DOI: 10.5604/08606196.1215441 Post N Med 2016; XXIX(8): 534-536

*Agnieszka Zaucha-Prażmo[1], Elżbieta Sadurska[2], Jerzy R. Kowalczyk[1]

The role of endothelin as an early marker of acute left ventricular dysfunction in children undergoing haematopoietic stem cell transplantation

Endotelina jako wczesny marker ostrej niewydolności mięśnia sercowego u dzieci po transplantacji komórek hematopoetycznych

[1]Department of Pediatric Hematology, Oncology and Transplantation, Medical University in Lublin
Head of Department: Professor Jerzy R. Kowalczyk, MD, PhD
[2]Department of Pediatric Cardiology, Medical University in Lublin
Head of Department: Elżbieta Sadurska, PhD

Keywords
endothelin-1, cardiotoxicity, haematopoietic stem cell transplantation

Słowa kluczowe
endotelina-1, kardiotoksyczność, transplantacja komórek hematopoetycznych

Summary

Introduction. Cardiotoxicity is a possible complication following haematopoietic stem cell transplantation (HSCT). The frequency and significance of cardiac abnormalities are unknown in patients undergoing HSCT in childhood. Endothelin-1 (ET-1) is a potent vasoconstrictor peptide, synthesized in the vasculature and the myocardium. Plasma ET-1 levels are elevated in patients with severe heart failure from different causes. In recent studies the correlation was found between ET-1 plasma level and the severity of heart failure, thus ET-1 can be useful as a marker for early detection of cardiotoxicity.

Aim. The aim of the study is to assess the frequency and significance of elevated ET-1 serum levels and changes in echocardiographic parameters in children in early postransplant period.

Material and methods. ET-1 serum levels were measured pretransplant and every week for 3 weeks in postransplant period by enzyme immunoassay. Shortening fraction (%FS) and ejection fraction (%EF) were assessed by echocardiography prior to HSCT and about day +30 and +100 after transplantation.

Results. In 6 out of 26 patients (23%) the concentration of ET-1 was increasing on days +14 and +21. In 2 of them the symptoms of transient cardiomyopathy were observed on day +30.

Conclusions. In analyzed group of patients symptoms of transient cardiotoxicity were observed only in children with elevated ET-1 serum levels. Children, who had increased ET-1 plasma concentrations during early postransplant period are at risk of developing cardiac insufficiency in the future.

Streszczenie

Wstęp. Uszkodzenie mięśnia sercowego jest powikłaniem mogącym wystąpić u chorych po transplantacji komórek hematopoetycznych (HSCT). Endotelina-1 (ET-1) jest peptydem o silnych właściwościach wazokonstrykcyjnych. Poziom ET-1 w surowicy krwi wzrasta u chorych z niewydolnością krążenia.

Cel pracy. Analiza częstości występowania podwyższonego poziomu ET-1 w surowicy krwi oraz występowania zmian w badaniu echokardiograficznym u dzieci po transplantacji komórek hematopoetycznych.

Materiał i metody. Badaniami objęto 26 pacjentów (20 chłopców i 6 dziewcząt) w wieku od 3 miesięcy do 17,9 roku (mediana 9,3 roku) po HSCT. U 8 pacjentów wykonano transplantacje autologiczne, u 18 allogeniczne. Pomiary stężenia ET-1 w surowicy krwi wykonano metodą ELISA u wszystkich pacjentów przed leczeniem kondycjonującym oraz trzykrotnie w odstępach tygodniowych po transplantacji. Frakcję skracania (%FS) oraz frakcję wyrzutową (%EF) oceniano w badaniu echokardiograficznym przed przeszczepem oraz w dniu +30 i +100 po HSCT.

Wyniki. Parametry echokardiograficzne %FS i %EF przed transplantacją były prawidłowe u wszystkich badanych dzieci. W dobie +30 po HSCT obserwowano spadek mediany FS i EF, ale wartości te pozostawały w normie. U 6 z 26 pacjentów (23%) obserwowano

Conflict of interest
Konflikt interesów
None
Brak konfliktu interesów

Address/adres:
*Agnieszka Zaucha-Prażmo
Department of Pediatric Hematology, Oncology and Transplantation
Medical University in Lublin
ul. Gębali 6, 20-930 Lublin
tel. +48 (81) 718-55-20
a.prazmo@umlub.pl

wzrost stężenia ET-1 w surowicy krwi w dobie +14 i +21 po HSCT. U 2 z nich wystąpiły objawy przejściowej niewydolności krążenia. U dzieci z prawidłowym poziomem ET-1 w surowicy krwi, parametry echokardiograficzne w analizowanych dniach były w normie.

Wnioski. Objawy przejściowej kardiotoksyczności obserwowano tylko u dzieci, u których stwierdzono wzrost stężenia ET-1 w surowicy krwi. Dzieci, u których stwierdzono podwyższony poziom ET-1, są w grupie ryzyka wystąpienia niewydolności krążenia w okresie poprzeszczepowym.

INTRODUCTION

Cardiac failure is a possible complication of haematopoietic stem cell transplantation. Various cardiac arrhytmias including cardiac arrest in patients treated with HSCT have been reported (1-5). Many factors which could potentially lead to cardiac damage in patients following HSCT have been described. Myocardial function can be impaired by cardiotoxic drugs used in conditioning regimens, iron overload, also by the use of hyperhydratation regimes, impaired renal function, sepsis, electrolyte abnormalities. It is important to identify biochemical markers of cardiac injury able to predict heart failure in children following HSCT. The levels of natriuretic peptides and troponins are elevated in patients with severe heart failure (2, 6). Other studies showed endothelin-1 (ET-1), as potentially useful marker for early detection of cardiotoxicity (7, 8). ET-1 levels are elevated in patients with severe heart failure. The correlation between ET-1 plasma level and the severity of heart failure was found.

AIM

The aim of the study was to assess the frequency and significance of elevated endothelin serum levels and changes in echocardiographic parameters (%FS, %EF) in children in early postransplant period.

MATERIAL AND METHODS

A total of 26 consecutive patients treated with HSCT were included into the study. Median age of the patients was 9.35 years (range from 0.3 to 17.9 years), there were 20 boys and 6 girls. 8 autologous and 18 allogeneic transplantations were performed: 9 from matched unrelated donors (MUD), 7 from matched sibling donors (MSD), 2 from mismatched family donors (MMFD).

The levels of endothelin were measured four times: pretransplant and every week for 3 weeks in postransplant period by enzyme immunoassay. The normal range of ET-1 serum concentration was 0.2-0.7 fmol/ml. A complete M-mode 2D Doppler echocardiograms were performed and shortening fraction (%FS) and ejection fraction (%EF) were assessed prior to HSCT and about day +30 and +100 after transplantation.

RESULTS

Baseline shortening fraction and ejection fraction were within the normal range (FS > 28%; EF > 55%) in all patients included into the study. Decrease of median value of SF was observed on days +30 and +100 in the analyzed group of children, but the values were still within normal range. The median SF values were 42, 37 and 38%; while the median EF were 68, 68 and 69% pretransplant, on day +30 and +100 respectively. Decrease of SF and EF values below normal range were diagnosed in one patient following MUD transplantation, on day +30. In 8 out of 26 patients (30.9%) plasma levels of ET-1 increased at least in one analyzed time point postransplant. Five of them was transplanted from MUD, 2 from MSD, one patient followed autologous transplantation. In two of them the symptoms of transient acute cardiac insufficiency (weakness, tachycardia, tachypnoe, dyspnoe, pulmonary edema) were diagnosed about four weeks postransplant. In one of them concomitant decrease in FS and EF values were diagnosed. No clinical symptoms of cardiac failure, nor echocardiographic abnormalities were observed in children with normal ET-1 values. Six patients died, 4 due to progression of the disease, 2 children because of postransplant complications: one child died with the symptoms of multiorgan failure (MOF) on day +15, one because of CNS infection.

Symptoms of transient cardiotoxicity were observed in 2 children with elevated ET-1 serum levels. Characteristics of patients according to the hematopoietic stem cell source and ET-1 serum level is shown in table 1.

Tab. 1. Characteristics of patients included into the study according to the hematopoietic stem cell source and ET-1 serum level

Type of transplant Total (n)	Pts number 26	Symptoms of cardiac failure (n) 2 (7.7%)	Patients with augmented ET-1 level (n) 8 (30.7%)	Died (n) 6 (23%)	Reason of death
AUTO	8	0	1	2	DP
MSD	7	0	2	0	0
MUD	9	2	5	3	1-MOF 2-CNS inf. 3-DP
MMFD	2	0	0	1	DP

AUTO – autologous transplantation; DP – disease progression; MUD – match unrelated donor; MOF – multiorgan failure; CNS inf. – CNS infection; MMFD – mismatch family donor; MSD – match sibling donor

DISCUSSION

Clinically significant cardiotoxicity after haematopoietic stem cell transplantation has been described in patients undergoing HSCT. The toxic effects of cyclophosphamide, TBI have been documented (1, 4, 8-10).

Pretreatment with anti-tumor antibiotics including anthracyclines and prior mediastinal irradiation are established risk factors of cardiotoxicity related with transplant procedure. Also iron overload resulting from transfusions of blood components or impaired renal function, common in patients in postransplant period may predispose to cardiac dysfunction (8-10). Early diagnosis of cardiac failure in children treated with haematopoietic stem cell transplantation is difficult, especially in complex clinical situation. There are many different methods used to assess acute cardiac failure, like echocardiography, electrocardiogram, radionuclide ventricuography, or biochemical markers (natriuretic peptides, troponins, endothelin) (2, 3, 5, 9, 10). Endothelin-1 is a vasoconstrictor peptide synthesized in the vasculature and the myocardium by the endothelial cells and ventricular myocytes. Elevated plasma levels of ET-1 have been reported in association with heart failure, but also in liver dysfunction observed postransplant (2, 6, 11). According to Zver et al. study brain natriuretic peptide (BNP) and ET-1 levels are much more sensitive indicators of myocardial injury than functional tests, such as echocardiography (8). Finding a sensitive and specific marker of cardiac dysfunction after HSCT is very important in early detection of cardiotoxicity, also in prevention of the appearance of late cardiac failure. In the present study, we analyzed ET-1 serum levels in conjunction with ECHO monitoring to find the early marker of left ventricular dysfunction in children in postransplant period. In analyzed group of patients, clinical symptoms of heart failure (weakness, tachycardia, tachypnoe, dyspnoe, pulmonary edema) together with slight, transient decrease in echocardiografical systolic parameters were observed in 2 out of 6 children with elevated ET-1 levels on day +14 and +21 postransplant. These children were transplanted from unrelated donor for acute lymphoblastic leukaemia and myelodysplastic syndrome. In one child with very high plasma endothelin levels observed pretransplant and one week postransplant. This was a boy with Omenn syndrome transplanted from unrelated donor who died on day +15 because of multiorgan failure.

CONCLUSIONS

In analyzed group of patients symptoms of transient cardiotoxicity were observed only in children with elevated ET-1 serum levels. Children, who had increased ET-1 plasma concentrations during early postransplant period are at risk of developing cardiac insufficiency in the future.

BIBLIOGRAPHY

1. Eames GM, Crosson J, Steinberger J et al.: Cardiovascular function in children following bone marrow transplant: a cross-sectional study. Bone Marrow Transplant 1997; 19: 61-66.
2. Snowden JA, Hill GR, Hunt P et al.: Assessment of cardiotoxicity during haematopoietic stem cell transplantation with plasma brain natriuretic peptide. Bone Marrow Transplant 2000; 26: 309-313.
3. Murdych T, Weisdorf DJ: Serious cardiac complications during bone marrow transplantation at the University of Minnesota, 1977-1997. Bone Marrow Transplant 2001; 28: 283-287.
4. Styler MJ, Topolsky DL, Crilley PA: Transient high grade heart block following autologouds bone marrow infusion. Bone Marrow Transplant 1992; 10: 435-438.
5. Socie G, Klingebiel T, Schwarze CP: Late complications of HSCT. Haematopoietic Stem Cell Transplantation. The EBMT Handbook Revised Edition, 2012.
6. Horacek JM, Pudil R, Tichy M et al.: The use of biochemical markers in cardiotoxicity monitoring in patients treated for leukemia. Neoplasma 2005; 52: 430-434.
7. Susuki T, Miyauchi T: A novel pharmacological action of ET-1 to prevent the cytotoxicity of doxorubicine in cardiomyocytes. Am J Physiol Regul Integr Comp Physiol 2001; 280(5): R1399-1406.
8. Zver S, Zadnik V, Bunc M et al.: Cardiac toxicity of high-dose cyclophosphamide in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. Int J Hematol 2007 Jun; 85(5): 408-414.
9. Morandi P, Ruffini PA, Benvenuto GM et al.: Cardiac toxicity of high-dose chemotherapy. Bone Marrow Transplant 2005; 35: 323-328.
10. Brockstein BE, Smiley C, Al-Sadir J: Cardiac and pulmonary toxicity in patients undergoing high-dose chemotherapy for lymphoma and breast cancer: prognostic factors. Bone Marrow Transplant 2000; 25: 885-891.
11. Akı SZ, Suyanı E, Cengiz M et al.: Association between Plasma Endothelin-1, Transforming Growth Factor-β, Fibroblast Growth Factor, and Nitric Oxide Levels and Liver Injury in Hematopoietic Stem Cell Transplantation Recipients with Persistent Iron Overload after Transplantation. Biol Blood Marrow Transplant 2015 May; 21(5): 948-953.

received/otrzymano: 06.07.2016
accepted/zaakceptowano: 27.07.2016