Cardiac troponin I: is it a marker to detect cordiotoxicity in children treated with doxorubicin?

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Doxorubicin has been used in the the treatment of malignant tumors in children. Its use is limited by cardiotoxic effects beyond a cumulative dose of 450 mg/m². To detect cardiotoxicity at an early stage and identify patients at risk for development of cardiotoxicity are matters of concern. Recently, cardiac troponin I (cTnI) has been reported to be useful for detecting minor myocardial damage. In the present study, we investigated whether cumulative doxorubicin-related myocardial cell damage can potentially increase cTnI levels above the expected values in 22 patients treated with cumulative doxorubicin doses of 120 to 450 mg/m². Impaired cardiac functions were found in three patients by echocardiography, but serum CTnI levels were within the ranges expected in healthy individuals both in patients with cumulative doxorubicin doses ≥400 mg/m² and in patients with disturbed cardiac functions. We found no relationship between serum cTnI, cumulative dose of doxorubicin, and echocardiographical findings.

Key words: cardiac troponin I, doxorubicin, cardiotoxicity.

Anthracyclines have been successfully used in the treatment of hematopoietic and solid tumors in children. They represent one of the most commonly used classes of anticancer agents. However, their use is limited by development of cumulative dose-dependent cardiomyopathy and congestive heart failure (CHF)[1]. cardiotoxicity of anthracyclines presents within weeks up to years after completion of the treatment. The most important risk factor for developing cardiotoxicity is the total cumulative dose of the anthracycline[2]. Deterioration of the cardiac functions commonly presents as CHF with high mortality rates. The majority of patients with ventricular dysfunction lack overt symptoms until late in their disease. Early detection of cardiac damage, medical intervention and intensive treatment are of importance to improve cardiac prognosis. Echocardiography is the most widely used tool that allows evaluation of the cardiac functions but its limited sensitivity in identifying cardiac damage at an early pre-clinical stage is a matter of concern[3,4]. New structural markers have been proposed to provide diagnostic information in patients with myocardial damage for the detection of anthracycline-induced cardiotoxicity. Recent studies demonstrated that cardiac troponins, endothelin-1 and brain natriuretic peptide are emerging as efficient tools for assessing myocardial damage in different clinical settings[5-7]. Cardiac troponin I (cTnI) has been increasingly reported as a highly sensitive marker for myocardial damage, and it is currently being evaluated for its usefulness in the detection of anthracycline-induced cardiotoxicity[8-10]. There is limited data regarding the serum levels of cTnI to identify the patients at high risk for development of anthracycline-induced cardiotoxicity[11].

The objective of this study was to define the potential role of cTnI for the determination of its serum level to predict anthracycline-induced cardiotoxicity in childhood cancer. We investigated the relationship between serum levels of cTnI, cumulative dose of anthracyclines, and echocardiographical findings and its sensitivity for screening for myocardial damage.

Material and Methods

Twenty-two patients who received doxorubicin for the treatment of their solid tumors at cumulative doses of 120 to 450 mg/m^2 were included in this study. Fourteen patients had completed their therapies before the study date and eight patients were still on therapy for their diseases. The patients had no clinical evidence of abnormal cardiac functions. Patients were excluded from the study if they had evidence of renal or hepatic disease. None of the patients had been given mediastinal irradiation before.

Serum cardiac cTnI levels were detected in each patient at Düzen Medical Laboratory Group, Ankara. The blood samples for the study were obtained from antecubital veins of the patients, centrifuged at 3000 rpm and stored at –70°C until the study date. Serum cTnI levels were measured using cTnI ELISA (enzyme-linked immunosorbent assay) (DRG International, Inc, USA), and the minimum detectable concentration of the test was 1.0 ng/ml.

All patients had undergone cardiac evaluation by chest X-ray, electrocardiography and echocardiography. We recorded the systolic and diastolic cardiac functions in the 24 hours after serum samples for cTnI were obtained. Echocardiograms were performed with Hewlett-Packard Sonos 1000 ultrasound imaging device. Using two-dimensional and Doppler echocardiography, the percent change in left ventricular dimension with systolic contraction (fractional shortening; FS), stroke volume as percent of end-diastolic left ventricular volume (ejection fraction; EF), and the ratio of early peak mitral flow velocity of the early rapid filling wave (E) to peak mitral flow velocity of the late filling wave due to atrial contraction (A) (E/A) were determined as systolic and diastolic function parameters. The abnormal systolic functions were defined when EF<55% and FS<29%[2]. Diastolic function parameters of three age-based healthy control groups (3-10 years, 11-20 years, and 21-30 years) from 24 healthy subjects were formed, and the diastolic functions of each patient were compared with these corresponding groups. The mean E/A for healthy subjects is 1.58±0.4. Diastolic functions were defined as abnormal when they were beyond defined limits.

Results

There were 22 patients (11 girls, 11 boys) who received cumulative doxorubicin doses of 120 to 450 mg/m^2. Their median age was 16 years (range: 6-22 years). Fourteen of the patients had completed their treatment before the study date; eight patients were still on doxorubicin-based therapy. The median time passed since the last doxorubicin administration in patients who had completed their therapies was 31 months (range: 6-74 months). The underlying malignancies were osteosarcoma[12], Ewing sarcoma[6], rhabdomyosarcoma[2], primitive neuroectodermal tumor[1], and malignant mesenchymal tumor[1]. The patients were divided into two groups according to their cumulative doxorubicin doses:

1st group: Patients with cumulative doxorubicin doses ≥420 mg/m^2 (n=10, median cumulative doxorubicin dose=450 mg/m^2).

2nd group: Patients with cumulative doxorubicin doses <420 mg/m^2 (n=12, median cumulative doxorubicin dose=245 mg/m^2).

The characteristics of the patients are shown in Table I. All 22 patients had normal radiological and electrocardiographical findings. In the 1st group, three patients (30%) had impaired cardiac functions detected by echocardiography. One of them had impaired systolic cardiac functions and two had impaired diastolic cardiac functions. All three patients had cumulative doxorubicin dose of 450 mg/m^2. In the 2nd group, no patient had impaired systolic or diastolic cardiac functions detectable by echocardiography. The echo-cardiographic findings with cumulative doxorubicin doses are shown in Tables II and III. All then serum cTnI levels obtained from the 22 patients were below the detectable limit (<1.0 ng/ml). There was no difference between the cumulative doxorubicin dose and serum cTnI level between the groups. The patients with impaired cardiac functions detected by echocardiography also had serum cTnI levels below the sensitivity level of the assay.

Table I. Characteristics of the Patients

	Group 1 (n=10)	Group 2 (n=12)
Age (years)	16-22 (median 18)	6-19 (median 11)
Sex M/F	6/4	5/7
Cumulative doxorubicin dose	≥420 mg/m^2 (median 450 mg/m^2)	<420 mg/m^2 (median 245 mg/m^2)
Serum cTnI levels	<1.0 ng/ml	<1.0 ng/ml
Diagnosis		
Osteosarcoma	9	3
Ewing's sarcoma	1	5
MMT	–	1
Rhabdomyosarcoma	–	2
PNET	–	1

TnI: cardiac troponin I; MMT: malignant mesenchymal tumor, PNET: primitive neuroectodermal tumor.

Table II. The Echocardiographical Findings of the Patients with Cumulative Doxorubicin Doses ≥420 mg/m^2

Patient	CDD	EF %	FS %	E/A
1	450	74	43	1.22
2	450	66	36	1.79
3	450	72	41	1.27
4	450	85	54	1.13
5	450	45	23	1.76
6	450	60	31	1.21
7	450	84	42	1.44
8	450	62	34	1.80
9	420	68	38	1.25
10	450	70	39	1.14

CDD: cumulative doxorubicin dose, EF: ejection fraction, FS: fractional shortening, E/A: The ratio of early peak mitral flow velocity of the early rapid filling wave (E) to peak mitral flow velocity of the late filling wave due to atrial contraction (A).

Table III. The Echocardiographical Findings of the Patients with Cumulative Doxorubicin Doses <420 mg/m^2

Patient	CDD	EF %	FS %	E/A
1	360	71	40	1.36
2	120	69	39	1.69
3	340	63	34	1.60
4	150	63	33	1.44
5	250	75	43	1.28
6	150	67	36	1.53
7	180	74	40	1.52
8	260	67	37	1.25
9	120	71	40	1.57
10	300	69	37	1.81
11	240	60	32	1.50
12	300	64	35	1.40

CDD: cumulative doxorubicin dose, EF: ejection fraction, FS: fractional shortening, E/A: The ratio of early peak mitral flow velocity of the early rapid filling wave (E) to peak mitral flow velocity of the late filling wave due to atrial contraction (A).

Discussion

Doxorubicin is a primary component of most treatment regimens for childhood malignancies. Its therapeutic value is limited by myocardial toxicity. It may cause both acute and long-term cumulative cardiotoxic effects. The incidence of clinical cardiotoxicity can be anticipated to increase rapidly beyond a cumulative dose of 450 mg/m^2, but individual patients may have a lower threshold and develop cardiotoxicity at lower doses[2,3]. Cumulative dose-dependent cardio-toxicity may appear during or several months or years after anthracycline therapy. To detect cardiac dysfunction, regular monitoring of the heart functions during and after doxorubicin treatment is essential. Identification of cardiac damage may lead to discontinuation or dose reduction of doxorubicin to prevent further cardiac deterioration[2]. Since the number of cancer survivors is growing and myocardial damage may be clinically occult, investigations are underway to detect cardiotoxocity at an early stage and to identify patients who are at risk for the development of CHF. Electrocardiographic changes are too nonspecific and occur too late to be predictive of myocardial damage and changes in cardiac function[2]. Echocardiography is a non-invasive tool that allows evaluation of cardiac function and is used frequently in cardiology[3]. Various parameters of systolic and diastolic functions, anatomic dimensions and afterload can be assessed[12]. The most commonly used parameters are FS and EF. Fractional shortening and EF below 29% and 55%, respectively, are considered to reflect systolic dysfunction[2]. However, Marchandise et al.[13] found no post-treatment left ventricular systolic

dysfunction but a decreased E/A ratio by 20% compared to baseline determination in 19 adult patients indicating diastolic dysfunction. Although echocardiography during exercise and dobutamine stress test has been investigated to detect cardiotoxicity at early subclinical stages, especially in adults, it is not practical in children. Since impairment in diastolic cardiac functions may occur in the absence of detectable systolic dysfunction, we studied both systolic and diastolic functions by echocardiography. Although some evidence suggests that some patients may develop subclinical or clinical cardiotoxicity below the threshold level (450 mg/m^2) during or many years after doxorubicin therapy, the incidence is minimized by restricting the cumulative doxorubicin dose to less than 400 mg/m^2[2,11]. Incidence of echocardiographically detected impaired systolic functions was reported as 14% after 4 to 6 years, 24% after 7 to 9 years and 38% after more than 10 years following anthracycline therapy in children[14]. The cumulative doxorubicin doses ranged between 120 to 450 mg/m^2 in our patients. Impaired systolic functions (EF=45% and FS=23%) were detected in only one patient. The cumulative doxorubicin dose of this patient was 450 mg/m^2. She had normal cardiac functions at the time f diagnosis and beginning of doxorubicin therapy. She was still on therapy, and so doxorubicin was withdrawn from the therapy, regimen. Although cardiotoxicity is now subclinical, she has high risk for development of CHF in future and needs close follow-up. Impaired diastolic functions (decreased E/A ratios) were detected in two patients. The cumulative doxorubicin dose of both patients was also 450 mg/m^2. One of these patients had completed the therapy 33 months before, and the other had been off therapy for 29 months. All disturbed echocardiographic parameters, systolic and diastolic, were detected in patients with a cumulative doxorubicin dose of 450 mg/m^2. Disturbed diastolic functions in two of the patients despite normal systolic functions were consistent with the findings reported by Marchandise et al[13]. Bossi et al.[4] found no correlation between cumulative anthracycline dose and echocardiographic parameters in 117 patients after seven years of completion of their treatments. The patients had a median cumulative doxorubicin dose of 214 mg/m^2 in that study. In our study, the patients were divided into two different groups according to their cumulative doxorubicin doses. The first group had received a median 450 mg/m^2 cumulative doxorubicin dose, approximately two times greater than that study, and this was near the threshold level at which CHF risk increases more logarithmically. Thus, abnormal echocardiographical results are not usual at 214 mg/m^2 cumulative doxorubicin dose. In our study no patient with a cumulative doxorubicin dose of <400 mg/m^2 had disturbed cardiac functions. Our findings suggest that a cumulative doxorubicin dose of 400 mg/m^2 is a threshold level at which anatomic damage increases linearly with the cumulative dose, and clinical manifestations increase more logarithmically at higher doses. Although standard monitoring regimens for cardiac functions for anthracycline-treated patients recommend following EF and FS, there may be impaired diastolic with preserved systolic functions.

Some biochemical markers seem to be useful for early detection of anthracycline-induced cardiotoxicity and for identifying the patients at risk for cardiotoxicity in future. Although cardiac troponins are known to be elevated mainly in patients with acute myocardial infarct, unstable angina, CHF and myocarditis, they have been reported to be potentially useful markers for the early detection of anthracycline-induced cardiotoxcity[5,7-9,11]. Lipshultz et al.[15] found elevated serum cardiac troponin (cTnT) levels in children treated with doxorubicin, and the degree of cTnT elevation predicted left ventricular dilatation and wall thinning nine months later, suggesting that an elevated cTnT level may predict subsequent subclinical and clinical cardiac morbidity. Missov et al.[16] reported elevated cTnI levels in 13 patients who had been treated with anthracyclines. However, the elevations were at low levels, the probable result of prolonged release of cTnI into plasma from initial myocardial injuries and a decrease in ability to recover. This low-level increment was termed submyocardial infarction range (0-10 ng/ml). Seino and colleagues[17] found elevated serum cTnT levels in rats given 1.5 mg/kg/week doxorubicin eight times. Herman et al.[18] found elevated serum cTnT levels with increments in cumulative doses and a correlation between average cTnT levels and cardiomyopathy scores in rats. They proposed that determining serum levels of cTnT is a

sensitive means for assessing the early cardiotoxicity of doxorubicin. However, Kısmet et al.[19] found no correlation between serum cTnT levels and cumulative doxorubicin levels in 24 patients treated with doxorubicin. In addition, they showed no correlation between serum cTnT levels and echocardiographically detected systolic and diastolic findings. In that study all of the patients had been given doxorubicin at cumulative doses of ≥400 mg/m^2.

In the present study, we investigated whether cumulative doxorubicin administration-related myocardial cell damage can potentially increase cTnI levels above the expected values. In healthy individuals they are expected to be under the detection limit. Although cTnI is a recently described sensitive biomarker for the detection of minor myocardial damage, its blood level was undetectable both in patients with cumulative doxorubicin doses ≥400 mg/m^2 and in patients with cumulative doxorubicin doses <400 mg/m^2. All values from both groups were within the ranges expected in healthy individuals.

The main finding was that there was no association between serum cTnI levels and cumulative doxorubicin doses in patients treated with doxorubicin. It does not seem reliable to make a correlation between serum cTnI levels and cumulative doxorubicin dose. One of our patients had impaired systolic cardiac functions and two of the patients had impaired diastolic cardiac functions with a cumulative doxorubicin dose of 450 mg/m^2, but none of these patients had detectable serum cTnI levels. It also seems that there is no relationship between low-level subclinical myocardial damage detectable by echocardiography and serum cTnI levels. Generally speaking, cardiotoxicity with cumulative doses above 450 mg/m^2 is a well-known adverse effect of doxorubicin. Lipshultz et al.[15] reported no elevation of serum cTnT levels after discontinuation of anthracycline therapy, but the cumulative doxorubicin doses of their patients was below 222 mg/m^2 and the number of the patients was very few. They found low-level serum cTnT elevations in patients continuing their doxorubicin therapies and suggested that these low-level elevations may persist for a time as an indicator of chronic inflammatory changes. cTnT's potential role as a predictive factor in monitoring anthracycline therapy is not clear. Our results support the claim that serum cardiac troponin elevation due to long-term anthracycline therapy is much lower than the elevations reported in acute myocardial injuries as a result of prolonged release of cardiac troponin into plasma and a decrease in ability to recover. It is probable that pervious studies and the present study might have missed the low-level anthracycline-related cardiac troponin elevations. The use of cTnI with increased analytical sensitivity to detect the low levels may demonstrate predictive value in delineating the high risk group of anthracycline-induced cardiotoxicity patients. A single measurement should not be relied on; serial measurements may provide useful information for accurate diagnosis because the deterioration in cardiac functions may appear months or years after the doxorubicin treatment. Although echo-cardiography may not detect early myocardial damage, it is still a non-invasive, practical and reliable method to identify consistent changes in cardiac performance.

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