (EF) and the aortic outflow peak velocity time integral (VTI). EF was calculated with the modified Quinones formule, from the systolic and diastolic left ventricular diameters obtained from the level of the mitral valve. EF was also assessed directly with acoustic quantification (AQ). Timing of systole and diastole was measured with the help of simultaneously recorded ECG.

3.2.2 Left ventricular diastolic function

Diastolic function was assessed by measuring the transmitral flow parameters, ie. early (E), atrial (A) waves and deceleration time (DT) and calculating the E/A ratio

3.2.3 Doppler index
Doppler index was calculated as the ratio of the sum of the isovolumetric relaxing time and the contracting time and the EF. This index is characterizing both the systolic and the diastolic left ventricular function.

3.2.4 Assessment of plasma ET-1 level

Blood samples were collected from the antecubital vein into ice-cold tubes containing EDTA. After centrifugation (3000 g for 10 minutes) samples were stored at -70 C until analysis. Plasma levels of ET-1 were measured using a conventional, 96-well, sandwich enzyme immunoassay (ELISA No. BI-20052) developed by Biomedica GmbH (Vienna, Austria).

3.2.5 Estimation of clinical signs of heart failure

For estimation of heart failure severity the New York Heart Association (NYHA) functional stages were used.
3.2.6 Statistical analysis

Our results are expressed as average ± SD. For statistical analysis the Wilcoxon and ANOVA tests were used.

4. RESULTS

4.1 Results after anthracycline treatment

- Plasma ET-1 level significantly decreased after anthracyline containing chemotherapy from 5.6 ± 3.54 pg/ml to 3.16 ± 0.97 pg/ml (p < 0.0006).
- EF also decreased both by calculation with the Quinones formula (56.45 ± 5.05 vs. 48.71 ± 5.1 %, p < 0.0001) and by direct measurement with AQ (53.13 ± 4.51 vs. 47.85 ± 5.54 %, p < 0.0001). There was no statistical difference between the two methods.
- DT increased significantly from 168.1 ± 36.83 ms to 206.5 ± 58.88 ms (p < 0.0073).
• There was a tendency in E/A ratio to decrease, but changes were not statistically significant.
• There were no significant changes in VTI and DI before and after the therapy.

4.2 Results after anthracycline treatment and at one year follow-up

• ET-1 plasma level has decreased significantly after treatment (5,47 ± 3,34 vs. 3,44 ± 0,69 pg/ml, p < 0,02) and this significant changes were observed at one-year follow-up (3,43 ± 0,57 pg/ml, p< 0,008).
• EF decreased significantly after chemotherapy (57,80 ± 4,73 % vs. 48,05 ± 5,65 %, p < 0,0001) and this remained until one year (50,65 ± 8,87 % p < 0,0007).
• The E/A ratio decreased significantly after treatment (1,35 ± 0,40 vs. 1,15 ± 0,40, p < 0,01) and a further decrease was observed at one year follow-up (1,10 ± 0,34, p < 0,003).
• DT increased after chemotherapy (177.00 ± 44.96 vs. 209.50 ± 66.25 ms, p < 0.04) and this change was observed at one year (223.25 ± 46.85 ms, p < 0.0022), too.
• There was no statistical measurable change in DI and VTI during the study.

4.3 Relationship between plasma ET-1 and echocardiographic parameters

There was no statistically proved relationship between plasma ET-1 levels and echocardiographic parameters.

4.4 NYHA functional stages

After chemotherapy 4 patients were in NYHA II and 1 in NYHA III functional stage, at one year this numbers were 4 and 2, respectively. Any of the patients presented with NYHA IV signs.
CONCLUSIONS

1. Decrease of EF, E/A ratio and increase of DT after anthracycline treatment indicates left ventricular systolic and diastolic dysfunction, therefore this parameters are suitable for detection and follow-up of developing cardiotoxicity.

2. Based on the results obtained at one year, anthracycline toxicity develops just after treatment and this effect remains for long time. Presumably the pathomechanism of this is development of endothel dysfunction and myocardial damage through production of intracellular free radicals.

3. We found that plasma ET-1 decreased after treatment and this decreased value was observed after one year. This may be the consequence of the direct cytotoxic effect of anthracycline, inhibiting the ET mRNA production.
4. Decreased ET-1 level may play role in the decrease of EF, because a certain ET-1 level is necessary for the physiological contraction of cardiomyocytes. Persistently low ET-1 level may be negative inotropic. Nevertheless, other, positive inotropic compounds (e.g. norepinephrine) may also have causative role in the development of left ventricular dysfunction.

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