PERGAMON

European Journal of Cancer 38 (2002) 686–689

European Journal of Cancer

www.ejconline.com

Troponin T in the first 24 hours after the administration of chemotherapy and the detection of myocardial damage in children

L.C.M. Kremer[a,*], B.A.J. Bastiaansen[a], M. Offringa[b], J. Lam[c], J.P. van Straalen[d], R.J. de Winter[e], P.A. Voûte[a]

[a]*Department of Pediatric Oncology, Academic Medical Center, Emma Kinder Ziekenhuis, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

[b]*Department of General Pediatrics, Academic Medical Center, Emma Kinder Ziekenhuis, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

[c]*Department of Pediatric Cardiology, Academic Medical Center, Emma Kinder Ziekenhuis, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

[d]*Department of Clinical Chemistry, Academic Medical Center, Emma Kinder Ziekenhuis, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

[e]*Department of Cardiology, Academic Medical Center, Emma Kinder Ziekenhuis, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands*

Received 29 June 2001; received in revised form 4 December 2001; accepted 13 December 2001

Abstract

Early detection of damage to cardiac myocytes after cardiotoxic chemotherapy in paediatric patients may allow timely preventive measures to be taken. We investigated the diagnostic value of cardiac troponin T (cTnT) after the administration of cardiotoxic chemotherapy. In 38 children, cTnT levels were measured at three time points during the first 24 h after 58 cardiotoxic chemotherapy cycles (163 samples). An abnormal cTnT level, defined as a cTnT > 0.010 ng/ml, was measured in only six samples from 3 patients. After completion of chemotherapy, 7 out of the 38 patients had left ventricular dysfunction (LV dysfunction). Only 1 of these 7 patients had an elevated cTnT level. 2 other patients with elevated cTnT levels did not develop LV dysfunction until 2 and 7 months after the cTnT measurement. Our data show that the measurement of cTnT within 24 h after administration of chemotherapy does not have a high sensitivity for the identification of patients with subsequent subclinical cardiotoxicity. © 2002 Published by Elsevier Science Ltd.

Keywords: Anthracyclines; Cardiotoxicity; Diagnosis; Troponin T; Children

1. Introduction

Early identification of patients at risk for cardiac damage after cardiotoxic therapy is important, especially in children. Children have a long life expectancy after surviving childhood cancer and they seem to be more susceptible to the cardiotoxic effects of anthracycline therapy than adults [1]. In a recent study we showed that 1 out of 20 children treated with anthracyclines develops anthracycline-induced clinical heart failure within 15 years after the start of treatment [2]. The possibility of early detection of cardiac damage during chemotherapy might have important clinical implications because subsequent preventive measures can limit further myocardial damage. Yet, no parameter during chemotherapy exists to predict which patients will develop cardiac dysfunction or heart failure.

Cardiac troponin T (cTnT), a part of the tropomyosin complex associated with the thin-filament of the myocardium, has been shown to be a very sensitive and specific marker for myocardial injury of various aetiologies [3,4]. Recently, cTnT has been suggested to also be an early marker of anthracycline-induced myocardial damage [5–9]. In animal studies, levels of cTnT increased after the administration of anthracyclines, and this increase was associated with the cumulative dose and histological cardiomyopathy scores [5]. Lipshultz and colleagues found elevated cTnT levels (> 0.03 ng/

* Corresponding author. Tel.: +31-20-566-3250.
E-mail address: l.c.kremer@amc.uva.nl (L.C.M. Kremer).

0959-8049/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0959-8049(01)00431-2

ml) in a group of 15 children treated with anthracyclines and a positive correlation between cTnT levels and subsequent echocardiographic abnormalities [6]. In another study, a minor increase was found in cTnT levels (>0.01 ng/ml) in 29% of the children treated with doxorubicin [9].

One of the questions arising from these observations was whether testing for cTnT can detect myocardial damage within 24 h after the administration of chemotherapy. Early changes within 24 h were seen in the myocardial nuclei in myocardial biopsy of patients treated with anthracyclines and in rats, biochemical changes caused by oxygen free radical-related mechanisms occurred approximately 2 h after the administration of anthracyclines [10,11]. Cardiac TnT is detected in human serum within 24 h after myocardial injury in the setting of the acute coronary syndromes [12]. We prospectively investigated whether cTnT levels can be detected in the first 24 h after drug administration in children treated with cardiotoxic chemotherapy and whether cTnT elevations predict echocardiographic myocardial dysfunction.

2. Methods

2.1. Patients

Between December 1998 and May 2000, we prospectively included children treated for various kinds of malignancies with cardiotoxic chemotherapy. The hospital ethics committee approved the study protocol. All parents, and patients older than 12 years of age, provided written informed consent.

2.2. Cardiac troponin T

Heparin-plasma samples were collected prior to, 4–6 h after and 24 h after the administration of chemotherapy. The samples were centrifuged immediately and were stored at -20 °C until further analyses. Troponin T was measured using the third-generation Elecsys Troponin T STAT immunoassay (Roche Diagnostics Mannheim, Germany), standardised with human recombinant cTnT [13]. An abnormal level was defined as a cTnT >0.010 ng/ml. The technician who performed the assay was blinded to both the clinical and echocardiographic results.

2.3. Echocardiography

Two-dimensional transthoracic echocardiography was performed in all patients treated with cardiotoxic chemotherapy before, during and after the last cycle of chemotherapy. Echocardiography was performed by one experienced echocardiographic technician who was unaware of the cumulative dose of chemotherapy and of the cTnT levels. Left ventricular shortening fraction (SF) was measured with M-mode according to the formula: LVEDD-LVESD divided by LVEDD multiplied by 100, where LVEDD is left ventricular end diastolic diameter and LVESD is left ventricular end systolic diameter. The mean of three measurements for each patient was considered the SF value.

2.4. LV dysfunction

In this study, we defined left ventricular dysfunction (LV dysfunction) as either a SF below 30% or a decline of 15% or more from the baseline SF [14–16]. In a paediatric study Sandor and colleagues determined the reproducibility of serial measurements of the SF in children, and found a maximum variability of the SF of 15% [16]. Cardiotoxic chemotherapy-induced clinical heart failure was defined as heart failure not due to factors other than cardiotoxic chemotherapy.

2.5. Data analysis

Mean differences in the continuous variables were compared by the Student *t*-test. Sensitivity and specificity of a cTnT ng/ml for LV dysfunction were calculated. The predictive values of elevated and non-elevated cTnT levels for LV dysfunction were calculated.

3. Results

3.1. Patients

38 patients, 16 with a solid tumour and 22 patients with leukaemia or lymphoma were included at different stages of their treatment. They were treated with cardiotoxic chemotherapy, i.e. doxorubicin (20 patients), daunorubicin (4 patients), epirubicin (9 patients) or mitoxantrone (5 patients). The characteristics of the patients are shown in Table 1.

3.2. Cardiac troponin T

A total of 163 blood samples were collected during 58 treatment cycles from 38 patients for cTnT measurements. Elevated levels of cTnT (0.018–0.040 ng/ml) were detected in 6 (4%) samples of 3 (8%) patients.

3.3. Echocardiography

In 6 patients (16%), no echocardiogram at the end of treatment was performed because they did not finish their treatment (2 patients) or left the country (2 patients) or because it was impossible to obtain a good echo window (2 patients). None of these 6 patients had

Table 1
Characteristics of the patients

Characteristics	Mean	Standard deviation
Age at diagnosis (years)	9.9	4.7
Mean cumulative dose at sampling (mg/m^2)		
Anthracycline	172	112.3
Mitoxantrone	67.5	26.4
Mean SF (%)		
Start of treatment	40.5	3.7
End of treatment	36.4	4.6
Mean cumulative dose at end of treatment (mg/m^2)		
Anthracycline	255	118.9
Mitoxantrone	106	13.7

SF, shortening fraction.

abnormal cTnT levels, nor did they have signs or symptoms of clinical heart failure.

The SF at the end of treatment was significantly different from the SF at the start of treatment (mean difference: 4.1%, SD: 4.8). 7 patients developed LV dysfunction. One of these 7 patients had clinical heart failure.

3.4. Relationship between cTnT and LV dysfunction

Table 2 shows the relationship between cTnT levels and SF in patients with LV dysfunction or patients with elevated cTnT levels. One of the 7 patients with LV dysfunction had an elevated cTnT level (patient 1) and developed anthracycline-induced clinical heart failure 6 months later. 6 patients with LV dysfunction showed no elevated levels of cTnT during treatment. In patients 2, 4 and 6, no elevation was seen also at the next cycle of chemotherapy 4 weeks later.

2 of the 3 patients with elevated cTnT levels did not develop LV dysfunction (patients 8 and 9). Patient 8 died 2 months after the end of treatment because of tumour progression. Patient 9 did not develop signs of cardiotoxicity until a cumulative dose of 300 mg/m^2 7 months after blood sampling.

The sensitivity of the cTnT test for LV dysfunction was 14% (95% Confidence Interval (CI): 0–40%) and the specificity was 94% (95% CI: 85–100%). The predictive value of an elevated troponin T level for LV dysfunction was 33% (95% CI: 0–87%). The predictive value of a non-elevated cTnT level $\leqslant 0.01$ ng/ml for a normal LV function was 83% (95% CI: 70–95%).

4. Discussion

Although the results on cTnT levels to detect early myocardial damage after anthracycline therapy are encouraging, so far there are no published data available on the time lapsed between the administration of cardiotoxic therapy and occurrence of detectable levels of troponin in children. The present study show a small number of patients with elevated levels and a low predictive value of cTnT for subsequent LV dysfunction. One possible explanation could be that sampling within 24 h after the administration of chemotherapy is too early to detect myocardial damage. It is unclear if the mechanisms of cardiotoxicity results in myocyte necrosis which can be detected by cTnT elevations in the first 24 h after administration of cardiotoxic chemotherapy. In adults conflicting data exist about the relationship between the time lapse between the administration of chemotherapy and occurrence of detectable levels of troponin [17,18]. Auner and colleagues reported a rise in the cTnT up to 2 weeks after the administration of chemotherapy [18].

The small number of patients with elevated cTnT levels measured within 24 h after the administration of cardiotoxic chemotherapy in the present study seem to conflict with the results of Lipshultz and colleagues. However, besides the possibility that sampling within 24 h is too early, it is not likely that differences in study groups or differences in cut-off levels of cTnT could explain this discrepancy. On the contrary, the cumulative dose

Table 2
Patients with left ventricular dysfunction or elevated cTnT levels

Patient no.	Chemotherapy	Total dose (mg/m^2)	cTnT			SF	
			Dose (mg/m^2)	cTnT (ng/mL) 0 hr	24 hr	Before therapy	End therapy
1	Daunorubicin	300	150	0.025	0	38	20
2	Daunorubicin	300	250	0	0	39	29
3	Doxorubicin	125	100/125	0/0	0/0	45	37
4	Mitoxantrone	120	84/96	0/0	0/0	40	30
5	Mitoxantrone	96	60/72	0/0	0/0	39	33
6	Mitoxantrone	96	96	0	0	45	34
7	Mitoxantrone	120	72	0	0	35	28
8	Epirubicin	450	450	0.019	0.040	35	38
9	Doxorubicin	300	90	0.019	0.018	44	39

cTnT, cardiac troponin T; SF, shortening fraction.

received by patients was higher in our study than in the study by Lipshultz and colleagues, and the third-generation cTnT assay that we used is the most sensitive and specific assay currently available [8,9,13]. We used a low detection threshold of 0.010 ng/ml, while Lipshultz and colleagues considered a level above 0.03 ng/ml as evidence of damage to the cardiac myocytes [8]. The small number of patients with elevated cTnT levels could also be based on coincidence due to the small number of patients studied in this study.

The present study shows a low sensitivity and predictive value of cTnT, measured within 24 h after the administration of cardiotoxic chemotherapy, for subsequent LV dysfunction, i.e. subclinical cardiotoxicity. A limitation may lie in the definition of cardiac damage we used. All echocardiographic parameters may eventually turn out to be surrogate markers for the outcome of cardiac damage after chemotherapy with clinical signs and symptoms, i.e. clinical cardiotoxicity. In children measurement of the LV SF is the most widely used tool in the detection of subclinical cardiotoxicity after anthracycline therapy. However, there are no reports of studies that evaluate the predictive value of measurements of SF with regard to the subsequent development of clinical cardiotoxicity. In studies which investigate the relationship between predictive markers and cardiac damage, clinical heart failure should be the only definitive endpoint. Thus far, no studies have reported a cTnT increase in relation to clinical heart failure. In our study, 1 patient developed clinical heart failure and this patient showed an elevated cTnT level 6 months before heart failure was observed. Cardiac TnT elevation was measured before the administration of daunorubicin. However, 24 h after this administration no elevation was measured.

Our data show that sampling of cTnT, within 24 h after the administration of chemotherapy, seems to be too early to identify patients who are at increased risk for developing LV dysfunction. In our opinion, serial cTnT levels over a longer period of time after the administration of chemotherapy have to be further studied before cTnT can be recommended as a diagnostic tool of cardiac injury after chemotherapy.

Acknowledgements

We are indebted to Professor G.T.B. Sanders and Y. Schouten of the Clinical Chemistry department for supporting the analysis of cTnT, to Cor van den Bos, MD, a paediatric oncologist, for practical assistance, to Ewoudt Straat, the echocardiographic technician.

References

1. Von Hoff DD, Rozencweig M, Layard M, Slavik M, Muggia FM. Daunomycin-induced cardiotoxicity in children and adults. A review of 110 cases. *Am J Med* 1977, **62**, 200–208.
2. Kremer LC, van Dalen EC, Offringa M, Ottenkamp J, Voute PA. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. *J Clin Oncol* 2001, **19**, 191–196.
3. Katus HA, Remppis A, Scheffold T, *et al*. Intracellular compartmentation of cardiac troponin T and its release kinetics in patients with reperfused and nonreperfused myocardial infarction. *Am J Cardiol* 1991, **67**, 1360–1367.
4. Newby LK, Christenson RH, Ohman EM, *et al*. Value of serial troponin T measures for early and late risk stratification in patients with acute coronary syndromes. *Circulation* 1998, **98**, 1853–1859.
5. Herman EH, Zhang J, Lipshultz SE, *et al*. Correlation between serum levels of cardiac troponin-T and the severity of the chronic cardiomyopathy induced by doxorubicin. *J Clin Oncol* 1999, **17**, 2237–2243.
6. Lipshultz SE, Rifai N, Sallan SE, *et al*. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. *Circulation* 1997, **96**, 2641–2648.
7. Kaplan S. Biochemical markers of myocardial injury in children. *Circulation* 1997, **96**, 2496–2497.
8. Lipshultz SE, Grenier MA, Colan SD. Doxorubicin-induced cardiomyopathy. *N Engl J Med* 1999, **340**, 653–654.
9. Lipshultz SE, Sallan S, Dalton V, *et al*. Elevated cardiac troponin-T as a marker for active cardiac injury during therapy for childhood acute lymphoblastic leukemia. *Proceedings of ASCO* 1998, 568a.
10. Unverferth DV, Magorien RD, Unverferth BP, *et al*. Human myocardial morphologic and functional changes in the first 24 hours after doxorubicin administration. *Cancer Treat Rep* 1981, **65**, 1093–1097.
11. Luo X, Evrovsky Y, Cole D, *et al*. Doxorubicin-induced acute changes in cytotoxic aldehydes, antioxidant status and cardiac function in the rat. *Biochim Biophys Acta* 1997, **1360**, 45–52.
12. de Winter RJ, Koster RW, Sturk A, Sanders GT. Value of myoglobin, troponin T, and CK-Mbmass in ruling out an acute myocardial infarction in the emergency room. *Circulation* 1995, **92**, 3401–3407.
13. Hallermayer K, Klenner D, Vogel R. Use of recombinant human cardiac Troponin T for standardization of third generation troponin T methods. *Scand J Clin Lab Invest Suppl* 1999, **230**, 128–131.
14. Bu'Lock FA, Mott MG, Oakhill A, *et al*. Early identification of anthracycline cardiomyopathy: possibilities and implications. *Arch Dis Child* 1996, **75**, 416–422.
15. Steinherz LJ, Graham T, Hurwitz R, *et al*. Guidelines for cardiac monitoring of children during and after anthracycline therapy: report of the Cardiology Committee of the Childrens Cancer study Group. *Pediatrics* 1992, **89**, 942–949.
16. Sandor GS, Schumacher P, Puterman ML, *et al*. Normal serial variability for M-mode and digitized echocardiography in a pediatric population. *Pediatric Cardiol* 1987, **8**, 23–26.
17. Cardinale D, Sandri MT, Martinoni A, *et al*. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol* 2000, **36**, 517–521.
18. Auner HW, Tinchon C, Quehenberger F, Linkesch W, Sill H. Troponins in prediction of cardiotoxic effects. *Lancet* 2001, **357**, 808.