The use of biochemical markers in cardiotoxicity monitoring in patients treated for leukemia*

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Cardiotoxicity is a serious and relatively frequent complication of antitumorous treatment. Anthracyclines represent the greatest risk. Biochemical markers of structural and functional myocardial damage have been gaining ground in cardiotoxicity monitoring. The aim of the study was to monitor cardiotoxicity of induction chemotherapy in acute myeloid leukemia (AML) patients and to assess the potential for use of biochemical markers in early diagnostics of cardiotoxicity. Fifteen consecutive adult patients with a newly diagnosed AML were studied. All patients received induction chemotherapy containing Idarubicin (IDA) 3x12 mg/m^2 and intermediate doses of Cytarabine (8x1.5 g/m^2). Serial measurements of plasma N-terminal pro brain natriuretic peptide (NT-proBNP) values were performed at the baseline, the day following each IDA infusion, after 14 days and after circa 1 month, i.e. before the next chemotherapy. Cardiospecific markers (cTnT, CK-MB mass) were measured at the baseline and after the last IDA infusion. The mean baseline value of NT-proBNP in newly diagnosed AML patients was 129.7±59.6 pg/ml. The mean NT-proBNP value increased after the first IDA infusion to 307.3±171.4 pg/ml (p=0.02). In most of the patients, the second and the third IDA infusions were not associated with a further increase in the NT-proBNP value and levels after 2 and 4 weeks were not significantly different from the baseline. However, in one of the patients the NT-proBNP values were increasing after each IDA infusion (after the last one 786.2 pg/ml) and within 14 days he developed congestive heart failure due to left ventricular diastolic dysfunction as assessed by echocardiography. At that time, the NT-proBNP value was 1184.0 pg/ml; after diuretics it decreased significantly. In all patients, plasma cTnT and CK-MB mass concentrations were within the reference interval at the baseline and after the induction chemotherapy. Our results suggest that induction chemotherapy in AML (IDA 36 mg/m^2 and intermediate doses of Cytarabine): 1. does not cause detectable damage of the myocyte structure, 2. is in all patients associated with acute neurohumoral activation (transient elevation of NT-proBNP) indicating acute subclinical cardiotoxicity, 3. may lead to congestive heart failure and NT-proBNP seems to be a promising early marker and predictor of this complication.

Key words: NT-proBNP, cardiospecific markers, cardiotoxicity, Idarubicin, acute leukemia

Anthracyclines (ANTs) are effective antineoplastic drugs available for chemotherapy of various hematological malignancies and solid tumors, both in adults and children. However, the therapeutic potential of these cytostatics is limited by cardiotoxicity, which is often irreversible and life-threatening [19]. The incidence of ANT-induced cardiotoxicity depends primarily on the cumulative dose of the drug [24]. The maximum recommended cumulative doses for individual ANTs have been established – 550 mg/m^2 for Doxorubicin and Daunorubicin, 100–150 mg/m^2 for Idarubicin (IDA). Other risk factors for ANT cardiotoxicity include extremes of age (<3 years, >65 years), irradiation of the mediastinum, other cardiotoxic chemotherapy (therapeutic combinations with cyclophosphamide, fluorouracil, paclitaxel...), female

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Abbreviations: AML – acute myeloid leukemia; ANP – atrial natriuretic peptide; ANT – anthracycline; BNP – brain natriuretic peptide; CK-MB – creatine kinase MB; cTnI – cardiac troponin I; cTnT – cardiac troponin T; ECHO – echocardiography, echocardiographic; IDA – Idarubicin; LV – left ventricular; NP – natriuretic peptide; NT-proBNP – N-terminal pro brain natriuretic peptide.

gender, heart damage caused by another disease, bolus administration of the drug. Four types of ANT cardiotoxicity are distinguished: acute, subacute, chronic and late-onset, which differ considerably as for clinical picture and prognosis [19]. ANTs are known to induce arrhythmias, "myocarditis-pericarditis syndrome", left ventricular dysfunction and rarely myocardial infarction. The most serious problem is the late-onset cardiotoxicity of ANTs, which can manifest as cardiomyopathy and chronic heart failure more than one year after completion of the treatment.

For that reason, it is important to monitor cardiac damage both during ANT treatment and after its completion. Echocardiography (ECHO) is a routine method in cardiotoxicity monitoring, it allows non-invasive assessment of cardiac function [14]. However, ECHO evaluation is time consuming, needs an expert and cannot be used in all patients (e.g. obesity, emphysema, mediastinal tumors etc.). Thus, there is a need for other means of cardiotoxicity monitoring.

Biochemical markers of structural and functional myocardial damage have been currently evaluated for their usefulness in this indication.

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) are hormones produced by the myocardium in response to wall stretch and pressure overload [23]. ANP is produced mainly by the atria. BNP is predominantly synthesized in the ventricles [11], released in a pro-form (proBNP) and then enzymatically cleaved to the active hormone BNP and the N-terminal pro brain natriuretic peptide (NT-proBNP). Increased levels of natriuretic peptides (NPs) have been observed in both symptomatic and asymptomatic left ventricular (LV) dysfunction [5, 16]. Although both NPs are increased in heart failure, BNP is more closely related to LV dysfunction [13, 16]. NT-proBNP has shown a similar or even better correlation [9]. In addition, NT-proBNP is more stable and has a longer half-time compared to BNP. Therefore, NT-proBNP seems to be very appropriate for examination of patients at high risk for LV dysfunction including those receiving ANTs.

The applicability of NPs as a marker for ANT-induced cardiotoxicity has been investigated in a few small studies [2, 17, 18, 20–22]. The results show that NPs are potential biochemical markers to detect ANT-induced cardiotoxicity, but at present they have been evaluated inadequately both during the treatment and during the follow-up.

Creatine kinase MB (CK-MB) and cardiac troponins – troponin T (cTnT) and troponin I (cTnI) – are specific markers for myocardial injury from various causes, not only ischaemic etiology. These cardiospecific markers, especially cardiac troponins, have been recently investigated in the diagnosis of ANT-induced cardiotoxicity [1, 6, 10, 12, 15].

The aim of our study was to monitor acute and subacute cardiotoxicity of induction chemotherapy containing IDA in a cumulative dose of 36 mg/m^2 by using biochemical markers and ECHO, and to determine the potential for use of biochemical markers in early diagnostics of cardiotoxicity.

Patients and methods

Fifteen consecutive adult patients with a newly diagnosed acute myeloid leukemia (AML) participated in this study. The patients consisted of 6 females and 9 males with a mean age 43.7±10.6 years (range 24–61). Two of the patients were treated for arterial hypertension, the other patients had no pre-existing cardiovascular disease. At the baseline, all patients had normal systolic and diastolic LV function as assessed by ECHO. One patient was febrile at the baseline, mean baseline CRP value was 17.1±19.5 mg/l. Mean baseline heart rate was 83.6±8.7 bpm, 2 patients had mild tachycardia. Mean hemoglobin concentration was 94.7±9.9 g/l at the baseline. All patients had normal renal and hepatic functions during the study period. All patients received induction chemotherapy containing IDA 12 mg/m^2/day intravenously on day 1, 3 and 5 (in total 36 mg/m^2 = $^1/_4$ of the maximum cumulative dose) and intermediate doses of Cytarabine (1.5 g/m^2 twice a day intravenously on day 1, 3, 5, 7; in total 12 g/m^2). After administration of induction chemotherapy 6 patients developed febrile neutropenia, however, only 2 of them were not afebrile at the measurement of biochemical markers. Overhydration was avoided. Corticosteroids were not given during the study period. Two patients with arterial hypertension were well compensated on betablockers, no other cardioactive medication was given.

Biochemical markers. Serial measurements of plasma NT-proBNP values were performed at the baseline (D0), the day following each IDA infusion (D2, D4, D6), after 14 days (D20) and after circa 1 month, i.e. before the next chemotherapy (D30–50). Cardiospecific markers (cTnT, CK-MB mass) were measured at the baseline (D0) and after the last IDA infusion (D6).

Venous blood samples were obtained from an indwelling catheter after 30 min of rest in supine position. The blood samples were withdrawn into chilled tubes containing EDTA. The whole blood was immediately centrifuged, the plasma was decanted, frozen and stored at –27 °C until assayed. Plasma concentrations of biochemical markers were measured on Elecsys 1010 immunoassay analyzer (Roche Diagnostics). Based on a number of studies NT-proBNP values bellow 125 pg/ml (100 pg/ml for male, 150 pg/ml for female) are considered normal and allow to rule out heart failure [4].

Echocardiography. ECHO was performed at the baseline (D0) and after the last IDA infusion (D6). The ECHO evaluation was done with Hewlett Packard Image Point ultrasound by an experienced echocardiographist. Parameters of systolic and diastolic LV function were assessed. The study scheme is shown in Table 1.

Statistical analysis was performed with the "Statistica for Windows, Version 5.0" program. Multivariate analysis of variance and paired, two tailed t-tests were used. The values are expressed as mean ±SD. A probability value <0.05 was considered statistically significant.

Table 1. Study scheme

Clinical evaluation	X	X	X	X	X	X	X	X	X
NT-proBNP	X		X		X		X	X	X
cTnT, CK-MB mass	X						X		
Echocardiography	X						X		
Idarubicin infusion		↑		↑		↑			
Days of treatment (D)	0	1	2	3	4	5	6	20	30–50

Results

The mean baseline value of NT-proBNP in newly diagnosed AML patients was 129.7±59.6 pg/ml (range 54.8–230.1). The baseline NT-proBNP values were above the normal range in 5 patients. The mean NT-proBNP value increased after the first IDA infusion to 307.3±171.4 pg/ml (p=0.02). In most of the patients, the second and the third IDA infusions were not associated with a further increase in NT-proBNP and values after 2 and 4 weeks were slightly elevated, but not significantly different from the baseline. However, in one of the patients the course of the NT-proBNP values was different. He was a 55-year-old male with no pre-existing cardiovascular disease, normal baseline ECHO and plasma NT-proBNP of 179.3 pg/ml. The NT-proBNP values were increasing after each IDA infusion – 314.9 pg/ml (D2), 610.2 pg/ml (D4) and 786.2 pg/ml (D6). On D6 ECHO was normal and the patient had no symptoms of heart failure. Only after 14 days (D20) he developed symptoms of congestive heart failure (dyspnea, peripheral edema). At that time, the NT-proBNP value was 1184.0 pg/ml and performed ECHO evaluation showed diastolic LV dysfunction (EF 60%, E/A 0.78, DT 220 ms, IRP 70 ms). The patient was treated with diuretics and the NT-proBNP value decreased to 245.4 pg/ml. During the study period, the patient was afebrile and his renal and hepatic functions were normal. The course of plasma NT-proBNP values during induction chemotherapy is shown in Figure 1 and Figure 2.

Induction chemotherapy is administered with intravenous hydration. To assess the possible influence of hydration on the NT-proBNP elevation after the first IDA dose, we used a control group of 15 patients treated for acute leukemia. The control group consisted of 5 female and 10 male patients with a mean age 42.8±9.4 years (range 22–53). All patients were afebrile, had no renal or liver dysfunction or history of heart failure. The patients were taken to hospital one day before scheduled admission for chemotherapy (D-1) and were given only intravenous hydration for 24 hours (2.5±0.6 liters of crystalloids i.v.) without any ANT. NT-proBNP values were measured just before and after administration of the crystalloids. The mean NT-proBNP value raised only slightly from 132.7±60.8 pg/ml (D-1) to 146.3±73.3 pg/ml (D0), NS (p=0.33). Moreover, most of the control patients were treated with ANTs previously, which could contribute to the slight increase in NT-proBNP.

Furthermore, we examined the possible role of other confounding factors, such as history of arterial hypertension, fever, heart rate, hemoglobin and CRP value on the changes in NT-proBNP. We did not find any significant associations between changes in NT-proBNP and these factors.

In all patients, plasma cTnT and CK-MB mass concentrations were within the reference interval at the baseline and after the induction chemotherapy and the differences were not statistically significant (Tab. 2).

ECHO was performed at the baseline (D0) and after induction chemotherapy (D6). No significant change in systolic LV function was observed (EF 64.5±5.2 vs. 64.5±4.1%, NS). The day after the last IDA infusion ECHO signs of diastolic LV dysfunction were found in 2 (13.3%) asymptomatic patients. Another one, as mentioned above, developed acute diastolic heart failure within 14 days after the last IDA infusion. After ANT administration, we found a significant prolongation of DT (deceleration time of early LV filling, one of the diastolic function parameters): 166.3±26.4 vs. 197.3±33.7 ms, p<0.01; differences in other parameters did not reach statisti-

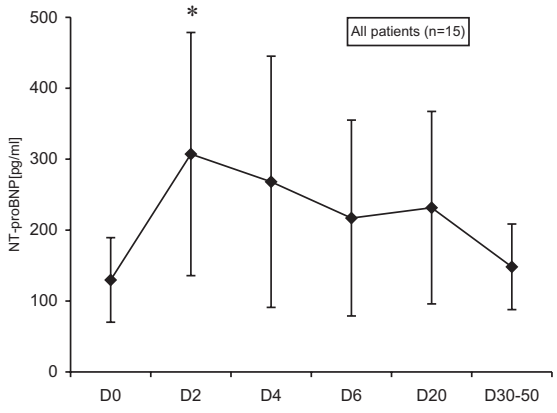

Figure 1. NT-proBNP values during induction therapy in AML patients (15 pts). The values are mean ±SD, *p<0.05 versus D0.

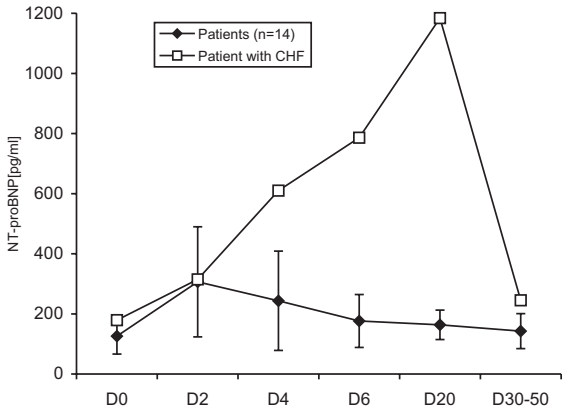

Figure 2. NT-proBNP values during induction therapy in AML patients (14 vs. 1 pt). The values represent mean ±SD.

Table 2. Concentrations of cardiospecific markers during induction therapy in AML patients (15 pts)

Cardiospecific markers	baseline (D0)	after Ida (D6)	p
cTnT (ng/ml)	< 0.01	< 0.01	NS
CK-MB mass (ng/ml)	0.85 ± 0.26	0.78 ± 0.22	NS

cTnT – sensitivity of the method 0.01 ng/ml, CK-MB mass – normal range 0.10–4.84 ng/ml

cal significance. After induction chemotherapy, a small pericardial effusion was newly detected in 3 (20%) of the patients.

Discussion

Cardiotoxicity is a well-known and serious complication of ANT treatment. Various methods have been recommended for monitoring of cardiac functions during the ANT treatment and during the follow-up [7, 14]. Biochemical markers of structural and functional myocardial damage have been studied as well.

NPs as a marker of LV dysfunction and heart failure have been recently investigated in the detection of ANT-induced cardiotoxicity. BAUCH et al measured plasma ANP levels prospectively in 16 children treated with ANTs. Two of 6 patients with elevated plasma ANP levels 3 weeks after completion of the ANT treatment developed congestive heart failure without a previous decline in LVEF [2]. In contrast, YAMASHITA et al found in 30 cancer patients treated with ANTs that elevated plasma ANP levels were a late phenomenon that coincided with the development of heart failure [22]. A follow-up study by TIKANOJA et al showed a significant increase in the serum N-terminal ANP levels in patients after ANT chemotherapy compared to age-matched controls (follow-up 0.9–13 years) [21]. SUZUKI et al found a significant increase in BNP levels during ANT-based chemotherapy, however, in most of these patients, these elevations were transient. On the other hand, 2 out of 3 patients with persistently elevated BNP levels subsequently died as a result of circulatory failure. Moreover, the increase in BNP levels correlated with diastolic LV dysfunction [20]. Thus, NPs seem to be useful for detection of subclinical cardiotoxicity during prolonged administration of ANTs.

However, acute effects of ANTs on NPs are poorly known. There is only one report on changes in NPs during and shortly after ANT administration [17]. NOUSIAINEN et al measured ANP and BNP concentrations during IDA administration in 10 patients with AML or myelodysplastic syndrome. Plasma concentrations of both NPs were increasing after each IDA dose and the increase in plasma BNP correlated significantly with LV dilation. They suggested that these changes indicate subclinical myocardial dysfunction. However, none of the patients experienced clinical cardiotoxicity.

In our study, we found a statistically significant increase in the NT-proBNP value only after the first IDA dose, not after the next IDA doses. In our control patients, we showed that solely hydration in acute leukemia did not cause significant elevation in plasma NT-proBNP. Thus, the increase in NT-proBNP after the first IDA dose was caused by the cardiotoxic effect of IDA itself. These findings suggest that IDA treatment is associated with acute neurohumoral activation, manifested by transient elevation of NT-proBNP that indicates acute subclinical cardiotoxicity of this drug.

Other biochemical markers that have been investigated recently in the diagnosis of ANT-induced cardiotoxicity are cardiac troponins (cTnT, cTnI) and CK-MB mass. These cardiospecific markers identify myocardial injury from various causes. In experimental studies, elevations in serum cTnT after ANT administration were found [1, 10]. Clinical studies are limited and the results are inconsistent. FINK et al studied 35 ANT-containing cycles in 22 children and found no increment in CK-MB mass and cTnT within 72 hours from ANT therapy [6]. On the other hand, LIPSHULTZ et al found elevated serum cTnT levels in 15 children treated with Doxorubicin. They found that the degree of elevation predicted LV dilation and thinning 9 months later, and suggested that an elevated cTnT level may predict subsequent subclinical and clinical cardiac morbidity [12]. MISSOV et al also reported elevated cTnI levels in 30 ANT-treated patients compared to both ANT-naive patients and healthy controls. However, high sensitivity immunoassay for cTnI was used (values in pg/ml) and the elevations in cTnI are clearly undetectable by conventional present-day assays. CK-MB mass concentrations were within the normal range in all patients [15].

In our study, administration of the induction chemotherapy containing IDA in the cumulative dose of 36 mg/m^2 was not associated with any increment in the concentrations of cardiospecific markers (cTnT, CK-MB mass). It means that IDA in this cumulative dose does not cause detectable damage of myocyte structure. Therefore, cardiospecific markers seem not to be of value in the detection of cardiotoxicity in patients with lower cumulative doses of ANTs.

ECHO is frequently used for cardiotoxicity monitoring. A typical manifestation of ANT cardiomyopathy is a gradual LV dilation with a progressive decline in LVEF [8]. It is known that diastolic LV dysfunction may be the first indicator of heart failure, it may precede the development of systolic LV dysfunction. Impairment of the diastolic LV function is considered a sign of subclinical ANT cardiotoxicity [3].

In the present study, the induction chemotherapy with IDA caused no decline in systolic LV function as assessed by ECHO. This was expected, since the cumulative dose of IDA was low and the examination was performed shortly after IDA administration. However, we demonstrated ECHO signs of diastolic dysfunction altogether in 3 (20%) patients and statistically significant prolongation of the deceleration time. These findings show that IDA already in the cumulative dose of 36 mg/m^2 causes deterioration of the diastolic LV function,

which is a sign of acute subclinical cardiotoxicity. Moreover, a development of pericardial effusion in 3 (20%) of the patients is a sign of induction chemotherapy toxic effect on the pericardium.

The number of participating patients was rather low, which is a limitation of this study. However, one of the patients experienced clinical cardiotoxicity within 2 weeks after induction chemotherapy. In this patient, ECHO signs of diastolic dysfunction coincided only with the development of symptoms of heart failure, while significant elevations in NT-proBNP values were observed more than 14 days before (already during IDA administration). Since the NT-proBNP elevations preceded development of congestive heart failure after induction chemotherapy, we conclude that NT-proBNP seems to be a promising early marker and predictor of this complication. Hence, we suggest that serial measurements of plasma NT-proBNP values could aid the early detection of cardiac dysfunction during ANT chemotherapy.

Whether these acute changes are able to predict chronic and late cardiotoxicity is not clear. Thus, studies are warranted in a greater number of patients and in patients with higher cumulative doses of ANTs and other risk factors for the development of ANT cardiotoxicity.

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