Assessment of Late Cardiotoxicity of Pirarubicin (THP) in Children With Acute Lymphoblastic Leukemia

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Background. Pirarubicin (tetrahydropyranyl-adriamycin: THP) is a derivative of doxorubicin with reportedly less cardiotoxicity in adults. However no studies of cardiotoxicity in children treated with THP have been reported. This study was performed to assess the THP-induced cardiotoxicity for children with acute lymphoblastic leukemia (ALL). ***Patients and Methods.*** This study comprised 61 asymptomatic patients aged from 7.6 to 25.7 years old. Median follow-up time after completion of anthracycline treatment was 8.1 years (range: 1.7–12.5). The cumulative dose of THP ranged from 120 to 740 mg/m^2 with a median of 180 mg/m^2. Patients underwent electrocardiogram (ECG), echocardiography, the 6-min walk test (6MWT), and measurements of serum brain natriuretic peptide (BNP) before and after exercise. ***Results.*** All subjects showed normal left ventricular function assessed by echocardiography. Ventricular premature contraction in Holter ECG and reduced exercise tolerance in the 6MWT were detected in 2/46 (3.3%) and 5/41(12.2%), respectively. Abnormal BNP levels were detected in 6/60 (10%) both before and after exercise. The cumulative dose of THP was significantly correlated with BNP levels after exercise ($r = 0.27$, $P = 0.03$), but not with any other cardiac measurements. Further analysis revealed that subjects with a high cumulative dose $\geqq$300 mg/m^2 had significantly higher BNP levels after exercise compared with subjects with a low cumulative dose $<$300 mg/m^2 ($P = 0.04$). ***Conclusions.*** No significant cardiac dysfunction was detected in long-term survivors who received THP treatment. The use of post-exercise BNP level to indicate high cardiotoxicity risk should be verified by further study. Pediatr Blood Cancer © 2011 Wiley-Liss, Inc.

Key words: BNP; cardiotoxicity; childhood ALL; pirarubicin

INTRODUCTION

During the past 30 years, the use of anthracyclines (AC) for the treatment of childhood cancers has significantly improved survival outcomes [1,2]. However, the therapeutic potential of these agents is limited by their cardiotoxicity: acute cardiotoxicity occurs immediately after treatment, early-onset chronic cardiotoxicity presents within 1 year after treatment, and late-onset chronic cardiotoxicity appears after a prolonged asymptomatic period with a latency of one or more years following AC therapy [3–5].

In children, late-onset cardiotoxicity is more common than acute or early-onset toxicity [6–11]. In an effort to reduce overall cardiotoxicity, various AC derivatives have been studied [5]. Pirarubicin (tetrahydropyranyl-adriamycin: THP) is a derivative of doxorubicin (DOX) with reportedly low cardiotoxicity in adult patients [12–20]. However, these reports were limited to acute cardiotoxicity immediately after THP treatment, and there are no available data of late-onset cardiotoxicity in both adult and childhood patients [21,22]. Since the 1990s, the Japanese Childhood Cancer and Leukemia Study Group (JCCLSG) has employed THP in the treatment of acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphomas, and recently, it reported long-term patient outcomes, finding a very low incidence of congestive heart failure among survivors [23–25]. This finding led to assessment of the incidence of subclinical cardiac abnormalities among these survivors, because many previous studies had shown a considerable proportion of asymptomatic childhood cancer survivors who had received AC therapy with possible abnormalities of cardiac function or myocardial biomarkers [26–31]. That is, the importance of longer follow up has become apparent with the increasing numbers of asymptomatic cancer survivors at risk of cardiac dysfunction late in life.

In this study, THP-induced late cardiotoxicity was evaluated for asymptomatic children who received THP therapy in three consecutive JCCLSG studies (ALL911/ALL941/ALL2000). The results showed that THP-induced late cardiac dysfunction was not detected in any subjects, but careful observation may be necessary for subjects who show elevated biomarker levels following the exercise test.

PATIENTS AND METHODS

Study Population

The 33 member institutes of the JCCLSG participated in three consecutive ALL trials, and the total number of long-term survivors was 825 (161 in ALL911, 381 in ALL941, and 283 in ALL2000). This study was performed on subjects from the 7 of these hospitals which had follow-up systems for long-term survivors with the collaboration of cardiologists. In each institute, survivors who had clinical heart failure, as defined by the New York Heart Association classification (NYHA, class III-IV) [32] or cardiovascular disease were excluded. Prior written informed consent was obtained from patients or legal guardians. Finally, 61 patients (9 in ALL911, 48 in ALL941, 4 in ALL2000) were enrolled in this study (Table I). Since many survivors from ALL911 (1991–1993) are now adults with no time to participate the study, and those from ALL2000 (2000–2003) have had a very short follow-up duration, 80% of patients consisted of survivors

Additional Supporting Information may be found in the online version of this article.

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TABLE I. Characteristics of Patients

Sex—male:female		30:31
Age at onset (years old)		5.7 ± 3.5
Age at evaluation (years old)		14.7 ± 3.5
Follow-up period (years)		7.2 ± 2.8
Treatment protocol		
ALL 911	Total	9
	LR	2
	IR	3
	HR	4
ALL 941	Total	48
	LR	7
	IR	21
	HR	17
	HHR	3
ALL 2000	Total	4
	IR	1
	HR	3
Total dose of THP (mg/m^2)		299 ± 192 (120–740; 180)[a]
Total dose of anthracyclins converted to THP (mg/m^2)		346 ± 206 (135–812; 207)[a]

Data are expressed as mean ± SD. HHR, high-high-risk; HR, high-risk; IR, intermediate -risk; LR, low-risk. [a]The number of parenthesis shows the range and median value.

from the ALL941 (1994–1999) study. Ages ranged from 7.6 to 25.7 years old with a median of 14.7, and the median follow-up time after completion of AC therapy ranged from 1.7 to 12.5 years with a median of 8.1. Ten age-matched healthy controls were also recruited (6 males and 4 females; mean age 13.8 ± 2.4 years old). They had normal cardiac function and had not received any treatment affecting the heart, kidneys, or fluid balance before the study.

Intralaboratory Exercise Testing

Master two-step intralaboratory testing with triple exercise loads was performed on every subject. The electrocardiogram (ECG) tracing was recorded before, immediately following, and 1 min after exercise. An abnormal ECG response was defined as a horizontal or downsloping ST segment depression of 0.10 mV (1 mm) for 80 msec [33].

Natriuretic Peptide

Blood samples for measuring brain natriuretic peptide (BNP) before intralaboratory exercise testing were obtained during fasting in the morning, and further samples were obtained after the exercise test. 1.5 ml of blood was drawn into ice-chilled tubes containing ethylene-diamine-tetraacetic acid while the subjects were in a supine position. The blood was centrifuged at 4°C to separate plasma, and stored below −20°C until analysis. Plasma BNP concentrations were measured using chemiluminescent enzyme immunoassay kits (Shionogi BNP; Shionogi & Co., Ltd., Osaka, Japan) [34].

Heart Rate Variability

Holter ambulatory ECG was recorded for every subject to evaluate heart rate variability (HRV). The measurements of heart rate adopted in the present study were standard deviation of NN intervals (SDNN) and co-variance of NN intervals (CVNN).

Heart periods with arrhythmia were excluded from the HRV analyses.

Echocardiography

Echocardiograms were recorded for each subject from the parasternal and apical windows. Two-dimensionally guided M-mode echocardiography was performed, and the measurements were expressed as indices [35]. Variables of systolic functions included: left ventricular diastolic dimension (LVDd), left ventricular end-systolic dimension (LVDs), ejection fraction (EF) defined as (LVDd3 − LVDs3)/LVDd3, and fractional shortening (FS) defined as (LVDd − LVDs)/LVDd. FS $< 28\%$ and EF $< 54\%$ were considered abnormal [36]. The end-diastolic and end-systolic phases were defined as the beginning of the QRS wave of the ECG tracing and the point at which the second heart sound was recorded by the phonocardiogram, respectively. The variable of diastolic function was the ratio between early (E) and late or atrial (A) ventricular filling velocity (the E/A ratio) [37,38] by a pulsed Doppler measurement. The sample volume was placed between the mitral anulus and the leaflet tips where the greatest velocities were found. Cardiac dysfunction was defined by abnormal FS, and abnormalities of the other determinations were used as confirmatory evidence.

The 6-Minute Walk Test

The 6-min walk test (6MWT) was used to evaluate the functional capacity of the subjects. The field test was performed on a running track to measure the furthest distance a subject can walk. Normal values according to age and sex were defined by Geiger et al. [39].

Statistical Analyses

Regression analyses were used to study the correlation between cumulative THP dose on one side and cardiac function and biomarkers. The unpaired Student's *t*-test was used for the comparison of mean values. SPSS statistical analysis software (SPSS 12.0 J, SPSS Japan Inc., Tokyo, Japan) was used for all computations.

RESULTS

Cumulative dose of THP ranged from 120 to 740 mg/m^2 with a median of 180 mg/m^2. In addition to THP, subjects in ALL941 and ALL2000 received DOX. Thus, total cumulative doses of AC (THP + DOX) ranged from 135 to 812 mg/m^2 with a median of 207 mg/m^2 (Table I). To calculate this, the DOX/THP ratio used was 1:1.08 based on the molecular weight ratio.

The measurements of cardiac functions and the number of abnormal subjects are listed in Table II. ECG at rest was normal in all subjects. However, abnormal ST elevation on ECG was found after laboratory exercise testing in one subject (1.6%). The Holter recording was performed on 59 subjects, and abnormal findings with supra-ventricular premature contraction were detected in 2 (3.3%). These two did not show any other cardiac abnormal measurements. Heart rate variability was normal in all

TABLE II. Measurements of Cardiac Functions

Tests	Measurements	Number of subjects	Results mean ± SD (range)	Number of abnormal subjects
ECG	At rest	61	Normal	0
	After exercise	61	ST elevation	1
Holter ECG	Arrhythmia	59	SVPC	2
	CVNN (%)	59	19.8 ± 3.2 (2.7–27.1)	0
Echocardiography	LVDd (mm)	61	43.9 ± 4.0 (36.1–52.0)	0
	LVDs (mm)	61	26.9 ± 3.4 (19.0–34.6)	0
	EF (%)	61	70.4 ± 6.2 (53.0–81.3)	1
	FS (%)	61	38.7 ± 4.6 (29.4–50.0)	0
	E/A ratio	48	2.08 ± 0.47 (1.43–4.0)	0
6MWT	Total (m)	41	563.4 ± 142.5	5
	Males (m)	18	650.4 ± 110.9 (362.0–904.5)	1
	Females (m)	23	495.4 ± 126.7 (252.0–699.6)	4
Laboratory exercise testing	BNP at rest (pg/ml)	60	13.3 ± 14.6 (2.0–70.8)	6
	BNP after exercise (pg/ml)	60	15.1 ± 15.4 (2.0–85.2)	6

6MWT, 6-min walk test; CVNN, co-variance of NN intervals; LVDd, left ventricular end-diastolic dimension; LVDs, left ventricular end-systolic dimension; EF, ejection fraction; FS, fractional shortening; SVPC, supra-ventricular premature contraction.

TABLE III. Plasma BNP Levels in Patients and Controls

	BNP (pg/ml)		
	At rest	After exercise	Difference
Patients (n = 60)	13.3 ± 14.7	15.1 ± 15.5	1.8 ± 8.7
Control (n = 10)	10.7 ± 9.3	11.1 ± 10.5	0.4 ± 1.8
P	0.60	0.53	0.63

Values are expressed as mean ± SD.

subjects. Echocardiographic studies showed no cardiac dysfunction, and abnormal measurement was recorded in only one subject with a subnormal EF value of 53%. The 6MWT was performed on 41 subjects, and a significantly short distance as compared to the standard values adjusted to sex and age was recorded in 5 (one male and 4 females). The elevated plasma BNP levels defined as greater than the mean + 2 SD of the 10 healthy controls were >28.3 pg/ml (before exercise) and >31.1 pg/ml (after exercise), respectively. Based on this criterion, abnormal BNP levels were detected in six subjects whose values were elevated both at rest and after exercise. The mean BNP values before and after exercise in patients and control subjects are shown in Table III, revealing no significant difference between the patients and controls.

Overall, some abnormal cardiac measurements were detected in 14 subjects, and the type of abnormality and cumulative AC dose for each subject are shown in Table IV.

Table V shows the correlation between cumulative THP dose and various cardiac measurements. The cumulative dose showed a significant correlation with plasma BNP levels after exercise (Fig. 1), but not with any other cardiac measurements. Further analysis of the plasma BNP levels after exercise revealed that 21 subjects who received a high cumulative dose $\geqq$300 mg/m^2 of THP had significantly higher BNP levels as compared with 39 other subjects who received a low cumulative dose <300 mg/m^2 (Table VI). This table also shows increments in BNP levels (ΔBNP) after exercise compared to base-line values (at rest) between the two groups. A significant rise in ΔBNP after exercise

TABLE IV. Cumulative Dose of Anthracyclins and Abnormal Cardiac Measurements

Case	Cumulative dose of anthracyclins (DOX/THP) (mg/m^2)	Exercise ECG	Holter ECG	6MWT	Plasma BNP	
					At rest	After exercise
1	25/180	−	+	−	−	−
2	0/180	−	−	+	−	−
3	25/160	−	−	−	+	+
4	75/600	−	−	−	+	+
5	75/730	+	−	−	−	−
6	75/150	−	+	−	−	−
7	75/120	−	−	+	−	−
8	75/740	−	−	−	+	+
9	75/590	−	−	−	+	+
10	15/160	−	−	−	+	+
11	0/135	−	−	−	+	+
12	25/180	−	−	+	−	−
13	25/180	−	−	+	−	−
14	75/740	−	−	+	−	−

+ and − denote positive and negative results for cardiac measurements, respectively. DOX, doxorubicin; THP, pirarubicin.

TABLE V. Correlation of Cardiac Measurements and Total Dose of THP

Measurements	Correlation coefficient	*P*
FS	0.01	0.09
EF	0.90	0.49
E/A ratio	0.08	0.57
CVNN	0.26	0.08
6MWT	0.02	0.88
BNP at rest	0.11	0.42
BNP after exercise	0.27	0.03

THP, pirarubicin; FS, fractional shortening; EF, ejection fraction. CVNN, co-variance of NN intervals; 6MWT, 6-min walk test.

was observed for subjects with $\geqq 300$ mg/m^2 of THP, but not for subjects with <300 mg/m^2 of THP. Although correlations between the measurements of left ventricular function (FS and EF) and cumulative THP dose or BNP levels were studied, no significant results were obtained (Supplemental Appendix).

DISCUSSION

THP is a derivative of DOX developed in Japan, and its cardiotoxicity may be lower than that of DOX [12–15]. Tsurumi et al. and Niitsu et al. reported that acute cardiotoxicity with THP was less frequent than that with DOX among adult lymphoma patients [17–20]. However, no studies for late cardiotoxicity of THP have been reported. In this study, cardiac function and biomarkers were measured in long-term survivors with ALL who received THP treatment and in whom no apparent cardiac dysfunction was detected. Thus, this is the first report of late cardiotoxicity of THP in cancer survivors.

The incidence of AC-induced cardiac dysfunction in childhood cancer survivors varied considerably across studies. The incidences of 14–24% for cardiac dysfunction assessed by echocardiography had been reported in five studies, in which median doses of cumulative AC ranged from 165 to 450 mg/m^2 [6,7,28,29,31]. Three other studies also reported that cumulative AC dose was significantly associated with reduced FS function, and high cumulative dose >300 mg/m^2 increased the risk of cardiac dysfunction [11,26,27]. When our results are compared with these findings, it appears that incidence of cardiac dysfunction after THP treatment

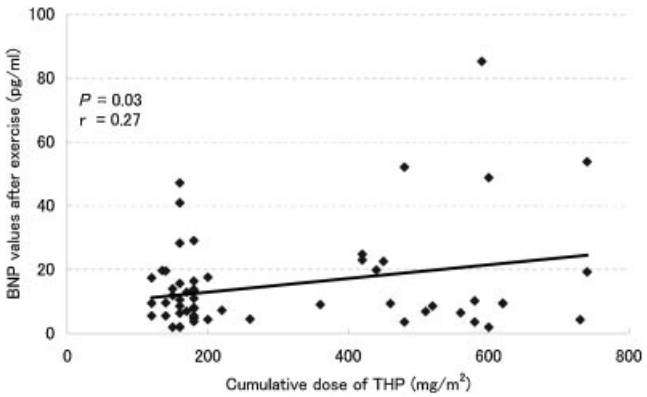

Fig. 1. Correlation between plasma BNP values after exercise and cumulative pirarubicin (THP) dose.

TABLE VI. Plasma BNP Levels According to Total Dose of THP

Total dose of THP	<300 mg/m^2 (n = 39)	$\geqq 300$ mg/m^2 (n = 21)	*P* value vs. <300 mg/m^2
BNP at rest (pg/ml)	12.5 ± 13.8	14.8 ± 15.8	0.56
BNP after exercise (pg/ml)	12.2 ± 9.9	20.6 ± 21.2	0.04
ΔBNP (pg/ml)	−0.3 ± 7.8	5.4 ± 8.1	0.01

Values are expressed as mean ± SD. THP, pirarubicin.

is relatively low. However, it should be noted that EF and FS may not be sensitive parameters for monitoring cardiac injury, because they often remain normal until critical point in the face of cardiac compensation [30]. Tissue Doppler echocardiography (TDE) has became widely available. Since TDE gives a more precise estimation for diastolic dysfunction than the E/A ratio used in this study, it may be helpful in future studies [40].

Non-invasive techniques for identifying patients who are at high-risk of developing AC-induced cardiomyopathy are critically important. For this purpose, natriuretic peptides including BNP and N-terminal fragment of BNP pro-hormone (NT-pro-BNP), are currently used for detection of cardiac injury in both adults and children [41]. Until now, 4 studies have reported BNP levels in childhood cancer survivors who received AC therapy [28–31]. In 3 of these, elevated BNP levels were detected [28,30,31], although the values did not significantly correlate with cumulative AC doses. Our study showed no significantly different BNP levels in patients from controls, but BNP levels after exercise were significantly correlated to cumulative THP dose. A similar finding was reported by Pinarli et al. [30], in which they found high BNP levels after exercise by treadmill, but no correlation with cumulative AC dose. Since augmented response in plasma BNP levels to exercise has been reported in adult patients with left ventricular dysfunction or exercise-induced ischemia [42,43], the increased BNP levels and ΔBNP after exercise in our study may be associated with subclinical myocardial injury. The stability of BNP in blood samples should be considered when interpreting BNP values after exercise. McNairy at al. found that post-exercise BNP returned to baseline levels within 60 min for normal subjects [44]. On the other hand, NT-pro-BNP is characterized by its stability against protease and longer half-life in comparison with BNP. Thus, the measurement of NT-pro-BNP may provide additional evidence in the early detection of anthracycline-induced cardiotoxicity in childhood and adolescence.

Currently, the 6MWT is considered to represent the most suitable method to assess the exercise tolerance. This self-paced test is easy to perform, well tolerated, and highly acceptable to children [39,45]. In our study, all subjects finished the test without difficulty or premature stopping. Consequently, the 6MWT may be used both in assessment and follow up of functional capacity in childhood cancer survivors.

In conclusion, the present study suggested that THP-induced late cardiac dysfunction is rare. However, further investigation is warranted to clarify the pathopsysiological significance of elevated BNP levels after the exercise test in asymptomatic patients.

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