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Cardiotoxicity of Oncological Treatment in Children

Kardiotoksyczność leczenia onkologicznego u dzieci

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Abstract

The incidence of complications after antineoplastic therapy is increasing in relation to the incidence of cancer and prolonged survival rate. Cardiotoxicity is one of the major complications, and it may occur during the therapy or many years after its termination, often leading to heart failure. Cardiotoxicity has been attributed particularly to cytostatics from the group of anthracycline antibiotics and radiotherapy, which are widely used in oncological treatment. The risk of developing cardiac complications depends on the cumulative dose of anthracyclines and the dose of chest irradiation, accompanying heart disorders, patient's age and sex. Acute myocardial damage occurs in the form of myocarditis and pericarditis. Late cardiotoxicity of anthracyclines manifests itself in the form of congestive cardiomyopathy, and late complications after radiotherapy also as valvular damage or restrictive cardiomyopathy. The incidence of asymptomatic myocardial dysfunction has been described in literature to range from 18 to 57% on long-term follow up of children after oncological treatment, and about 5% of children develop heart failure. For these reasons, attempts to develop schemes for monitoring patients after termination of antineoplastic treatment have been undertaken. The standards should include ECG, chest X-ray and echocardiography performed prior to, during and after oncological therapy. Biochemical markers, such as troponin or natriuretic peptide, may prove helpful. The frequency of cardiac function monitoring depends on the underlying risk. Long-term follow up of patients who have undergone antineoplastic therapy in childhood is recommended, with special attention paid to individual risk factors. The follow-up should also consider additional, well-known risk factors for cardiovascular diseases (*Adv Clin Exp Med* 2012, 21, 3, 281–288).

Key words: chemotherapy, radiotherapy, anthracyclines cardiotoxicity, children.

Streszczenie

Z powodu wzrostu zachorowalności na nowotwory i wydłużenia okresu przeżycia po ich leczeniu obserwuje się wzrost częstotliwości powikłań terapii przeciwnowotworowej. Jednym z najpoważniejszych jest kardiotoksyczność, która może występować podczas leczenia lub wiele lat po jego zakończeniu, prowadząc często do niewydolności krążenia. Potwierdzoną kardiotoksyczność wykazują cytostatyki z grupy antybiotyków antracyklinowych, 5-fluorouracyl, cyklofosfamid i izofosfamid oraz radioterapia. Ryzyko rozwoju powikłań kardiologicznych zależy od dawki kumulacyjnej antracyklin i dawki napromieniowania klatki piersiowej, zastosowania łącznego cytostatyków kardiotoksycznych, współistniejących chorób serca, wieku pacjenta – dzieci poniżej 4 lat są bardziej narażone – i płci. Ostre uszkodzenie mięśnia sercowego występuje w postaci zmian zapalnych mięśnia serca i osierdzia. Późna toksyczność antracyklin objawia się jako kardiomiopatia zastoinowa, a opóźnione powikłania po radioterapii także w postaci choroby naczyniowej serca, uszkodzenia zastawek, rzadziej kardiomiopatii restrykcyjnej. Opisywana w publikacjach częstość bezobjawowej dysfunkcji mięśnia sercowego wynosi 18–57% w długoterminowej obserwacji dzieci leczonych onkologicznie, a u około 5% dzieci występuje jawna niewydolność krążenia. Dlatego poszukuje się prostych metod diagnostycznych ułatwiających identyfikację dzieci narażonych na rozwój powikłań. Podejmuje się próby ustalenia schematów monitorowania pacjentów po zakończeniu leczenia przeciwnowotworowego. Standardem powinno być wykonanie EKG, RTG klatki piersiowej oraz echokardiografii przed rozpoczęciem, podczas i po zakończeniu leczenia onkologicznego. Częstość kontroli czynności serca powinna zależeć od ryzyka rozwoju powikłań sercowych. Zaleca się długoterminową opiekę u pacjentów leczonych przeciwnowotworowo w dzieciństwie z uwzględnieniem indywidualnego ryzyka – dawki kumulacyjnej antracykliny, stosowania radioterapii i dawki napromieniowania oraz wieku zakończenia terapii. Powinna ona też uwzględniać dodatkowe znane czynniki ryzyka rozwoju powikłań sercowo-naczyniowych (*Adv Clin Exp Med* 2012, 21, 3, 281–288).

Słowa kluczowe: chemioterapia, radioterapia, kardiotoksyczność antracyklin, dzieci.

Cancer represents one of the most important health problems, in Poland as well as all over the world. In Poland there are about 1100–1200 new cases of cancer diagnosed each year in the child population. Cancer is believed to be the second most common cause of death (after accidents, injuries and intoxication) in children [1]. Thanks to the use of modern therapies, treatment is becoming more and more effective, resulting in a prolonged survival rate of oncological patients and decreased mortality. Five year survival for the majority of pediatric cancers nowadays reaches 80% [2, 3]. However, complications after oncological treatment are observed more and more commonly. Early complications sometimes preclude continuation of therapy, late occurring complications may result in death. Studies performed on a group of over 10,000 adult patients who had been treated for cancer in their childhood demonstrated a significantly elevated risk of chronic diseases, first of all secondary cancers, then cardiovascular disease, kidney diseases, musculoskeletal diseases and endocrinopathy in comparison to the control group (non-oncologically-treated siblings) [3]. Morbidity in this group of patients increases with age and does not reach a plateau.

Cardiotoxicity is the most severe of chronic complications of antineoplastic therapy. Mortality for cardiac reasons is 10-fold higher among children who survived cancer in comparison to the control group at the same age [2].

Adverse effects may occur during oncological treatment as well as many years after conclusion of treatment.

Drug toxicity may manifest itself in the following forms:

- acute – may occur during therapy following a single dose or a therapeutic cycle,
- chronic – occurs within 12 months after termination of therapy, and
- chronic delayed – occurring after a year to 5 years after termination of therapy [4].

Cardiotoxicity has been evidenced in cases of anthracycline antibiotics (such as doxorubicin, daunorubicin, epirubicin, idarubicin, and mitoxantrone – anthracycline derivatives) as well as 5-fluorouracil, cyclophosphamide and isophosphamide [4, 5].

Anthracyclines

Anthracyclines are widely used in oncological therapy. They are highly effective and are included in numerous therapeutic schemes for solid tumors as well as hematological cancers [5]. However they are notorious for causing significant cardiotoxicity, which was first documented in the 70s of the 20th century [2, 6].

Toxicity Risk Factors

The best known toxicity risk factors are:

- cumulative lifetime dose – permanent damage to the heart muscle is more commonly observed when the upper limit of the cumulative dose for a given drug has been surpassed. In adult patients, the upper limit for doxorubicin is 550 mg/m² [7]. On the basis of retrospective analysis of three clinical studies, Swain observed that exceeding the dose of 550 mg/m² caused symptomatic circulatory failure in 26% of patients, and doses exceeding 700mg/m² caused the symptoms in as many as 48% of patients [8]. Children are more vulnerable to the cardiotoxic effect of anthracyclines, which occurs after an even lower cumulative dose than in adults. On long-term follow up, 32% of children who were administered a dose above 410 mg/m² presented with impaired function of the left ventricle [9]. Other authors report that 10% of children developed clinical circulatory failure on long-term follow up after surpassing the cumulative dose of 550 mg/m² [10];
- combined administration of cardiotoxic cytostatics and repeated oncological therapy for secondary cancers;
- preceding irradiation of the chest (with a dose above 20 G);
- coexisting heart diseases – heart defects, history of myocarditis, hypertension, and liver diseases;
- patient's age – below the age of 4 and above the age of 65;
- being female (also in children);
- Down syndrome (in association with a more common incidence of inborn heart pathology);
- black African ancestry;
- individual sensitivity of the patient, which is often conditioned by gene polymorphism associated with drug metabolism [4, 11–14].

Studies performed on 607 children treated with anthracyclines demonstrated a significantly increased incidence of clinical heart failure with a cumulative dose of anthracycline above 300 mg/m². Analysis of multifactor variations revealed that it was the only risk factor for the development of symptomatic cardiomyopathy [10].

Mechanisms of Cardiotoxicity

The mechanism of the toxic action of anthracyclines is multifactorial. One of the factors includes mitochondrial damage. Molecules of the drug combine with cardiolipins in the mitochondrial internal membrane, causing disturbances in the transport of electrons in the respiratory chain,

and thus depletion of ATP and the phosphocreatinine pool, which leads to decreased contractibility of the heart muscle. Moreover, anthracyclines contribute to the formation of free radicals and oxidative stress, which causes further damage of the cell membranes and leads to cell death [2, 5]. Another reported mechanism includes induction of cascades of apoptosis [4, 7].

Morphological changes of the heart muscle ultrastructure are visible in the form of muscle fiber loss, oedema, and breaking of the endoplasmic reticulum. Mitochondrial oedema and necrosis may be of various severity and the changes may be diffuse or focal. Cardiomyocyte damage is accompanied by stromal fibrosis [2, 15].

Acute cardiotoxicity of anthracyclines may occur in the form of mild, transient changes in the ECG. Most commonly it includes sinus tachycardia during inflow and supraventricular or ventricular arrhythmia. Repolarisation disturbances or prolonged QT interval may also occur, although these are non-specific symptoms and may be associated with other causes, e.g. electrolyte disturbances [4–6, 15].

Acute myocardial damage manifests itself during echocardiography evaluation, mainly as decreased contractility of the heart muscle. The presence of exudates within the pericardium is less commonly observed. The above inflammatory lesions in the heart muscle and pericardium may develop up to several weeks from administration of the drug and then they are referred to as sub-acute toxicity [15, 16].

Late toxicity of anthracyclines manifests itself as congestive cardiomyopathy, i.e. permanent, irreversible damage to the heart muscle leading to circulatory failure. It leads to a decrease in heart muscle contractility with diminished ejection fraction and secondary left ventricular hypertrophy [15, 16]. Children with early left ventricle contractility disturbances are demonstrated to develop late cardiotoxicity more often [12].

Studies on a large group of children with anthracycline-related cardiomyopathy (165 cases) published in 2010 revealed that cardiomyopathy, on average, developed within 7 years [14]. A report from American heart transplantation centers described 19 children requiring heart transplantation for anthracycline-induced cardiomyopathy, and the mean time-lapse from the diagnosis of cancer to heart transplant was 9 years [17].

A study in 2010 on 200 patients with the symptoms of anthracycline-related cardiomyopathy (LVEF below 45%) demonstrated significantly worse response to cardiac failure therapy when onset of therapy was delayed. In cases of a 6-month delay since termination of chemotherapy to the in-

stitution of heart failure therapy, normalization of cardiac muscle contractibility was not observed. In a multifactorial analysis the time from termination of chemotherapy and advancement of circulatory failure (class III and IV according to NYHA) were the only factors determining the lack of response to therapy [18].

In patients with anthracycline-related cardiomyopathy, normalization of the ejection fraction may be achieved by quick diagnosis and treatment of heart failure.

Antimetabolites

5-fluorouracil exerts a toxic effect on the heart muscle by causing contractions of the coronary vessels, and also by inflicting indirect damage to the heart muscle resulting in myocardial ischemia and arrhythmias [5, 11].

Alkylating Drugs

Cyclophosphamide and cyclophosphamide metabolites exert a toxic effect. They contribute to the endothelial damage, and cause extravasation of blood and formation of an intravascular hematoma and reactive oedema. Clinically, the cardiotoxicity of cyclophosphamide manifests itself in the form of mild pericarditis or slight changes in ECG. Myocarditis and progressive heart failure may also be observed in more severe cases. The symptoms usually appear within two weeks from administration of the drug. Toxicity, as in the case of anthracyclines, depends on the drug dose and also on the individual predisposition of the patient. Similar clinical symptoms were observed after the administration of isophosphamide, a cyclophosphamide isomer. They are usually of a transient nature and, following cessation of the therapy, the heart muscle resumes its normal function. Additionally, transient arrhythmias may set in due to isophosphamide-associated dyselectrolythemia [5, 11].

Radiotherapy

Irradiation of the chest is a commonly used therapy for mediastinal tumors, lymphomas, thymomas and lung cancer. Early post-radiation disturbances in the form of acute pericarditis occur within several weeks after radiation therapy [5, 16]. Coronary disease, which occurs 10–15 years after radiotherapy, is the most common late complication. Irradiation may trigger or accelerate sclerotic processes. The mechanism of this effect is not fully

understood. It is assumed that the inflammatory process evoked by the action of free oxygen radicals formed in the effect of irradiation, induces endothelial damage. The inflammatory reaction within the endothelium leads to decreased availability of nitrogen oxide, contributing to the development of atherosclerosis [2, 19]. Chronic exudative pericarditis or exudative-constricting pericarditis and cardiomyopathy are other symptoms of late cardiotoxicity of radiotherapy. Irradiation may also cause indirect damage of the heart muscle, leading to hampered contractibility and congestive cardiomyopathy. Damage of the heart valves, mainly mitral and aortal, leads to their insufficiency, and, less commonly, stenosis. Valvular disease usually develops 3–5 years after therapy [2, 16, 20].

The risk factors for cardiac complications of radiotherapy include:

- dose,
- technique of radiotherapy administration,
- the heart volume in the irradiation field,
- patient's age.

Younger age is a risk factor for cardiovascular disease. The longer the time from exposure, the higher the incidence of complications. Maximum safe doses in relation to the part of the heart subjected to irradiation have been determined for adult patients. They are about 60 Gy for 25% of the heart volume and 45 Gy, when 65% of the heart volume is subjected to radiotherapy by means of a fraction method 2Gy in 24 hours [20].

Protection of the Heart Muscle

Dexrazoxane (Cardioxane) is registered in Poland as a drug protecting the heart against anthracycline-related cardiac complications. It is a derivative of ethylenediaminetetraacetic acid (EDTA). The most probable mechanism of dexrazoxane action is to chelate intracellular iron ions, what may decrease doxorubicin-induced formation of free radicals which exert damaging effect on the cardiomyocytes [4, 5, 21]. The drug reduces the incidence of congestive heart failure in patients treated with anthracyclines [21]. Experience of the drug use in children is limited. Children and adolescents administered the drug together with the therapy for acute lymphoblastic leukemia demonstrated significantly reduced increase of cardiomyocyte necrosis markers (21% vs 50%) in comparison to children who were only on oncological therapy [22]. Recent studies revealed a similar percentage of children free from complications in a group of patients treated with doxorubicin alone and doxorubicin with additional administration of

dexrazoxane (77% versus 76%) [23]. The American Society of Clinical Oncology (ASCO) guidelines of 2002 do not recommend the use of dexrazoxane in children [24] in view of insufficient data to recommend the drug to this group of patients. Further long-term observations are necessary.

Studies performed in adults revealed that initiation of angiotensin converting enzyme inhibitor (ACEI) therapy in high risk patients may prevent the development of late cardiotoxicity [25]. The use of an ACE inhibitor is the only well-documented myocardial damage preventive measure during and after oncological therapy [11]. The latest studies have demonstrated that the treatment of contractibility disturbances with angiotensin converting enzyme inhibitors, angiotensin receptor antagonists and beta-adrenolytic drugs also prevents the development of anthracycline-related symptomatic cardiomyopathy [18].

The Incidence of Cardiotoxic Complications

It is estimated that 12% of patients with congestive cardiomyopathy were treated for cancer in their childhood [26].

A report of 1991 describes evident circulatory failure in 5 out of 115 children treated with anthracyclines within 11 years after the therapy; 57% of oncologically-treated children demonstrated echocardiographic evidence of impaired function of the left ventricle [9].

In a group of 125 children treated with anthracyclines, 19% demonstrated diminished ejection fraction, and 5% developed circulatory failure in the terminal phase of oncological treatment [27].

The latest studies, involving 124 children treated for acute myeloblastic leukemia, demonstrated acute cardiotoxicity in 13 (7%) children and chronic cardiotoxicity in 17 (4%) children; early toxicity being a risk factor for late complications. Subclinical forms of the heart damage (diminished contractility without clinical symptoms) subsided spontaneously in all but one child; symptomatic forms of cardiomyopathy required prolonged therapy. Two children died and 6 required prolonged treatment [28].

The described incidence of asymptomatic heart muscle dysfunction ranges from 18 to 57% on long-term follow up of children submitted to oncological treatment [9, 29, 30, 31].

Long-term observations of 607 children revealed the presence of anthracycline-related circulatory failure in 2.1% of patients in the first year after termination of therapy and in 4.7% after 15 years [10].

It has been estimated that mortality for cardiac reasons is 10-fold higher among patients who had been treated for cancers in their childhood than in their counterparts [2].

Diagnosis

Symptoms and signs appear quite late, thus routine diagnostic examinations are mandatory. The standards should include 12-lead ECG, chest X-ray and echocardiography prior to, during and after termination of oncological therapy.

Long-term follow up after anthracycline therapy revealed the incidence of prolonged QTc segment, disturbances of the repolarization period, but these belong to late symptoms. For this reason ECG is not useful in early diagnosis. This examination is recommended at the onset of oncological therapy and after its termination in every patient [2].

Echocardiography – According to the guidelines of the ACC (American College of Cardiology) and AHA (American Heart Association), this examination is recommended in primary and periodic evaluation of patients submitted to the cardiotoxic effects of chemotherapeutics [32]. It may reveal disturbances in the heart function in the asymptomatic period. Evaluation of systolic function is most commonly based on two parameters – the shortening fraction (FS) and the ejection fraction (EF). The lower limit of normal values for the shortening fraction is 28%, and 50–55% for the ejection fraction. Diastolic function is evaluated directly by means of measuring the blood flow through the bicuspid valve – the rapid ventricular filling phase (E wave) and the phase of filling the ventricle after atrial contraction (A wave). Impaired diastolic function of the left ventricle is manifested by reversed E/A ratio [2, 16].

Diastolic function should be evaluated in patients with normal body temperature and hemoglobin level not lower than 9 g/dl, preferably 3 weeks after the last administration of anthracyclines, in order to rule out the systolic hyperkinetics associated with catecholamine release [11].

In case of technical problems with transthoracic echocardiography, radioisotope examination should be performed, e.g. by means of the multigated radionuclide angiography method. The assessment of the ejection fraction in this method is characterized by a significant reproducibility [2, 11].

Anthracycline therapy should be discontinued if the shortening fraction or the left ventricular ejection fraction drop by 10% or more below the lower order of normal values until heart contractibility normalizes [6].

Biochemical Exponents

Myocardial damage prognostic markers are still being sought. Troponins are specific proteins, components of myofibrils, and they are exponents of cardiomyocyte necrosis. They appear in elevated concentration in the blood plasma in acute heart damage, myocarditis, and acute coronary disease [33]. The majority of reports did not point to any clinical usefulness of troponin measurement [2, 15] as a predictive factor for the development of anthracycline-related cardiomyopathy. The level of troponins was not found to change despite administration of high cumulative doses of doxorubicin and diminished contractility. In children, elevated levels of cardiomyocyte necrosis markers in the early stages of heart damage were often demonstrated only following the first administration of anthracyclines [34].

Other studies demonstrated the usefulness of this biochemical parameter in the prognosis of myocardial damage [2, 15]. In order to confirm this, further longitudinal studies on a larger group of patients are required.

B-type natriuretic peptide is secreted in conditions of excessive stretching of the walls of the left ventricle and atrium associated with an increased volume of fluids – congestive heart failure, kidney failure, primary hyperaldosteronism, also in conditions of excessive secretion of glucocorticosteroids, and thyroid diseases [35]. ProBNP is the B-type natriuretic peptide precursor. During its proteolysis, an inactive polypeptide, N terminal proBNP and active BNP are detached. Presently, Nt-proBNP has found application in medical diagnostics, as its level is maintained longer in the blood and it can be detected more easily [15, 36]. Studies on small groups of patients have confirmed the usefulness of monitoring the blood level of this marker in prognosis of the cardiotoxicity risk of oncological treatment [2, 15, 37, 38]. These still have to be confirmed. Recent guidelines of the Children's Oncology Group for long-term follow-up of survivors of childhood, adolescent or young adult cancers do not recommend standard use of cardiac biomarkers in long-term monitoring in patients on oncological therapies [39].

Cardiotoxicity Monitoring

There are no official guidelines concerning cardiotoxicity monitoring in pediatric patients after oncological treatment [2].

Some authors suggest echocardiographic examinations performed 3, 6 and 12 months after termination of anthracycline therapy, followed by examinations every 2 years [40].

The frequency of cardiac function monitoring should depend on the risk of the development of cardiac complications – the child's age on antineoplastic therapy, the dose of anthracyclines and the administration of combined therapy [2].

In asymptomatic, low-risk children, who received a dose of anthracyclines below 250 g/m² and did not have radiotherapy, the risk is low and the benefits of echocardiographic monitoring are not high [41]. However an annual check-up with special attention paid to cardiovascular symptoms is recommended.

In pediatric patients above 5 years of age, who had radiotherapy as the only risk factor at a dose below 30 Gy, evaluation of the circulatory system (the heart and blood vessels) should be performed every 5 years. Children treated with higher doses of anthracyclines, or a combined therapy, are increased risk patients and more frequent cardiological check-ups are recommended [2].

Recent guidelines (from the Cardiology Committee of the Children's Cancer Study Group for monitoring acute and late manifestations of doxorubicin cardiotoxicity in childhood cancer survivors and the Children's Oncology Group for childhood cancer survivors) recommend periodic evaluation of left ventricular function by means of echocardiography or radioisotope ventriculography [2, 6, 39].

It should be stressed that if children develop symptoms of cardiomyopathy after oncological treatment, it is a progressive disease with poor prognosis. Treatment may only alleviate its course. Despite introduction of new pharmacotherapeutic methods, the efficacy of this treatment has not been evidenced in studies on large groups of pediatric pa-

tients. There is no data on the efficacy of Cardiac Resynchronisation Therapy (CRT) in the treatment of heart failure in children. Heart transplantation still remains the only therapeutic method for chemotherapy-associated cardiomyopathy, with a 50% chance for 10-year survival from the date of the procedure in children. Another problem of Polish transplantation is the lack of pediatric organ donors.

Conclusions

Currently, the risk of damaging the heart muscle as a result of antineoplastic therapy is increasing, in view of the increased incidence of cancer, the use of more aggressive therapeutic methods, and prolonged survival of patients with cancers. This should be remembered about the late cardiotoxic complications of oncological treatment, as their early management can significantly prolong life and improve its comfort, which is especially important in pediatric patients – children and young adults. This is an interdisciplinary issue, requiring cooperation and supervision of not only pediatric cardiologists and oncologists, but also first contact doctors.

Long-term follow-up of patients after antineoplastic therapy in their childhood is recommended, with special attention paid to individual risk factors – the cumulative dose of anthracyclines, the use of radiotherapy and irradiation doses, as well as the age on termination of therapy. The follow-ups should also consider additional known risk factors for cardiovascular disease – hypertension, dyslipidemia, overweight and a family history of cardiovascular disease.

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