JMA

Jurnal Medical Aradean (Arad Medical Journal)
Vol. XIX, issue 3, 2016, pp. 5-7

ECOCARDIOGHAPHIC DATA IN HEART FAILURE PATIENTS WITH PRESERVED EJECTION FRACTION TREATED WITH DOXORUBICIN

[1]ADINA POP-MOLDOVAN, [1]MIHAI-NELU TROFENCIUC, [1]MARIA PUŞCHIŢĂ

Faculty of Medicine, Pharmacy and Dental Medicine, "Vasile Goldiş" Western University of Arad Romania

ABSTRACT. Echocardiography is considered to be a top noninvasive method for monitoring current patients on chemotherapy. The purpose of this study was to determine optimal timing of cardiac function monitoring and the risk factors for early induced doxorubicin cardiotoxicity by echocardiographic monitoring a 50 consecutive patients group with oncological pathology undergoing Doxorubicin chemotherapy. Because early detection of cardiac involvement would be useful in order to prevent progression to intractable heart failure, into our study group these determinations leaded to anthracycline treatment interruption and start of heart failure treatment. Also, we recommend a strict monitoring including a 3 months follow-up after the initiation of therapy with doxorubicin, not just at 6 weeks or at 6 months; we find this protocol necessary to early prevent cardiotoxicity elements and to intervene where necessary.
KEYWORDS: anthracycline, echocardiography, doxorubicin, cardiotoxicity, cardiomyopathy

PREMISES AND OBJECTIVES

Echocardiography is the standard noninvasive method for monitoring the patients on chemotherapy. The purpose of this study was to determine optimal timing for cardiac function monitoring and the risk factors for early induced doxorubicin cardiotoxicity. Anthracycline (doxorubicin, daunorubicin) are potent but cardiotoxic chemotherapeutic agents are essential for treating many childhood malignancies (Singal PK et al., 1998). Cardiotoxicity can be acute (within a month of initiation of therapy), early-onset chronic progressive (within a year after therapy) and late-onset chronic progressive (after a year of therapy) (Lipshultz SE et al., 2008; Monsuez JJ et al., 2010 ; Erdogan D. et al., 2016 ; Belham M. et al., 2007). Cardiac involvement may be seen as systolic and/or diastolic dysfunction, cardiomyopathy, arrhythmias and pericardial effusion (PE) (Barry E. et al., 2007 ; Gharib MI. Et al., 2016 ; Galderisi M. et al., 2007).

MATERIAL AND METHOD

The study group consisted of 50 consecutive patients with oncological pathology undergoing Doxorubicin chemotherapy.

Echocardiographic and clinical parameters and data collection timings were determined and monitored in outpatient or cardiology department prior to treatment with doxorubicin, then at 6 weeks after initiation of treatment and finally at 6 months.

Additionally, 25 control subjects with non-oncological pathology were recruited randomly and investigated for the same echocardiographic and clinical data. A Siemens Acuson X300 echocardiography unit was used for all measurements.

The main echocardiographic parameters obtained by following the above timing plan were: left ventricle end-diastolic diameter(LVIDD), left ventricular end-systolic diameter(LVISD), left ventricular ejection fraction (LVEF), left atrial diameter (LAD), aortic ring size, aortic cusps separation (ACS), posterior wall thickness (PWTd), interventricular septum thickness in diastole (IVSd), early diastolic filling velocity maximum (E), late diastolic filling velocity maximum shrinkage atrial (a), E / A ratio , deceleration time of E wave (TDE), isovolumetric relaxation time (TRVIV), Tissue Doppler imaging (TDI). LVM (left ventricular mass) was calculated using the formula ASE. All patients had heart failure with systolic and/or diastolic dysfunction (Sohn DW. Et al., 2015; Ommen SR. Et al., 2000).

Of the total of 50 oncologic patients in the ,18 patients (36%) were diagnosed with various hematological malignancies and 32 (64%) of solid tumors. Of these cases with acute lymphoblastic leukemia (ALL) 6 (33.33%), 4 (22.22%) cases acute myeloid leukemia (AML), 8 (44.44%) cases with non-Hodking lymphoma (NHL).

Regarding data collection, all the obtained, documented, processed, and managed data's and other patients related information's and findings were hosted on a dedicated web-server-portal at our University Informatics Center; patient privacy and data security agreement were applied.

RESULTS

Clinical and echocardiographic comparative data resulting from pre-treatment evaluation and assessment at 6 weeks showed no notable differences or other evidence to indicate a clear pathology of cardiotoxicity.

Regarding the initial (pre-treatment) echocardiographic and clinical parameters data

Jurnal Medical Aradean (Arad Medical Journal)
Vol. XIX, issue 3, 2016, pp. 5-7

compared to the 6 months set, study patients had higher values for systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, left ventricular posterior wall dimension, inter-ventricular septal wall size, DT, RWT and LVM compared to controls. So, diastolic blood pressure (DBP) was inversely proportional to the ratio E / A (r = -0.359, p <0.05) and directly related to the IVRT (0.397, P <0.05) but not with DT. Systolic blood pressure (SBP) was directly related to IVRT - izovolumic relaxation time as a single element (r = 0.487, P <0.05) but not in DT and E / A ratio. (*Table 1*)

Tabel 1. Echocardiographic monitoring result

Parameters	Control (n=25)	Baseline (n=50)	6 weeks (n=50)	6 months (n=50)	P value
Age (years)	55.0±7.9	56.9±11.9	56.9±11.9	56.9±11.9	0.396
Males (n)	13 (52%)	23 (46%)	23 (46%)	23 (46%)	0.478
SBP (mmHg)	138.9±12.9	147.0±24.7	149.0±12.6 (0.5)	151.0±11.2(0.2)	0.003*
DBP (mmHg)	78.6±10.3	89.4±12.3	91.2±9.7 (0.3)	92.8±11.2 (0.1)	0.004*
EF (%)	66.8± 12.9	58.6±14.5	57.3±12.5 (0.7)	54.7±13.2 (0.1)	0.01*
E/A	1.3±0.4	0.98±1.21	0.97±1.11 (0.9)	0.95±2.3 (0.9)	0.01*
IVRT (ms)	79.9 ±17.4	100.8±27.9	101.2±22.4 (0.8)	102.0±25.9 (0.7)	0.01*
LVMI (g/m2)	64.4±19.0	86.4±36.1	87.2±28.2 (0.9)	88.3±37.8 (0.8)	0.006*

* Statistically Significant; SBP - Systolic blood pressure; DBP - diastolic blood pressure; EF - ejection fraction; IVRT - izovolumic relaxation time; LVMI - left ventricular mass index. Data are expressed as mean followed by "±" mean standard deviation (SD

The mean ratio E/A was higher in controls (1,3±0,4) than in the patient group (0,98±1,21) (p<0,005 , n=75) (for initial and 6 months comparison).

The average value of EF was 58,6%±14,5% (for the entire study period).

In our oncological group, prior to treatment were observed 33 patients (66%) who had a value of EF> 64%; thereafter assessment at 6 weeks under the influence of chemotherapy, their number decreased dynamic to 28 patients (56%) and at the 6 month end for echocardiographic monitoring 23 patients (46%) presented a EF> 64%.

After about 24 months of clinical follow-up, the current status of the patients was as follows: A total of 31 patients (62%) completed chemotherapy, 8 patients (16%) are in the cancer therapy and 11 patients (22%) are deceased.

DISCUSSION

Endomyocardial biopsy is considered to be the most sensitive and specific test for this purpose, its use is limited by its invasiveness. In daily practice oncologists make use of parameters of systolic function (left ventricular ejection fraction, or fractional shortening) to detect cardiotoxicity, but these methods are not able to identify cardiotoxicity at an early stage. Diastolic dysfunction in clinical study subjects may be the result of an interaction between the left ventricular volume and pressure changes in context with anthracycline chemotherapy. The actual medical literature, however, does not clarify and explain the pathological mechanisms, for the evolution anthracycline induced cardiotoxicity of patients undergoing chemotherapy.

According to current guidelines and in accordance with all international norms universally accepted and respected both within the European medical community and the US, our study revealed manifestation of cardiotoxicity with a value within reported intervals (in the literature) that mentions a maximum incidence of 65% in late cardiotoxicity installed after follow up to a maximum of 6 years (Mornoş C. et al., 2013 ; Hare JL. et al., 2009).

CONCLUSIONS

A more agressive surveillance of chemotherapy patients with early detection and treatment of doxorubicin-induced cardiotoxicity with or with-out HF is essential to cardiotoxicity reversal. To maximize the benefits of these drugs (anthracyclines), a high-risk population need to be identified and also new strategies to predict and investigate for monitoring and minimizing toxic effects (Nousiainen T. et al., 2012; Zuppinger C. et al., 2007).

Analyzing the overall monitoring at 6 months, we can say that diastolic dysfunction was determined in a total of 32% of patients with either disorder compliance (52%) or impaired relaxation (48%).

We recommend a strict monitoring including a 3 months follow-up after the initiation of therapy with doxorubicin, not just at 6 weeks or at 6 months; we find this protocol necessary to early prevent cardiotoxicity elements and to intervene where necessary. If patients have known cardiovascular disease, or undergoing treatment for mediastinal irradiation, or show ECG changes and requiring

concomitant cardiotoxic chemotherapy, measuring LVEF should be repeated at 400 mg/m2 instead of 450 mg/m2 and LVEF should be monitored every dose administration.

REFERENCES

Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med 1998;339:900–5.

Lipshultz SE, Alvarez JA, Scully RE .Anthracycline associated cardiotoxicity in survivors of childhood cancer. Heart 2008;94:525–33

Monsuez JJ, Charniot JC, Vignat N, et al. .Cardiac side-effects of cancer chemotherapy. Int J Cardiol 2010;144:3–15.

Erdogan D, Yucel H, Alanoglu EG, et al.Can comprehensive echocardiographic evaluation provide an advantage to predict anthracycline-induced cardiomyopathy? Turk Kardiyol Dern Ars 2016;39:646–53.

Belham M, Kruger A, Mepham S, et al.Monitoring left ventricular function in adults receiving anthracycline-containing chemotherapy. Eur J Heart Fail 2007;9:409–14.

Barry E, Alvarez JA, Scully RE, et al.Anthracycline-induced cardiotoxicity: course, pathophysiology, prevention and management. Expert Opin Pharmacother 2007;8:1039–58.

Gharib MI, Burnett AK. Chemotherapy-induced cardiotoxicity: current practice and prospects of prophylaxis. Eur J Heart Fail 2016;4:235–42.

Galderisi M, Marra F, Esposito R, et al.Cancer therapy and cardiotoxicity: the need of serial Doppler echocardiography. Cardiovasc Ultrasound 2007;5:4.

Sohn DW, Chai IH, Lee DJ, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. J Am Coll Cardiol 2015;30:474–80.

Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: a comparative simultaneous Doppler-catheterization study. Circulation 2000;102:1788–94.

Mornoş C, Petrescu L. Early detection of anthracycline- mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. Can J PhysiolPharmacol. 2013;91(8):601-7.

Hare JL, Brown JK, Leano R, Jenkins C, Woodward N, Marwick TH. Use of myocardial deformation imaging to detect preclinical myocardial dysfunction before conventional measures in patients undergoing breast cancer treatment with trastuzumab. Am Heart J. 2009;158(2):294-301

Nousiainen T, Jantunen E, Vanninen E, et al. Early decline in left ventricular ejection fraction predicts doxorubicin cardiotoxicity in lymphoma patients. Br J Cancer 2012;86:1697–700.

Zuppinger C, Timolati F, Suter TM. Pathophysiology and diagnosis of cancer drug induced cardiomyopathy. Cardiovasc Toxicol 2007;7:61–6.

CORRESPONDENCE

Pop-Moldovan Adina
Faculty of Medicine, Pharmacy and Dental Medicine "VasileGoldiş" Western University of Arad, Romania
Arad, 86 Liviu Rebreanu St.
E-mail: ppmldvn68@yahoo.com