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The usefulness of cardiac biomarkers for cardiac evaluation in children with leukemia treated with anthracyclines**

Przydatność oznaczania biomarkerów kardiologicznych w ocenie czynności serca u dzieci chorych na białaczkę, leczonych antracyklinami

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S u m m a r y

The introduction of anthracyclines to treatment protocols for acute leukemias has contributed to significant improvement in treatment outcomes, mortality reduction and prolongation of survival, however, it is associated with the occurrence of adverse effects, of which the most serious is damage to the myocardium.

The paper presents the usefulness of the determination NT-proBNP measurment in the diagnostics of early and late anthracycline-induced cardiotoxicity.

The study included 156 children aged from 9 months to 17 8/12 years, treated for acute lymphoblastic leukemia, with anthracyclines in a dose 180-480 mg/m^2. In all the children plasma NT-proBNP and troponin T was measured. In 128 children (82%) simultaneously with plasma level echocardiography with the assessment of left ventricular systolic function was performed. All the assessments were performed before and after anthracycline therapy.

Almost half of the determinations of plasma NT-proBNP (42.3%) was above the median of the levels found in the control group. Most elevated NT-proBNP levels (28.7%) occurred in the children monitored up to three years since the completion of anthracycline therapy. In children receiving an anthracycline dose of more than 240 mg/m^2 studied in the fourth and fifth years after anthracycline therapy, the lower levels of fractional shortening (%SF) and ejection fraction (%EF) correlated with the higher levels of plasma NT-proBNP ($p = 0.08$ and $p = 0.09$, respectively). In none of the children there was an elevated level of plasma troponin T found.

Measurements of plasma NT-proBNP levels proved to be useful for monitoring cardiotoxicity in children with acute lymphoblastic leukemia treated with anthracyclines.

Key words: anthracyclines, natriuretic peptides, NT-proBNP, troponin, acute lymphoblastic leukemia

S t r e s z c z e n i e

Wprowadzenie antracyklin do protokołów leczenia ostrych białaczek przyczyniło się do znacznej poprawy wyników leczenia, obniżenia śmiertelności i wydłużenia czasu przeżycia. Jednak związane jest to z występowaniem działań niepożądanych, z których najpoważniejszym jest uszkodzenie mięśnia sercowego. W pracy przedstawiono przydatność oznaczania biomarkerów kardiologicznych: NT-proBNP i troponiny T w diagnostyce wczesnej i późnej kardiotoksyczności antracyklin u dzieci z ostrą białaczką limfoblastyczną.

Badaniami objęto 156 dzieci w wieku od 9 miesięcy do 17 8/12 lat, leczonych z powodu ostrej białaczki limfoblastycznej, z antracyklinami w dawce 180-480 mg/m^2. U wszystkich dzieci oznaczano stężenia NT-proBNP i troponiny T. U 128 dzieci (82%) jednoczasowo wykonano badanie echokardiograficzne z oceną funkcji skurczowej lewej komory. Wszystkie badania były wykonywane przed i po terapii antracyklinami.

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Prawie połowa oznaczeń stężenia NT-proBNP (42,3%) była powyżej średnich poziomów w grupie kontrolnej. Większość podwyższonego stężenia NT-proBNP (28,7%) stwierdzono u dzieci badanych do trzech lat od zakończenia leczenia antracyklinami. U dzieci otrzymujących antracykliny w dawce ponad 240 mg/m^2 badanych w czwartym i piątym roku po zakończeniu leczenia antracyklinami, stwierdzono, że niższy poziom frakcji skracania (%SF) i frakcji wyrzutowej (EF%) korelował z wyższym poziomem stężenia NT-proBNP (odpowiednio p= 0,08 oraz p = 0,09).

U żadnego z dzieci nie stwierdzono podwyższonego stężenia troponiny T.

Oznaczanie stężenia NT-proBNP okazało się przydatne do monitorowania kardiotoksyczności u dzieci z ostrą białaczką limfoblastyczną leczonych antracyklinami.

Słowa kluczowe: antracykliny, peptydy natriuretyczne, NT-proBNP, troponina, ostra białaczka limfoblastyczna

INTRODUCTION

Acute lymphoblastic leukemia is the most common (25.4%) cancer diagnosed in children and adolescents under 18 years of age, which accounts for about 350 new cases per year in Poland, and over half of them are observed in preschool children (1). Polish Paediatric Leukaemia/Lymphoma Study Group (PPGLBC) recommends the ALL-IC-BFM 2002 protocol, in which one of the fundamental drugs are anthracyclines.

Event-free survival (EFS) for children treated with the ALL IC-BFM 2002 protocol, after 4 years of use, is 83% (2). The introduction of anthracyclines to treatment protocols for acute leukemias has contributed to significant improvement in treatment outcomes, mortality reduction and prolongation of survival, however, it is associated with the occurrence of adverse effects, of which the most serious is damage to the myocardium observed in up to 57% of patients (3, 4).

In the majority of patients, the initial development of heart failure is often asymptomatic or oligosymtomatic and is characterized by very discrete changes. Widely recognized risk factors for anthracycline-induced cardiotoxicity in children are: a cumulative dose, the young age of the patient under treatment, the time since the completion of the therapy and female gender (5-9).

The recommended methods for diagnosing and monitoring anthracycline-induced cardiotoxicity include: electrocardiography, echocardiography and isotopic angiocardiography (10). With the development of biochemical diagnostics, biochemical markers such as natriuretic peptides, particularly type B (NT-proBNP) and troponin T may be included into noninvasive diagnostics of anthracycline-induced myocardial damage (11).

AIM

The main aim of the study is to evaluate the usefulness of cardiac biomarkers: NT-proBNP and troponin T measurment in the diagnostics of early and late anthracycline-induced cardiotoxicity in children with acute lymphoblastic leukemia. Additional objectives comprise the evaluation of left ventricular systolic function with echocardiography, plasma NT-proBNP and troponin T levels, depending on the time since the completion of anthracycline therapy, an applied dose of anthracyclines, age at the diagnosis of acute lymphoblastic leukemia and gender of the patient.

In addition, to assess the relationship between plasma NT-proBNP and troponin T levels, and left ventricular systolic function in relation to the time since the completion of anthracycline therapy and the anthracycline dose used.

MATERIAL

The study included 156 children (72 girls and 84 boys) aged from 9 months to 17 8/12 years (median 5.1 years) treated for acute lymphoblastic leukemia, from September 1990 to April 2006 at the Department of Pediatrics, Hematology and Oncology of Warsaw Medical University.

In all the children plasma NT-proBNP and troponin T was measured, while in 128 children (82%) simultaneously with plasma level measurements of biochemical markers echocardiography with the assessment of left ventricular systolic function was performed. All the assessments were performed before (Group 0) and after anthracycline therapy (in the first year (Group 1), in the second and third years (Group 2), in the fourth and fifth years (Group 3) and five or more years after anthracycline therapy (Group 4).

The control group for NT-proBNP and troponin T measurements consisted of 47 healthy children (17 girls and 30 boys), and for echocardiography 67 healthy children (38 girls and 29 boys) in the corresponding age.

All the children from the study group were treated with chemotherapy protocols containing anthracyclines in a dose (180-480 mg/m^2) depending on the severity of the disease and the treatment protocol used. Until November 2002, children had been treated according to the BFM or New York protocol while later according to the ALL IC-BFM 2002 protocol. All the children before each administration of anthracyclines received dexrazoxane in a dose in accordance with the manufacturer's instructions, to protect against cardiotoxic activity of anthracyclines.

METHODOLOGY

Plasma NT-proBNP levels were measured with an ELISA kit of Biomedica. Plasma Troponin T was measured by electrochemiluminescence method with a Roche Elecsys 2010 biochemical apparatus, with an Elecsys Troponin T STAT test. Echocardiography with the assessment of left ventricular function was per-

formed by one cardiologist using a Sonos 1500 Hewlett Packard apparatus.

STATISTICAL METHODS

For categorical variables descriptive statistics were presented as a number and percentage of patients in each class of the considered feature. For continuous variables they are presented as the mean and standard deviation as well as the median, Ist and IIIrd quartile, minimum and maximum.

Comparisons of plasma NT-proBNP and %SF and %EF in the selected groups were performed using the Mann-Whitney test. The correlation between plasma NT-proBNP, %SF, %EF, and age in each period was assessed using Spearman's rank correlation coefficient and its significance test. The calculations were performed using the SPSS 12.0 and R 2.9.0 statistical packages

RESULTS

Measurements of plasma NT-proBNP levels proved to be useful for monitoring cardiotoxicity in children with acute lymphoblastic leukemia treated with anthracyclines. Almost half of the determinations of plasma NT-proBNP (42.3%) was above the median of the levels found in the control group. Most elevated NT-proBNP levels (28.7%) occurred in the children monitored up to three years since the completion of anthracycline therapy.

Determination of plasma NT-proBNP levels proved to be particularly useful in monitoring early cardiotoxicity, as the highest and statistically significant plasma NT-proBNP median was found in children studied in the first (Group 1) and in the fourth and fifth years (Group 3) after anthracycline therapy ($p = 0.04$). With time passing after anthracycline therapy there was a decline in the plasma NT-proBNP median (NT-proBNP normalization).

Plasma Troponin T measurments were found useless in monitoring cardiotoxicity in children with acute lymphoblastic leukemia treated with anthracyclines. In none of the children there was an elevated level of plasma troponin T found.

In the children studied **prior to the anthracycline therapy,** both plasma NT-proBNP levels and the mean values of fractional shortening (%SF) and ejection fraction of the left ventricle (%EF) were normal.

In those studied in the fourth and fifth years after anthracycline therapy (Group 3) significantly **lower fractional shortening (%SF) and ejection fraction (%EF) in the older children** compared with the younger children (%SF $p = 0.05$, %EF $p = 0.02$) were found and in **girls**, both in comparison with the control group and the boys (%SF **$p = 0.04$**, %EF **$p = 0.03$** and %SF **$p = 0.017$**, %EF **$p = 0.026$**, respectively).

In the whole group the applied cumulative anthracycline dose (below or above 240 mg/m^2) had no influence on both plasma NT-proBNP and the results of the fractional shortening (%SF) and ejection fraction (%EF) in the appropriate time intervals prior to and after anthracycline therapy.

In the whole study group, **the child's age** at the diagnosis of acute lymphoblastic leukemia and the **patient's gender** had no influence on plasma NT-proBNP levels. In children studied in the fourth and fifth years after anthracycline therapy (Group 3), with normal values of fractional shortening, significantly higher median values of plasma **NT-proBNP levels ($p = 0.041$)** were found.

In children receiving an anthracycline **dose of more than 240 mg/m^2** studied in the fourth and fifth years after anthracycline therapy (Group 3), the lower levels of fractional shortening (%SF) and ejection fraction (%EF) correlated with the higher levels of plasma NT-proBNP levels (high negative correlation of **-0.70 and -0.71,** respectively with a coefficient close to significance – **$p = 0.08$ and $p = 0.09$**, respectively).

The analysis of the findings **in these same patients**, in the neighboring time intervals showed that using **higher doses of anthracyclines** (over 240 mg/m^2) **the reduction of ejection fraction (EF%) correlates with the increased levels of NT-proBNP** over the time since the end of anthracycline therapy (between 2 and 3 years compared with the children studied in the first year) **($p = 0.014$).**

CONCLUSIONS

Our results do not allow to answer explicitly to the question whether the determination of plasma NT-proBNP only in the assessment of the changes in the myocardium after anthracycline therapy is superior to the assessment of left ventricular systolic function (%SF and %EF) with echocardiography.

Nevertheless, noticeable differences between plasma NT-proBNP and left ventricular systolic function indicate a need to determine both plasma NT-proBNP levels and echocardiographic parameters. Both assessments are perfectly complementary.

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