

CLINICAL STUDY

Glycogen phosphorylase BB as a potential marker of cardiac toxicity in patients treated with anthracyclines for acute leukemia

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Abstract: *Objectives:* The aim of the presented study was to assess plasma glycogen phosphorylase BB (GPBB) concentrations in acute leukemia patients treated with anthracycline containing chemotherapy.

Background: Anthracyclines represent the highest risk for development of cardiotoxicity. GPBB belongs to proposed biomarkers of cardiac injury with a very limited experience in this context.

Methods: Totally, 24 adult patients with acute leukemia were enrolled. Plasma GPBB concentrations were measured by ELISA at diagnosis (before chemotherapy), after first chemotherapy with anthracyclines and 6 months after the completion of treatment. The cut-off value for GPBB positivity was 10.00 µg/L as recommended by the manufacturer.

Results: Before chemotherapy, the mean plasma GPBB concentration was 5.25±3.81 µg/L, increased above the cut-off in 1 patient (4.2 %). After the first chemotherapy, the mean GPBB was 6.61±5.54 µg/L, positive in 7 (29.2 %) patients. Six months after treatment, the mean GPBB was 10.06±11.41 µg/L, positive in 8 (33.3 %) patients. Six months after treatment, we found a significant correlation between elevation in GPBB and diastolic left ventricular dysfunction on echocardiography ($r=0.621$; $p<0.0001$). The differences in plasma GPBB between healthy blood donors and patients treated for acute leukemia were statistically significant ($p<0.01$ in all cases).

Conclusion: Our results suggested that GPBB could become a potential biomarker for detection of acute and chronic cardiotoxicity associated with anthracycline containing chemotherapy. The predictive value for development of treatment-related cardiomyopathy in future is not clear and will be evaluated during the follow-up. Further studies are needed to define the potential role of GPBB and other biomarkers in the assessment of chemotherapy-induced cardiotoxicity (Ref. 21). Text in PDF www.elis.sk.

Key words: glycogen phosphorylase BB, cardiac toxicity, chemotherapy, anthracyclines, acute leukemia.

Cardiotoxicity induced by anticancer therapy remains an unresolved problem strongly impacting the quality of life and the overall survival of cancer patients. From cytostatics, anthracyclines represent the highest risk for development of cardiotoxicity (1–3). Echocardiography and electrocardiography are routinely used for monitoring of cardiotoxicity in oncology (4–6). However, the conventional methods are not sensitive enough to detect minor, subclinical and potentially reversible cardiac injury induced by anticancer therapy when an appropriate management could still improve the patient's outcome. Biomarkers of cardiac

injury, especially cardiac troponins and natriuretic peptides, have been extensively studied for the early identification, assessment and monitoring of cardiotoxicity in oncology (7–13). Glycogen phosphorylase BB (GPBB) is a newer perspective marker of myocardial ischemia and necrosis, recently evaluated in the diagnostics and risk stratification of acute coronary syndromes (14–16). Experience with GPBB in the assessment of chemotherapy-induced cardiotoxicity is very limited (17).

The aim of our study was to assess plasma GPBB concentrations in acute leukemia patients treated with anthracycline containing chemotherapy to detect acute and chronic cardiotoxicity, and to compare plasma GPBB concentrations in acute leukemia patients to healthy blood donors.

Methods

Totally, twenty-four acute myeloid leukemia patients (mean age 47.2±11.6 years; 13 males, 11 females) treated with three to six cycles of anthracycline containing chemotherapy were studied. The study was carried out with the ethics committee approval and in accordance with the relevant national guidelines. All patients gave an informed consent before they were included in the study. All patients had normal liver and renal functions during the study. Before chemotherapy, all patients had normal systolic

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and diastolic left ventricular (LV) function on echocardiography. We previously used biochip array (Randox, UK) for simultaneous testing of multiple cardiac biomarkers including GPBB (18). This time, we used a more precise ELISA method for a single quantitative detection of GPBB in plasma (Diagenics, Germany). Plasma GPBB concentrations were measured at the diagnosis (before chemotherapy), the day after first chemotherapy with anthracyclines (mean cumulative dose 125.4 ± 27.6 mg/m²) and at 6 months after completion of treatment (mean total cumulative anthracycline dose 458.3 ± 109.2 mg/m²). Twenty-four healthy blood donors were used as the control group. The cut-off value for GPBB positivity was 10.00 µg/L, as recommended by the manufacturer. Echocardiographic assessment of systolic and diastolic LV function was performed before chemotherapy and at 6 months after treatment. Systolic LV dysfunction was defined as ejection fraction (LVEF) below 55 %. Diastolic LV dysfunction was defined as E/A inversion and E-wave deceleration time above 220 ms on the transmitral Doppler curve (impaired relaxation).

Statistical analysis was performed with the “Statistica” program. The analysis of variance test was used. Correlations were evaluated with normal and the Spearman correlation tests. The values were expressed as the mean \pm SD. Probability values $p < 0.01$ and lower were considered statistically significant.

Results

Before chemotherapy, the mean plasma GPBB concentration was 5.25 ± 3.81 µg/L, increased above the cut-off in 1 patient (4.2 %). After the first chemotherapy, the mean GPBB was 6.61 ± 5.54 µg/L, positive in 7 (29.2 %) patients. Six months after treatment, the mean GPBB was 10.06 ± 11.41 µg/L, positive in 8 (33.3 %) patients. The difference between GPBB concentrations before chemotherapy and 6 months after treatment were statistically significant ($p < 0.01$). The patient with GPBB positivity before chemotherapy (18.55 µg/L) had a higher GPBB positivity in the subsequent samples (20.53 and 32.16 µg/L). Six months after treatment, we found a significant correlation between elevation in GPBB and diastolic LV dysfunction on echocardiography ($r = 0.621$; $p < 0.0001$). No patient had manifestation of cardiotoxicity with symptoms of congestive heart failure during the study. In our cohort, we did not find a significant correlation between the total cumulative anthracycline dose and GPBB positivity or LV dysfunction on echocardiography after treatment.

The mean GPBB concentration in 24 healthy blood donors was 2.14 ± 0.28 µg/L (range 1.81–3.05), negative in all subjects. The differences in plasma GPBB concentrations between healthy blood donors and patients treated for acute leukemia were statistically significant ($p < 0.01$ in all cases).

Discussion

GPBB belongs to perspective markers for an early detection of myocardial ischemia and necrosis, recently evaluated in the acute coronary syndrome setting (14–16, 19, 20). GPBB is a glycogenolytic enzyme providing glucose for heart muscle

tissue. During glycogenolysis in ischemic tissue, GPBB is released from the sarcoplasmic reticulum into the cytoplasm and then into the circulation through the damaged cell membrane. GPBB is released into the circulation 2–4 hours after myocardial injury, returning to normal values within 24–36 hours of damage occurrence. In the acute coronary syndrome setting, GPBB is regarded as an early marker of cardiac injury due to an acute myocardial ischemia (21). However, the main mechanism of cardiac injury caused by anticancer therapy is mainly non-ischemic and prior cyclic exposition to anthracycline agents may play a role (chronic and late cardiotoxicity). Thus, it is difficult to estimate the kinetics of GPBB release from cardiomyocytes in this setting. The experience with this perspective biomarker in the assessment of cardiotoxicity induced by anticancer therapy is very limited (17, 18).

The results of our study suggested that GPBB could become a potential biomarker for the detection of an acute and chronic cardiotoxicity associated with anthracycline chemotherapy. Acute leukemia patients treated with anthracycline containing chemotherapy have significantly higher plasma GPBB concentrations in comparison with healthy subjects. Plasma GPBB concentrations at 6 months after treatment were significantly higher in comparison with the baseline values and correlated with diastolic LV dysfunction on echocardiography. A possible mechanism could be that prior cyclic exposition to anthracyclines causes metabolic changes and chronic minor injury to cardiomyocytes resulting in GPBB release into the bloodstream. In asymptomatic patients, these changes are considered as a sign of chronic subclinical cardiotoxicity. The predictive value for development of treatment-related cardiomyopathy in the future is not clear and will be evaluated during the follow-up. Based on our data, a larger prospective and multicenter study is needed to define the potential role of GPBB and other proposed biomarkers of cardiac injury in the assessment of cardiotoxicity induced by anticancer therapy.

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