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□ Original Article : Clinical Study □

Plasma B-type natriuretic peptide (BNP): a useful marker for anthracycline-induced cardiotoxicity in Korean children with cancer

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Purpose : The anthracyclines (AC) are widely used chemotherapeutic agents for pediatric cancers. However, the therapeutic use of these agents is limited by their cardiotoxicity. The aim of the present study was to investigate the usefulness of plasma B-type natriuretic peptide (BNP) levels as a marker for AC-induced cardiotoxicity compared to echocardiography in Korean children with cancer.

Methods : Fifty-five pediatric cancer patients who had received chemotherapy including AC were enrolled. The cumulative AC doses, clinical symptoms, and two echocardiography parameters, left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF), were studied and compared with plasma BNP levels.

Results : In 55 patients, plasma BNP levels were measured 115 times and echocardiographies were performed 64 times. The median cumulative dose of AC was 325 mg/m^2 (range 120-600; mean 345) and the median plasma BNP level was 10 pg/mL (range 5-950; mean 31). The cumulative AC doses correlated significantly with the plasma BNP levels (P=0.002). The plasma BNP levels correlated significantly with LVFS (P=0.018) and LVEF (P=0.025). Dilated cardiomyopathies were identified in three patients. LVFS and LVEF decreased and plasma BNP levels increased in a patient with acute dilated cardiomyopathy and in that with symptomatic chronic dilated cardiomyopathy. However, LVFS, LVEF and plasma BNP levels were normal in a patient with asymptomatic chronic dilated cardiomyopathy.

Conclusion : The results of this study demonstrated that plasma BNP levels could be used as a marker for AC-induced cardiotoxicity; they showed good correlation with echocardiography findings in pediatric cancer patients. Plasma BNP levels may be used for the detection and management of AC-induced cardiotoxicity in Korean children with cancer. **(Korean J Pediatr 2007;50:774-780)**

Key Words : Anthracycline, Cardiotoxic, B-type natriuretic peptide

Introduction

Cardiotoxicity occurs during chemotherapy with several cytotoxic drugs such as the anthracyclines (AC). Furthermore, cardiotoxicity may cause long-term side effects with severe morbidity in long-term survivors of childhood cancer. This is an important issue in pediatric oncology[1].

Cardiotoxicity is related to the cumulative dose of administered medications[2]. Acute or subacute injury may occur immediately after initiation of treatment[3, 4]; chronic AC-induced cardiomyopathy usually occurs within one year of the start of treatment[5]. However, late-onset toxicity appears after a prolonged asymptomatic period[6]. Therefore, use of ACs for cancer therapy requires early detection and monitoring of AC-induced cardiotoxicity.

The cardiac status of patients has been monitored by different methods such as electrocardiography, echocardiography, radionuclide angiocardiography, and endomyocardial biopsy[7]. Among these methods, evaluation of AC-induced cardiotoxicity is most simply accomplished by serial echocardiography which provides a sensitive and non-invasive method[8]. However, echocardiography is an expensive test and is not covered by health insurance in Korea. It should be performed and interpreted by experienced pediatric cardiologists. Therefore, in cases where echocardiography may not

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be an option, or for routine follow up of AC-induced cardiotoxicity, a relatively low-cost and easily accessible alternative test is needed.

Hereupon, the possibility of a simple blood test was investigated that could be used to monitor AC-induced cardiotoxicity. Brain or B-type natriuretic peptide (BNP), a 32-amino-acid peptide, is a cardiac hormone released from the heart predominantly from the ventricular myocardium in response to ventricular volume expansion and pressure overload[9, 10]. It is a biochemical marker for left ventricular (LV) dysfunction with diagnostic and prognostic implications [11]. Studies have demonstrated that levels increase in proportion to the severity of congestive heart failure (CHF) in adults and children[12, 13].

The aim of the present study was to evaluate the potential usefulness of plasma BNP levels as a marker for AC-induced cardiotoxicity compared to echocardiography in Korean children with cancer.

Materials and Methods

Between May 2005 and December 2006, at the Department of Pediatrics, Yeungnam University Hospital (YNUH), 55 pediatric cancer patients (22 girls, 33 boys) who had received chemotherapy including ACs were enrolled. The ACs included doxorubicin, daunorubicin and idarubucin; the patients received a single AC or multiple ACs. Some patients had discontinued AC treatment before starting the study and some patients discontinued AC treatment during the study; others continued AC treatment with cumulative AC doses of 300 mg/m^2 or more. No patient had underlying cardiovascular disease or had a history of cardiac irradiation. In addition, no patient received a cardioprotectant such as dexrazoxane during the treatment phase or the cardiotoxicity evaluation period. The cumulative AC doses, clinical symptoms, and two echocardiography parameters, left ventricular fractional shortening (LVFS) and left ventricular ejection fraction (LVEF), were studied and compared with plasma BNP levels.

One pediatric cardiologist performed transthoracic M-mode and 2-dimensional (2D) echocardiography to measure the LVFS and LVEF in each patient using an ACUSON Sequoia C256 (Siemens Medical Solutions USA, Inc., Malvern, PA, USA). An LVFS below 28% and an LVEF less than 55% were considered abnormal[14].

Plasma BNP levels were evaluated with Triage Meter (Biosite Inc., San Diego, CA, USA) for rapid in vitro quantitative measurement of BNP in human plasma specimens using EDTA as an anticoagulant[15]. For the pediatric age group, from two weeks to 17.6 years, plasma BNP levels of 7±5.9 and 10.1±8.6 pg/mL have been reported in healthy boys and girls, respectively. The 95th percentile of plasma BNP levels were reported to be 24.5 pg/mL in boys and girls younger than 10 years, and 30.4 pg/mL in girls versus 12.1 pg/mL in boys older than 10 years[16]. In children younger than 10 years, values of plasma BNP more than 25 pg/mL were considered abnormal. In children older than 10 years, values of plasma BNP more than 30 pg/mL were considered abnormal in girls and more than 12 pg/mL were considered abnormal in boys.

Statistical analysis was performed using SPSS for Windows (version 14). Data are presented as mean±standard deviation (SD) if not stated otherwise. Differences within groups were tested by the T-test. Correlations between variables were studied using the Pearson's correlation test. Associations of variables with cumulative AC doses were determined by χ^2 analysis. A $P<0.05$ was considered statistically significant.

This study was reviewed and approved by the Ethics Committee of YNUH. Informed consent was obtained from the parents of the study patient.

Results

Fifty-five patients were enrolled in the study including 22 girls (40%) and 33 boys (60%). The median age of the patients was six years (range 2 months-13 years) for the initial diagnosis of cancer, and was 10 years (range 1-23 years) at the time of enrollment into the study. The patients were treated for acute lymphoblastic leukemia (n=31), acute myeloblastic leukemia (n=6), non-Hodgkin's lymphoma (n=4), hepatoblastoma (n=4), and other malignancies (n=10). Thirty patients (55%) received doxorubicin and daunorubicin, and 20 patients (36%) received doxorubicin only. The characteristics of the study population are presented in Table 1. Plasma BNP levels were measured 115 times and echocardiographies were performed 64 times, in the enrolled patients. The mean cumulative AC dose was 345±92 mg/m^2, and the median cumulative AC dose was 325 mg/m^2 (range 120-600). The mean plasma BNP level was 31±99 pg/mL, and the median plasma BNP level was 10 pg/mL (range 5-950).

Two patients had symptoms of dyspnea, one had discon-

tinued AC 127 months prior to the study and had chronic dilated cardiomyopathy (DCM); this patient had a cumulative AC dose of 477 mg/m^2. The other discontinued AC six months before starting the study and had normal LVFS, LVEF and plasma BNP levels with a cumulative AC dose of 400 mg/m^2.

The cumulative AC doses were found to correlate significantly with plasma BNP levels (P=0.002) (Fig. 1). In addition, the plasma BNP levels were significantly correlated with LVFS (P=0.018) (Fig. 2A) and LVEF (P=0.025) (Fig. 2B). However, there was no significant correlation between the cumulative AC doses and LVFS (P=0.604) (Fig. 3A) and LVEF (P=0.855) (Fig. 3B). There was no significant difference in cumulative AC doses between normal LVFS (334±59 mg/m^2) and abnormal LVFS (370±199 mg/m^2) (P=0.650); similarly between normal LVEF and abnormal LVEF. However, there was a significant difference in the cumulative AC doses between normal BNP levels (AC dose : 322±64 mg/m^2) and abnormal BNP levels (AC dose : 444±127 mg/m^2) (P=0.000) (Fig. 4).

In seven cases (10.9%) among the 64 echocardiographies, both LVFS and LVEF were abnormal. Five (9%) of 55 patients showed either an abnormal LVFS or an abnormal LVEF. Among the 115 plasma BNP levels, abnormal BNPs were noted in 21 cases (18%). Seven (13%) out of 55 patients showed abnormal BNPs.

Detection of abnormal LVFS or LVEF was associated with a high specificity and negative predictive value of plasma BNP levels, 89% and 94%, respectively. However, since there were only a few patients with abnormal values

Table 1. Characteristics of the Study Population

Number	55
Female/male	22/33
Age in years at diagnosis of cancer (median; range)	6 (0.2-13)
Age in years at time of enrollment (median; range)	10 (1-23)
Diagnosis	
Acute lymphoblastic leukemia	31
Acute myeloblastic leukemia	6
Non-Hodgkin's lymphoma	4
Hepatoblastoma	4
Osteosarcoma	3
Others	7
Underlying cardiovascular disease	0
Cardiac irradiation	0
Anthracyclines	
Doxorubicin and daunorubicin	30
Doxorubicin	20
Daunorubicin	2
Idarubicin	2
Idarubicin and daunorubicin	1

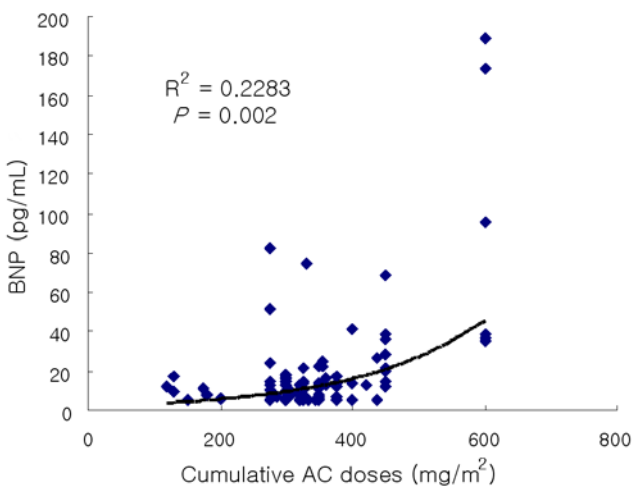

Fig. 1. Correlation between plasma BNP levels and the cumulative AC doses.

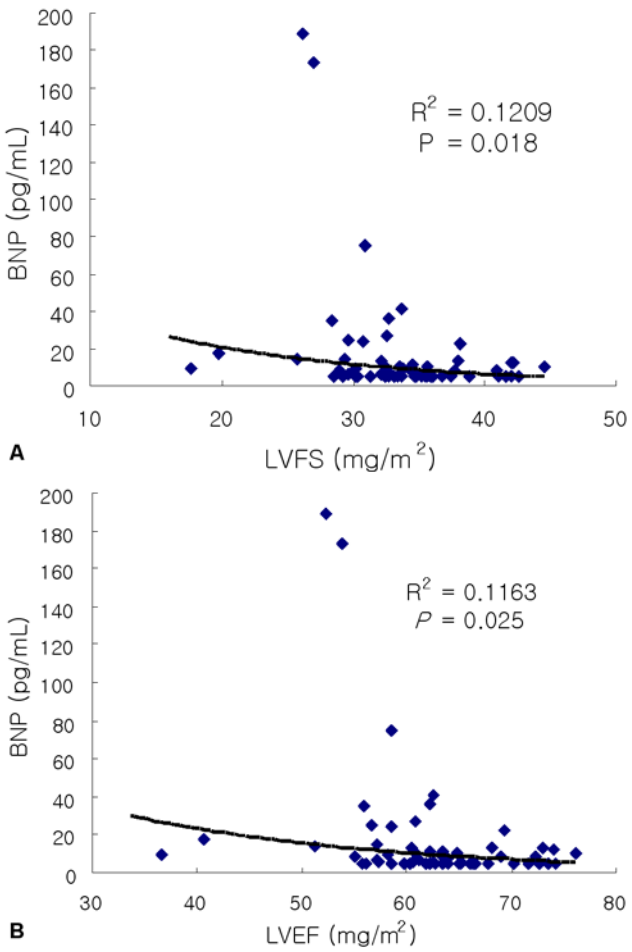

Fig. 2. Correlation between plasma BNP levels and LVFS (A) and LVEF (B).

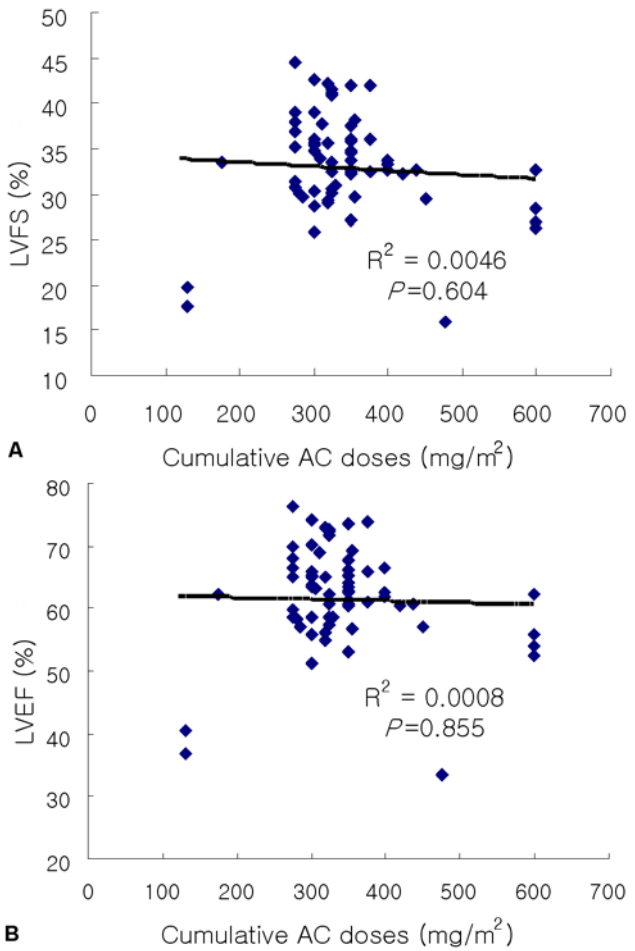

Fig. 3. Correlation between cumulative AC doses and LVFS (A) and LVEF (B).

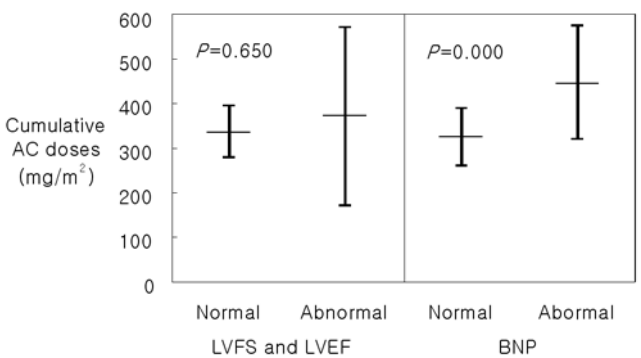

Fig. 4. Differences in cumulative AC doses associated with abnormalities of LVFS, LVEF and BNP. Whisker lines represent the standard deviations; and the middle line, the mean.

for both plasma BNP and LVFS or LVEF, the sensitivity and positive predictive value were low, 40% and 25%, respectively.

DCMs were detected in three patients. Their mean cumulative AC dose was 532.9±135.7 mg/m^2 (range 175-600) and the mean plasma BNP level was 195.6±293.9 pg/mL (range 10.8-950). In patients without DCM, the mean cumulative AC dose was 328.0±64.2 mg/m^2 (range 120-450), and the mean plasma BNP level was 16.8±40.7 pg/mL (range 5-82.3). There were significant differences in the cumulative AC doses (P=0.000) and the plasma BNP levels (P=0.000), based on the presence or absence of DCM. LVFS and LVEF were decreased and plasma BNP levels were increased in an acute DCM patient and in a symptomatic chronic DCM patient. However, LVFS, LVEF and plasma BNP level were normal in an asymptomatic chronic DCM patient (Table 2). Follow up with plasma BNP levels and two echocardiography parameters, LVFS and LVEF, in the patient with acute DCM are presented in Fig. 5.

Table 2. Results of Patients with Dilated Cardiomyopathy

	LVFS (%)	LVEF (%)	BNP (pg/mL)
Acute DCM			
No symptom	28.6±2.5	56.1±3.8	114±77
Chronic DCM			
Dyspnea	16.0	33.6	950.0
No symptom	33.5	62.3	10.8

Abbreviations : DCM, dilated cardiomyopathy; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; BNP, B-type natriuretic peptide

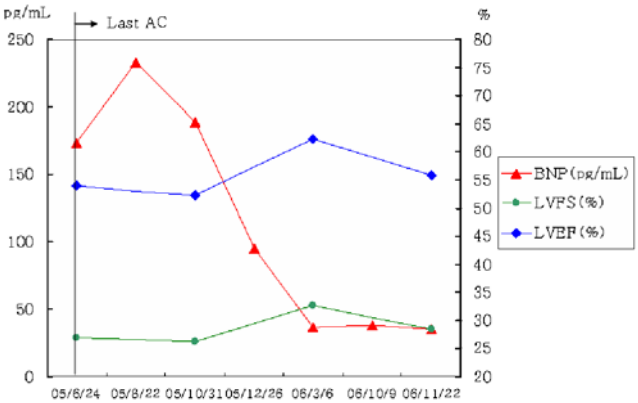

Fig. 5. Follow up with plasma BNP levels and two echocardiography parameters, LVFS and LVEF, in a patient with acute DCM.

Discussion

AC therapy is known to be potentially cardiotoxic[17]. The ACs (doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone) are widely used chemotherapeutic agents for pedi-

atric cancers. The exact mechanism of AC-induced cardiotoxicity is unknown. However, the proposed mechanism is that of free radical formation and interference with the mitochondrial electron transport chain[18]. The heart is rich in mitochondria and has a relatively poor ability to rid itself of free radicals due to its reliance on the glutathione-glutathione peroxidase cycle[19]; it is therefore particularly vulnerable to free radical attack. ACs have been reported to cause cardiomyopathy, CHF, electrocardiographic changes, and dysrhythmias (e.g. nonspecific ST-T changes, bundle branch block, prolongation of corrected QT interval, supraventricular- and ventricular-dysrhythmias[20]).

Cumulative dose, age, prior mediastinal irradiation, concomitant administration of other cardiotoxic agents and underlying heart disease are considered to be risk factors for AC-induced cardiotoxicity[21]. Among these, the cumulative dose appears to be the most important factor. At cumulative doses of more than 450-550 mg/m^2 of doxorubicin, cardiomyopathy and CHF occur more frequently. However, signs of cardiotoxicity have also been seen with cumulative doses below 300 mg/m^2 [17]. Von Hoff et al. estimated the cumulative probability of doxorubicin induced cardiotoxicity: 0.18 at a cumulative dose of 700 mg/m^2, 0.07 at 550 mg/m^2 and 0.03 or less at 400 mg/m^2 [2]. The maximum cumulative dose needed for minimal cardiotoxicity varies among the different ACs. With epirubicin a lower frequency of cardiotoxicity at therapeutic doses is reported in comparison with doxorubicin (i.e. an incidence of 0.03 at 900 mg/m^2 of epirubicin). In addition, a lower frequency of cardiotoxicity has been reported for mitoxantrone[22, 23].

The Cardiology Committee of the Children Cancer Study Group has developed the guidelines, using a variety of detection techniques, for cardiac monitoring of children during and after AC therapy including: electrocardiography, echocardiography, radionuclide angiocardiography, and endomyocardial biopsy[24]. Currently, LVEF is routinely used to screen for AC-induced cardiotoxicity. LVEF obtained by radionuclide angiocardiography is more accurate than LVEF estimated by echocardiography. However, there are some disadvantages associated with radionuclide angiocardiography including exposing patients to ionizing radiation and its high cost and time requirements. Consequently, monitoring of AC-induced cardiotoxicity is most simply accomplished by serial echocardiography which is a sensitive and non-invasive procedure[8]. LVFS and LVEF are widely used parameters for evaluating LV systolic function[24]. However, since echocardiography is quite expensive and a skilled procedure, performing echocardiography for routine follow up of AC-induced cardiotoxicity is not always available to at risk patients. Therefore, a relatively low cost and easily accessible alternative screening method is needed.

Sparano et al. suggested that circulating biochemical markers such as troponins and natriuretic peptides could potentially serve as such monitoring tools[25]. The cardiac biomarker troponin T reflects myocardiocyte damage and is currently used for the diagnosis and the prognosis of myocardial ischemia. Troponin T elevations have been observed after initial doxorubicin therapy in children treated for ALL. These elevations were, however, well below those observed in patients with myocardial infarction or myocardial ischemia without infarction[25, 26].

Another possible biochemical marker is BNP. Natriuretic peptides contain three major peptides: atrial natriuretic peptide (ANP), BNP and C-type natriuretic peptide (CNP). Among these peptides, ANP and BNP are hormones that are secreted by the myocytes of the heart[10]; their plasma concentrations are increased in patients with LV dysfunction. The plasma concentration of BNP is a sensitive indicator of moderate to severe LV dysfunction, and is more sensitive and specific than ANP for the detection of LV dysfunction [27, 28].

Recently, studies concerning the relationship between BNP and AC-induced cardiotoxicity have been published. The measurement of BNP in 27 adult patients, treated with ACs for hematological cancers, showed significant BNP elevations after AC treatment (basal levels, 31.1±7.16; after chemotherapy, 58.1±12.8 pg/mL). The study findings were limited by a short follow up and small sample size and therefore could not be statistically related to the existing cardiotoxicity[29]. In children older than two weeks, the mean plasma concentration of BNP is lower than in adults[16]. Daugaard et al. found a positive correlation between LVEF and BNP, for LVEF <0.50. Whereas, no significant correlation was found for LVEF 0.50 in 107 adult patients receiving AC for malignant disease[30]. It has been documented that BNP >29 pmol/L (100 pg/mL) was observed only in patients with LVEF <50% and heart failure symptoms. BNP of 11.4 pmol/L (39.3 pg/mL) showed a negative predictive value of 80% for decrease of EF by more than 10%, in 55 adult patients with malignant lymphoma treated with ACs. However, the cutoff values were considered too high for children [31]. Pinarli et al. measured plasma BNP levels before and

after exercise testing, in 34 pediatric patients with solid tumors treated with ACs and in 16 healthy controls. They found the mean plasma BNP levels of the patients (10.56±10.22 pg/mL) were significantly higher than that of the healthy controls (4.09±2.26 pg/mL), before exercise testing. Although the mean plasma BNP levels of the patients (15.70±14.06 pg/mL) were higher after exercise compared to the resting state, the difference was not statistically significant[32]. Aggarwal et al. found that the mean±SD plasma BNP levels were significantly higher in the presence of abnormal cardiac function (23.4±25.3 pg/mL versus 14.2±8.9 pg/mL) in 63 AC-treated children with cancer. Plasma BNP levels were higher with low LVFS (32.4±34.9 pg/mL versus 15.6±12.4 pg/mL)[33]. A study of 34 pediatric patients, previously treated with doxorubicin containing chemotherapy, showed that the mean plasma BNP level, in eight patients with cardiac dysfunction, was 29.0±31.2 pg/mL. These levels were significantly elevated compared to 19 healthy controls (5.6±3.8 pg/mL) and 26 patients with normal cardiac function (9.0±14.8 pg/mL). Plasma BNP levels were significantly correlated with cardiac systolic function including LVEF, LVFS, mean velocity of circumferential fiber shortening (mVcf), and left ventricle systolic time interval (LVSTI)[34].

In this study, we identified a strong correlation between LVEF, LVFS and plasma BNP levels. This is consistent with the aforementioned studies which demonstrated that increased plasma BNP levels reflect impaired cardiac function as revealed by echocardiography findings in pediatric cancer patients treated with ACs.

In conclusion, plasma BNP levels as a marker for AC-induced cardiotoxicity in pediatric cancer patients, demonstrated good correlation with echocardiography findings. Therefore, plasma BNP level may be a useful test for the detection and following up of AC-induced cardiotoxicity. However, since this study was a single center investigation with a limited number of patients, further studies are needed, with a larger patient population, at different centers to confirm our findings.

한 글 요 약

한국인 소아암 환자에서 anthracycline 유발 심독성에 대한 지표로서 BNP 혈장농도의 유용성

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목 적 : Anthracycline(AC) 계 약물은 소아암에 널리 쓰이지만 심독성으로 인하여 사용에 제한을 받게 된다. 이에 소아암 환자에서 AC 유발 심독성에 대한 지표로서 혈장 B-type natriuretic peptide(BNP)의 유용성을 심초음파와 비교하여 알아보고자 본 연구를 시도하였다.

방 법 : 2005년 5월 1일부터 2006년 12월 31까지 영남대학교 병원 소아과에서 소아암으로 진단 받고 치료받은 환자 중에서 AC 계 약물을 투여 받은 환자 55명을 대상으로 AC 축적량과 임상증상을 조사하고, 심초음파 검사 중 좌심실 구획 단축률(left ventricular fractional shortening, LVFS)과 좌심실 박출 계수(left ventricular ejection fraction, LVEF) 결과와 BNP 혈장농도를 비교하였다.

결 과 : 환자 55명에서 BNP 혈장농도를 115회 측정하였고, 심초음파를 64회 시행하였다. AC 축적량의 중앙값은 325 mg/m^2 (범위 120-600; 평균 345)이었고, BNP 혈장농도의 중앙값은 10 pg/mL(범위 5-950; 평균 31)이었다. AC 축적량은 BNP 혈장농도와 좋은 상관관계를 나타내었다(P=0.002). 그리고 BNP 혈장농도는 LVFS(P=0.018), LVEF(P=0.025)와 역시 좋은 상관관계를 나타내었다. 확장형심근병증이 발생한 경우는 3명이었다. 급성기의 확장형심근병증 환자와 검사 시행 당시 급성호흡곤란 증상이 있었던 만성기의 확장형심근병증 환자에서는 LVFS과 LVEF이 비정상적으로 감소하면서 BNP 혈장농도가 비정상적으로 증가하였고, 증상이 없는 만성기의 확장형심근병증 환자에서는 LVFS, LVEF, BNP 혈장농도가 모두 정상이었다.

결 론 : 본 연구에서 한국인 소아암 환자의 AC 유발 심독성에 대한 지표로서 BNP 혈장농도는 심초음파 검사와 좋은 상관관계를 나타내어, AC로 치료받은 소아암 환자에서 심초음파를 시행할 수 없는 경우나 정기적인 추적관찰을 하기 위하여 유용한 검사로 생각된다.

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