Cardiac Troponin I Seems to Be Superior to Cardiac Troponin T in the Early Detection of Cardiac Injury Associated with Anthracycline Treatment

Jan M. Horacek^{a, d} Radek Pudil^b Milos Tichy^{c, d} Ladislav Jebavy^{a, d} Alena Strasova^a
Martina Ulrychova^c Pavel Zak^a Jaroslav Maly^a

^a2nd Department of Medicine – Clinical Hematology,

^b1st Department of Medicine,

^cInstitute of Clinical Biochemistry and Diagnostics, Faculty of Medicine and University Hospital Hradec Kralove,

^dDepartment of Internal Medicine, University of Defence, Faculty of Military Health Sciences Hradec Kralove, Czech Republic

Cardiac toxicity is among the undesirable side effects of oncology treatment. Of the cytostatics, anthracyclines represent the greatest risk for development of cardiotoxicity [1]. Various methods have been recommended for monitoring cardiotoxicity in oncology [2, 3]. Echocardiography and electrocardiography are routinely used, and recently, the applicability of cardiac troponins in the detection of cancer therapy-induced cardiotoxicity has been investigated [4]. In some studies, administration of anthracyclines did not cause any elevation of cardiac troponins [5–7]. In other studies, cardiac troponins became positive after anthracycline treatment, correlated with disease severity, and were suggested as predictors of subsequent major cardiac events during follow-up [8–10]. The results of clinical studies are inconsistent, and cardiac troponins have not been established in clinical practice for monitoring cardiotoxicity in oncology.

The aim of our study was to evaluate acute and chronic cardiotoxicity of anthracyclines with cardiac troponins. We used current immunoassays for cardiac troponin T (cTnT; Roche Diagnostics, Mannheim, Germany) and cardiac troponin I (cTnI; Randox Laboratories Ltd., Crumlin, Co. Antrim, UK), and correlated the results with echocardiography findings. A total of 23 patients (mean age 47.0 ± 11.1 years; 14 males, 9 females) with acute leukemia were studied. The patients were treated with 3–6 cycles of conventional chemotherapy (CT) containing anthracyclines at a total cumulative dose of 472.1 ± 115.0 mg/m²; to calculate the total cumulative anthracycline dose, we applied conversion factors derived from the maximum recommended cumulative doses for the individual agents used (idarubicin, daunorubicin, mitoxantrone). Six patients were treated for arterial hypertension; other patients had no history of cardiovascular disease. All patients had normal

liver and renal function during the study. Cardiac evaluation was performed at baseline (before CT), the day after the first CT with anthracyclines (mean cumulative dose 135.8 ± 28.5 mg/m², median 150), the day after the last CT with anthracyclines (mean cumulative dose 472.1 ± 115.0 mg/m², median 423), and approximately 6 months after completion of CT. Concentrations of cardiac troponins diagnostic for cardiotoxicity of oncology treatment have not yet been established. In our study, values above the reference range recommended by the manufacturer were considered elevated. The cut-off value for cTnT was 0.01 µg/l (Roche Diagnostics), and for cTnI 0.40 µg/l (Randox Laboratories Ltd.). Echocardiographic evaluation was performed on a Hewlett Packard Image Point machine by an experienced echocardiographer who was blinded to the cardiac troponin data. Parameters of systolic and diastolic left ventricular (LV) function were assessed. Systolic LV dysfunction was defined as LV ejection fraction (LVEF) $\leq 55\%$. Diastolic LV dysfunction was defined as E/A inversion and a E wave deceleration time above 220 ms on the transmitral Doppler curve (impaired relaxation). Statistical analysis was performed with Statistica for Windows, version 5.0 (StatSoft, Tulsa, OK, USA). Analysis of variance test was used. Correlations were evaluated with normal and Spearman correlation tests. The values are expressed as mean $\pm$ standard deviation (SD). Probability values (p) of < 0.01 were considered statistically significant. The results are summarized in table 1.

Of the cardiac troponins, only cTnI became positive on the days after the first and last CT with anthracyclines, which was observed in a total of 4 (17.4%) patients. Positivity of cTnI correlated with systolic and diastolic LV dysfunction on echocardiography: $r = 0.712$; $p < 0.00001$ and $r = 0.591$; $p < 0.0001$,

Table 1. Abnormal cardiac findings during treatment and follow-up of acute leukemia (n = 23)

Abnormal cardiac findings	Before CT, n (%)	After first CT, n (%)	After last CT, n (%)	6 months after CT, n (%)
cTnT above 0.01 µg/l	0	0	0	3 (13.0)
cTnI above 0.40 µg/l	0	4 (17.4)	4 (17.4)	6 (26.1)
Systolic LV dysfunction	0	1 (4.3)	3 (13.0)	5 (21.7)
Diastolic LV dysfunction	1 (4.3)	4 (17.4)	6 (26.1)	10 (43.5)

CT = Chemotherapy; cTnI = cardiac troponin I; cTnT = cardiac troponin T; LV = left ventricular.

respectively. Patients with cTnI positivity during anthracycline treatment had a significantly greater decrease in LVEF during follow-up compared to cTnI-negative patients ($12.2 \pm 7.4\%$ vs. $3.3 \pm 4.2\%$, $p = 0.003$). Two patients with early cTnI positivity during anthracycline treatment developed anthracycline-induced cardiomyopathy with symptoms of heart failure during the follow-up. Positivity of cTnT within 6 months of treatment only coincided with LV dysfunction and cardiomyopathy on echocardiography. In asymptomatic patients, abnormal cardiac findings during and after anthracycline treatment are considered subclinical cardiac toxicity, and require further follow-up. In our cohort, we did not find a significant correlation between the reached total cumulative dose of anthracyclines and elevation of cardiac troponins or LV dysfunction on echocardiography after treatment.

Our results suggest that evaluation of cTnI – in contrast to cTnT – during anthracycline treatment could identify patients

at risk of developing anthracycline-induced cardiomyopathy in the future. cTnI seems to be superior to cTnT in the early detection of cardiac injury associated with anthracycline treatment in acute leukemia. A possible explanation could be the difference in molecular weight and release kinetics of cTnI and cTnT. cTnI is somewhat smaller than cTnT (23.5 kDa and 38 kDa, respectively), and thus might be released more easily and earlier from the cardiomyocytes injured by anthracycline CT. Based on our preliminary data, a larger prospective and multicentric study would be most desirable.

Acknowledgement

The study was supported by the research projects MO 0FVZ 0000503 (Czech Ministry of Defence), MZO 00179906 (Czech Ministry of Health), and MSM 0021620817 (Czech Ministry of Education).

References

- Shan K, Lincoff AM, Young JB: Anthracycline-induced cardiotoxicity. *Ann Intern Med* 1996;125: 47–58.
- Ganz WI, Sridhar KS, Ganz SS, Gonzalez R, Chakko S, Serafini A: Review of tests for monitoring doxorubicin-induced cardiomyopathy. *Oncology* 1996;53:461–470.
- Meinardi MT, van der Graaf WT, van Veldhuisen DJ, Gietema JA, de Vries EG, Sleijfer DT: Detection of anthracycline-induced cardiotoxicity. *Cancer Treat Rev* 1999;25:237–247.
- Sparano JA, Brown DL, Wolff AC: Predicting cancer therapy-induced cardiotoxicity. The role of troponins and other markers. *Drug Saf* 2002;25: 301–311.
- Fink FM, Genser N, Fink C, Falk M, Mair J, Maurer-Dengg K, Hammerer I, Puschendorf B: Cardiac troponin T and creatine kinase MB mass concentrations in children receiving anthracycline chemotherapy. *Med Pediatr Oncol* 1995;25:185–189.
- Kismet E, Varan A, Ayabakan C, Kismet E, Varan A, Ayabakan C, Alehan D, Portakal O, Büyükpa-mukçu M: Serum troponin T levels and echocardiographic evaluation in children treated with doxorubicin. *Pediatr Blood Cancer* 2004;42:220–224.
- Clark SJ, Pippon M, Hemsworth S, Newland P, Pizer B: Cardiac troponin T following anthracycline chemotherapy in children and adolescents. *J Chemother* 2007;19:332–334.
- Auner HW, Tinchon C, Linkesch W, Tiran A, Quehenberger F, Link H, Sill H: Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. *Ann Hematol* 2003;82:218–222.
- Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, Civelli M, Peccatori F, Martinelli G, Fiorentini C, Cipolla CM: Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation* 2004;109:2749–2754.
- Kilickap S, Barista I, Akgul E, Aytemir K, Aksoyek S, Aksoy S, Celik I, Kes S, Tekuzman G: CTnT can be a useful marker for early detection of anthracycline cardiotoxicity. *Ann Oncol* 2005;16:798–804.