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Evaluation of Anthracycline Effects on NT-ProBNP Plasma Level in Children with Malignancy

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Abstract

Background: NT-proBNP is a marker that is released from ventricles in response to pressure and volume overload. Raised plasma level of NT-proBNP is seen in ventricular dysfunction, ventricular muscular mass reduction or ventricular ischemia. Anthracyclines are widely used in treatment of pediatric cancer but their use is associated with cardiotoxicity which increases mortality and morbidity.

We measured the plasma levels of NT-proBNP to determine whether it might serve as a simple prognostic indicator of anthracycline-induced cardiotoxicity and to estimate the toxic levels of anthracyclines in children with malignancy treated with anthracycline containing regimens in Tehran's Mofid hospital.

Materials and Methods: This study was performed as a before and after clinical trial. Twenty-nine pediatric patients less than fifteen years old with newly diagnosed cancer were enrolled in this study. All patients received anthracycline-containing chemotherapy with 120 to 150 mg/m² in accumulative dose. Serial measurements of plasma NT-proBNP levels and echocardiographies were taken before onset of chemotherapy, simultaneous with accumulative dose of 120 to 150 mg/m² and two weeks after that dose.

Results: Plasma levels of NT-proBNP were within normal limits before treatment and increased significantly after the mentioned accumulative dose (P=0.002) in 26 patients out of 29. All patients had normal echocardiograms and none developed heart failure during the two-year period of the study.

Conclusion: NT-proBNP levels increases significantly after 120 to 150 mg/m² as accumulative dose in a subset of pediatric cancer patients. This increase is not associated with echocardiographic or clinical evidence of cardiac dysfunction. Longer follow-up of these patients is necessary to determine whether NT-proBNP can be used as an early and prognostic marker for anthracycline-induced cardiotoxicity and whether 120 to 150 mg/m² as accumulative dose of anthracycline is a safe dose or not.

Keywords: NT-proBNP, Child, Malignancy, Cardiac dysfunction.

Introduction

Among pediatric malignancies, leukemia is the most common malignancy and ALL is the most common form of it. Anthracycline antitumor antibiotics are essential elements in successful treatment protocols for the majority of pediatric cancers. [1-3] Cure rates in pediatric malignancies have improved in the last few decades and now 75% of all children diagnosed with cancer become long-term survivors[4] and till 2010, one in every 250 adult people is a long-term survivor of pediatric cancers. Half of these people have history of anthracyclines consumption. [5] Chronic anthracycline cardiac toxicity that develops months to years after treatment with anthracyclines is one of the most dangerous side effects and is dependent on the cumulative dose delivered. [6,7] Several methods are currently used to detect early, subclinical signs of cardiotoxicity in children who receive anthracyclines such as determination of the

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serum levels of cardiac enzymes (CK-MB and troponin T) have low sensitivities and specificities.[2] The most widely used methods are echocardiography and radionuclide angiography. [8]

Echocardiography has a low sensitivity for detecting anthracycline-induced cardiac damage, and radionuclide angiography has a high sensitivity but low specificity and exposes patients to ionizing radiation. [9,10] Several studies have demonstrated elevated BNP levels in adult patients and children with anthracycline-induced cardiotoxicity and have suggested this marker as a prognostic factor. [11, 12]

The anthracycline antitumor antibiotics are essential elements in successful treatment protocols for the majority of pediatric cancers, including leukemia, lymphoma and sarcomas.

The cytotoxic action of anthracyclines is based on inhibition of the enzyme topoisomerase II, and possibly mediated through a DNA intercalating effect, too. As with most effective cytotoxic agents, anthracyclines have significant side effects which include myelosuppression, mucositis, alopecia and extravasation injury. In contrast to these transient and mostly reversible side effects, anthracycline administration is also associated with damage to cardiac myocytes and subsequent development of an irreversible cardiomyopathy .The mechanism by which anthracyclines cause cardiotoxicity is mediated through formation of iron-free radicals. [13]

According to indetermination of a safe dose for anthracyclines, this study can be helpful to determine the usefulness of NT-proBNP for early detection of anthracycline-induced cardiotoxicity prior to echocardiographic changes and to prevent more cardiac damage by changing the chemotherapy protocol.

Materials and Methods

Between winter 2007 and fall 2009, all newly under 15 years old children with diagnosed cancer who were admitted at the Mofid Pediatric Hospital Hematology-Oncology Unit were offered enrollment in the study. The diagnosis of malignancy was made according to complete blood count (CBC) and bone marrow aspiration (BMA) for leukemias (ALL and AML) and was based on pathologic report for solid tumors. The anthracyclines dose was specified by disease-specific treatment protocols (cumulative dose 120-150 mg/m²) and was administrated through an indwelling central venous catheter.

Patients with congenital heart disease, hypertension, ischemic heart disease, renal failure, cardiac hypertrophy, pervious treatment with anthracyclines or mediastinal radiation, older than 15 years or with body mass index more than 95% for their age were excluded from the study.

This study was performed as a before and after design clinical trial. All patients received anthracycline-containing chemotherapy with 120 to 150 mg/m² in accumulative dose. Serial measurements of plasma NT-proBNP levels and echocardiographies (left ventricle mass and ejection fraction) were taken before the onset of chemotherapy, simultaneous with accumulative dose of 120 to 150 mg/m² and two weeks after that dose. Each patient served for his/her own control.

Non-fasting blood samples (3 cc) for NT-proBNP measurement were taken from peripheral veins after each mentioned anthracyclines dose upon admission. NT-proBNP measurement were performed using electrochemiluminescence immunoassays (ECLIA) that were intended for use on Elecsys and cobas e-immunoassay analyzer systems (proBNP II kit, Roche, Mannheim, Germany).

Echocardiographic studies were performed in M-mode with GE VINGMED CFM800.

All patients were treated by Anthracyclines, which were produced in Pharmacia Italia S.P.A. laboratory, driven from streptomyces peuceticus varcaesius. Data were analyzed by SPSS software ver. 11.5 (Chicago, IL). Paired data were compared by paired t-test and Freidman test.

Results

32 patients were included in the study. 3 patients died during the study. The study was completed with 29 patients. The mean age at the time of diagnosis was 5.3 years. There were 16 girls and 13 boys. The diagnoses are listed in Table 1.

Plasma levels of NT-proBNP were within normal limits before treatment and increased significantly after the accumulative dose (P=0.002). There were statistically significant differences between NT-proBNP values measured simultaneous with accumulative dose of 120 to 150 mg/m² and their

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Table 1. *Number and percentage of diagnoses*

Diagnosis	Number	Percentage
ALL	20	69
ALL.TC	1	3.4
Hodgkin lymphoma	1	3.4
Rhabdomyosarcoma	2	6.9
PNET	2	6.9
AML	2	6.9
Hepatoblastoma	1	3.4
Total	29	100

Table 2. *Plasma levels of NT-proBNP differences before onset of chemotherapy; simultaneous with accumulative dose of 120 to 150 mg/m² and two weeks after that dose.*

Time points comparison groups	NT-proBNP MD	SD/SE	CI 95%	P
Bef. versus Sim.	155.48	239.85/44.54	246.72,64.25	0.002
Bef. versus Aft.	9.08	83.73/15.55	-22.77,40.93	0.564
Sim. versus Aft.	146.40	200.76/37.28	70.03,222.77	0.001

Bef., before onset of chemotherapy; Sim., simultaneous with the accumulative dose; Aft., 2 weeks after the accumulative dose; MD, mean difference; SD, standard deviation; SE, standard error; CI95%, 95% confidence interval for mean difference; P, p-value

values two weeks after that dose (P=0.001). However, there was no statistically significant differences between plasma levels of NT-proBNP before the onset of chemotherapy and two weeks after the accumulative dose of 120 to 150 mg/m²(P=0.56, Table 2).

Ejection fractions were evaluated before onset of chemotherapy, simultaneous with accumulative dose of 120 to 150 mg/m² and two weeks after that dose. Ejection fractions were within normal limits before treatment, after the mentioned accumulative dose and two weeks after that dose (P > 0.05).

Discussion

NT-proBNP is a cardiac marker secreted from the myocytes of ventricles, in response to ventricular volume and pressure overload.[10,14] The most important stimulus for cardiac secretion of NT-proBNP is stretch of cardiac myocytes.[15] BNP is synthesized as a 108-aminoasid-long prohormone termed proBNP.[13]

The most important stimulus for cardiac secretion of NT-proBNP is stretch of cardiac myocytes. [16] The stretch signals rapidly by the activation of the proBNP gene, which results in de novo myocytes peptide synthesis and secretion. [17] The resulting increase in plasma peptide concentration is correlated with the amount of stretch. Many cardiac aliments are accompanied by increased intracavity pressures correlated with disease severity. Therefore, the peptide plasma level reflects the severity of the underlying disturbances. [17]

Several studies have shown increased levels of BNP in adult patients and children with cardiac toxicity due to anthracyclines and suggested this marker as a useful prognostic factor. [11, 12]

Hayakawa et al. reported that out of 34 pediatric patients who had previously received doxorubicin, 8 patients (23.5%) developed left ventricular dysfunction shown by echocardiography and also elevated plasma BNP levels in comparison with healthy controls. [11]

Ekestien et al. [13] evaluated the plasma level of NT-proBNP in 23 children (mean age: 10 years, range: 8 months to 23 years) under anthracyclines treatment. Non-fasting blood samples before and after drug administration were taken within 1 to 3 hours. Treatment durations were 1 to 9 months and

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cumulative dose of anthracyclines were 30-300 mg/m². During the follow up period none of the patients developed signs of congestive heart failure.

The average dose of the first anthracycline dose was equivalent to 26.52 mg/m² doxorubicin. The average level of NT-proBNP before the first treatment was 151 pg/ml, not different from control children (P= 0.13). After the first anthracycline dose the average NT-proBNP level was 206 pg/ml which was significantly higher than controls (P= 0.025).

We observed an increase in proBNP immediately after injection of anthracycline like the results of Ekestien et al[13]. This suggests that the injection of anthracyclines was the cause of increase in NT-proBNP.

Echocardiograms, which were obtained at beginning of treatment and at the end of follow-up, demonstrated normal function of the left ventricle (shortening fraction 28% to 44%). The elevated NT-proBNP levels were not associated with clinical or echocardiographic evidence of cardiac dysfunction which reflects a greater sensitivity of BNP for cardiac damage. [13]

Aggarwal et al. [18]in a cohort study included 63 patients with cumulative anthracyclines dose of 150-520 mg/m². They observed that mean plasma BNP levels were significantly higher in the presence of abnormal cardiac function (P=0.02) as higher plasma BNP levels were observed when shortening fraction was low (P<0.008).

Germanakis et al.[19] studied 19 children treated with cumulative anthracyclines dose of 240 mg/m² in 2006. They observed a high prevalence of reduced left ventricle mass that was associated with increased NTpro-BNP in patients with normal systolic function in echocardiography and suggested high NTpro -BNP as an early prognostic marker of subclinical cardiotoxicity.

Suzuki et al.[20] in 1998 reported raised BNP levels in patients receiving anthracyclines. He studied 27 adult patients (13 men and 14 women with mean±SD age of 47.9 ±8.7 years and 53.2 ±4.6 years) who had undergone anthracycline administration for hematologic malignancies with cumulative dose of 221.4 ± 53.7 mg/m². Basal BNP levels were raised and showed further marked elevations after drug administration. Most patients showed transient increases with peak levels within 3 to 7 days after administration that returned to baseline within 2 weeks. 66% of patients with persistently elevated BNP levels subsequently died from circulatory failure, which suggests a prognostic role for BNP. Our protocol for proBNP measurement was the same as Suzuki et al. study. In their study, proBNP levels returned to baseline levels 2 weeks after the accumulative dose [20]. In this study, 26 patients (90%) had significantly increased BNP levels after anthracyclines administration (P=0.002) which shows high sensitivity of this cardiac marker after anthracyclines administration compatible with Suzuki and Ekestien's findings [13, 20].

Zhu et al. studied 44 patients with coronary artery disease and observed that the NT-proBNP examination has higher sensitivity for CHD diagnosis (88%) than ECG (52%).[21]

Goode et al. in 2008 studied prescreening using NT-proBNP and QRS width to find heart failure in patients who had not signs and symptoms. He described QRS width had lower sensitivity than NT-proBNP to detect heart failure. [22]

Our study results demonstrated significantly increased BNP levels simultaneous with accumulative dose of 120 to 150 mg/m² and that BNP levels were within normal limits two weeks after that dose in 26 patients (90%, P=0.001) which is consistent with the findings of Suzuki's et al.[20]

In 3 patients, elevated BNP levels at the time of the accumulative dose did not reduce enough to reach normal range 2 weeks after that dose. 2 patients out of these 3 patients had increased BNP levels before initiation of treatment accompanied with normal echocardiographies in all 3 steps. One of the mentioned 3 patients died during the study, another one did not respond to treatment properly and the third one was still on treatment at the completion of the study which demonstrates the prognostic value of BNP. That is compatible with Suzuki's finding which showed 66% mortality in patients with persistent raised BNP levels. Nevertheless, there is a difference between these two studies: the cause of death in Suzuki et al. study was heart failure in long-term follow up while in our study it was infection in short-term follow up. We did not include long-term follow up in the study protocol, a limitation of the current study.

In all types of the studied malignancies, we observed significantly raised BNP levels

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simultaneous with accumulative dose of 120 to 150 mg/m² relative to their values before the onset of chemotherapy. (all P<0.001 and other malignancies P=0.013)

In our study ejection fraction and left ventricular mass were normal in all 3 steps of echocardiograms which, like Ekestien's findings [13], suggests BNP level is a more sensitive marker than echocardiogram for heart dysfunction.

Although the safe dose of anthracyclines has not been reported but most of our patients had normal levels of BNP two weeks after accumulative dose of 120 to 150 mg/m² which may suggested accumulative dose of 120 to 150 mg/m² as a safe dose of anthracyclines.

Conclusion

At the end we suggest in patients with persistent raised BNP levels, echocardiographic studies should be performed in short intervals to have better judgment for modifying anthracyclines dose or its replacement it by other drugs.

Raised BNP level as a prognostic marker in patients with malignancies could be investigated in more detailed and in long-term studies.

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