Radiotherapy and anthracyclines – cardiovascular toxicity

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The subject of this paper is to analyze the impact of radiotherapy and anthracyclines on the cardiovascular system, based on a survey of contemporary literature. Currently, high efficiency of anticancer therapies has increased the rate of survival in patients treated for cancer. It should be emphasized, however, that these treatments damage not only the affected but also the healthy tissue. Consequently, with the increase of survival rate in these patients, the number of patients with complaints regarding numerous organs and systems also increases as a result of earlier treatment. Thus, during the first decade of the 21st century, a number of concerns about the relationship between cancer treatment and dysfunction of the cardiovascular system were resolved. Anthracyclines, as well as radiotherapy, are capable of damaging the cardiovascular system, both at the central level, by the deterioration of cardiac function, and at peripheral levels, by increasing the hemodynamic and thrombotic changes.

Key words: radiotherapy, anthracyclines, chemotherapy, toxicity, cancer.

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Introduction

In the literature, the devastating effects of cancer treatment on the cardiovascular system are often referred to as so-called cardiotoxicity. The National Cancer Institute defines it in a very general way, namely as "toxicity affecting the heart" [1, 2]. So far, no standardized definition of cardiovascular toxicity that would precisely explain its nature has been adopted. What is certain is that, regardless of whether the anticancer therapy is physical (ionizing radiation), chemical, hormonal or biological (targeted therapy), it has a negative effect on the cardiovascular system [3]. Drugs administered and radiation can damage the cardiovascular system, both at the central level, by the deterioration of cardiac function, and at the peripheral level, by increasing the hemodynamic and thrombotic changes [1]. It is worth noting that the level of toxicity of anticancer therapy may be increased by the impact of cardiovascular disease risk factors, as well as those related to the method of anti-tumor therapy itself (Table 1).

Suter and Ewer have proposed two types of cardiotoxicity in anticancer treatment [4]. The first type is related to the administration of anthracyclines or radiotherapy. It is characterized by irreversible changes in cardiomyocytes, leading to apoptosis, and is dependent upon the dose of the drug and ionizing radiation used. The second type, however, relates to trastuzumab (Herceptin) monoclonal-antibody therapy and, unlike type I, is not dose-dependent. It probably causes cardiac dysfunction. It is believed that the cardiotoxicity may be reversible upon cessation of treatment [4–8].

The Childhood Cancer Survivor Study research experiment has shown that the risk of cardiovascular events in patients with cancer is probably greater than the risk of another tumor, especially in those treated with anthracyclines and radiotherapy. The results of those studies have shown that in children who have survived cancer the incidence of congestive heart failure is fifteen-fold higher, the incidence of cardiovascular diseases is ten-fold higher, and the incidence of stroke has increased nine-fold in comparison with the control group. Similar numbers were observed in the study from Scandinavia, which showed that these patients have a 5-year cardiac mortality of 5.9% [9].

In view of these reports of serious and irreversible changes in the circulatory system that may be the result of treatment with anthracyclines and radiotherapy, the subject of this paper is to analyze the impact of radiotherapy and anthracyclines on the cardiovascular system. The analysis is based on a review of contemporary literature. It should be noted, however, that a comprehensive evaluation of data published on the subject is difficult to perform, as the studies investigating the effects of cancer treatment on the cardiovascular system differ in regard to methodology and the definition of cardiotoxicity; therefore it is not always possible to draw reliable conclusions.

Radiotherapy

Irradiation-induced cardiovascular diseases include a number of dangerous effects, ranging from subclinical histopathological symptoms to clinical-

Table 1. Risk factors for cardiovascular cardiotoxicity, pathogenesis, and cardiovascular pathological manifestations caused, in regard of the method of treatment used [2, 4–6, 8, 9, 11, 14, 19–22, 30]

Therapy	Risk factors	Pathomechanism	Cardiovascular manifestation
Radiotherapy	1. Younger age at exposure 2. Overall dose (> 30–35 Gy) 3. Division into fractions (> 2 Gy) 4. The heart was exposed to ionizing radiation (toxicity increases with increasing volume) 5. Use of cytotoxic chemotherapy 6. Irradiation technique (teleradiotherapy is more toxic than brachytherapy) 7. Radiation in the morning hours (between 6 am and noon) 8. Longer time since exposure	There are two mechanisms causing tissue damage during radiation therapy: Direct ionization of cell components Indirect radiolysis of intra-and extracellular water	1. Acute pericarditis 2. Chronic pericardial effusion 3. Myocarditis 4. Congestive heart failure 5. Valvular stenosis 6. Regurgitation mainly of mitral and aortic valves 7. Fibrosis of the conduction system 8. Disturbed heart rate 9. Complete or incomplete heart block
Chemotherapy	1. Patient age < 18 years of age and > 65–70 years of age 2. Overall drug dose (doxorubicin > 550 mg/m^2, epirubicin > 900 mg/m^2, idarubicin > 90 mg/m^2) 3. Division of the total dose into sessions 4. Female gender (especially in the pediatric population) 5. Manner of administration of the drug 6. Combination of drugs administered 7. Sequence of administration of medicines 8. Prior or concomitant radiotherapy (in particular of left side of chest and mediastinum) 9. Prior therapy with anthracyclines 10. Concurrent therapy with other anti-cancer drugs (drug interaction) 11. Hyperthermia 12. Liver diseases 13. Genetic peculiarities	There are two molecular mechanisms causing damage associated with: Reactive oxygen species Alcoholic metabolites	1. Left ventricular dysfunction 2. Heart failure 3. Myocarditis 4. Arrhythmia

ly overt diseases. The spectrum of these complications can be manifested in a variety of structures, such as pericardium, ventricles, cardiac muscle, cardiovascular system and the conduction system [10, 11]. It is estimated that radiotherapy-induced cardiovascular diseases occur in 10% to 30% of patients within 5–10 years following treatment. In 88% of patients the abnormalities are asymptomatic [12], and thus the disclosure of pathological cardiovascular lesions is often delayed, and as such can often be misleading [13]. It is important that patients treated with ionizing radiation are systematically monitored by methods of cardiac diagnosis recommended for these patients (Table 2), as radiation can cause a wide variety of pathological cardiovascular manifestations (Table 1).

There are two mechanisms causing tissue damage during radiation therapy (Table 1). It is believed that the radiolysis of water may be the key mechanism contributing to the occurrence of peroxidation processes in cell membranes [14].

The often-described result of exposure to ionizing radiation is the fibrosis of the pericardium, causing it to become rigid and constricted. This pathology is caused by the accumulation of collagen fibers in the mesothelium of the epicardium, visceral pericardium and in the interstitium. This accumulation leads to the replacement of the peripheral pericardial fat pad, increasing the thickness of the fibrous layer [15]. Production of protein-rich fluid inside the pericardial sac occurs and its rapid accumulation may even lead to lethal cardiac tamponade [12, 15].

The most frequently observed form of pericardial radiation syndrome is its chronic inflammation, appearance of which is often delayed. It occurs in about 4–20% of patients within 10 years after the termination of radiotherapy. A literature review has shown that acute pericarditis is rare, but may occur within several weeks after irradiation [11]. It can manifest itself with a fever, tachycardia, chest pain and pericardial sac effusion [16]. It is believed that acute pericarditis is mainly caused by the inflammation and the necrosis of large tumors in the mediastinal area, rather than directly by the toxic effects of thoracic irradiation [11].

Abnormalities affecting cardiovascular valves can be caused by ionizing radiation or fibrosis of the cardiac mus-

Table 2. Recommended methods for monitoring patients undergoing radiotherapy or chemotherapy to diagnose cardiovascular abnormalities [4, 8, 31, 32]

Cardiovascular monitoring	
Radiotherapy	Chemotherapy
• *Coronary artery disease:* lipid profile, exercise stress test, radionuclide, angiography, echocardiogram, electrocardiography • *Pericarditis*: electrocardiography, chest X-ray and echocardiogram • *Cardiomyopathy*: electrocardiography, echocardiogram, and radioisotopic angiography • *Arrhythmias:* electrocardiography and 24-h electrocardiography • *Valvular disease:* echocardiogram, electrocardiography, cardiac catheterization	• *Left ventricular dysfunction:* electrocardiography, magnetic resonance imaging, multiple-gated acquisition scan, sampling of serial troponin and/or NT-proBNP levels

cle, which is adjacent to their rings. Consequently, their distortion and loss of functionality occur as a result of calcification [13]. These changes include mostly the mitral, aortic and tricuspid valve. It is worth noting that radiation-induced valvular dysfunction frequently affects the left side of the cardiac muscle. Studies reveal that the aortic valve pathology is diagnosed more often than mitral or right-chamber pathology [11]. This is explained by the fact that higher intracardiac pressure occurs there, and also by accompanying higher intracardiac blood flow velocities. It is possible that such location of the pathology may also result from the irradiation techniques applied. The literature states that the average time of detection of asymptomatic valvular pathology is 11.5 years, and 16.5 years for symptomatic pathology. Thus, the process is slow, but gradually progressing [11, 17].

Myocardial damage may contribute to the development of progressive diastolic dysfunction and hemodynamic instability (≥ 1 year after irradiation). Consequently, congestive cardiac muscle failure occurs. These complications correlate with extensive fibrosis and microvascular damage leading to occlusion of capillaries [12], whereas systolic myocardial dysfunction may occur following combined treatment with anthracyclines [16].

Radiation damage in the circulatory system may concern the capillaries, veins, and small and large arteries. It usually appears > 10 years after completion of radiation therapy [13]. There are two hypotheses explaining the biological mechanisms that lead to a higher incidence and mortality due to blood vessel diseases resulting from ionizing radiation treatment. The first states that radiation increases the occurrence of myocardial infarction by intravascular proliferation and accelerated development of atherosclerosis in the arteries [12, 15, 18]. Blood vessel arteriosclerosis may lead to fatal cardiac ischemic necrosis [6]. The second hypothesis is that the radiotherapy-induced increased mortality is related to the decrease in myocardial tolerance to the above-mentioned acute ischemic necrosis induced by microvascular disorders. It is worth noting that these hypotheses are not mutually exclusive, and the mechanisms described may occur simultaneously, contributing to the development of clinical cardiac diseases [12].

All major ionizing radiation-induced coronary diseases presumably include processes such as increased vascular permeability, intimal hyperplasia, fibroblast proliferation, collagen deposition, fibrosis and scarring of the vascular wall outer membrane [11, 17]. Many of these mechanisms reflect the formation of atherosclerosis. However, in comparison to atherosclerosis occurring in the general population, irradiation leads to the formation of plate which is more fibrotic and is characterized by a lower content of lipid components.

Capillary endothelial cells display high radio-sensitivity. Their growth occurs as a result of exposure to ionizing radiation, leading to occlusion of the capillaries and lumen and density loss. Impairment of microcirculatory function can cause extensive damage, leading to ischemia, necrosis of myocardial cells and finally their fibrosis [11].

Heart rate, being controlled by the autonomic nervous system, is an important predictor of cardiovascular disease. It is believed that fibrosis of the myocardial tissue resulting from radiotherapy may explain the pathological changes in its functioning. It causes certain changes in the electrocardiography, including premature re-polarization abnormalities and premature ventricular complexes. Approximately 50% of patients with mediastinal irradiation are exposed to these abnormalities [12]. Its motor disorder results in the emergence of mechanisms compensating for its function. Thus, the sympathetic nervous system is activated, and the level of catecholamines and density of adrenergic receptors are changed. Consequently, the nervous system causes the heart muscle to be more intensively stimulated to work and compensate for its own impairment [14].

Anthracyclines

Anthracyclines are a group of antibiotics that are among the most active representatives of chemotherapeutics, and since the 1960s have been a key component in many cytotoxic anticancer regimens. Commonly used drugs of

this group are doxorubicin, daunorubicin, epirubicin and idarubicin [19]. It has been known since the 1970s that anthracycline therapy is associated with increased risk of a heart failure. Treatment with these drugs, compared to the treatment without their use, increases the risk of clinical cardiotoxicity 5.43-fold, subclinical 6.25-fold and the risk of death related to cardiac problems 4.94-fold [20]. Table 1 shows the cardiovascular pathological manifestations triggered by anthracycline therapy. It is important that the patients subject to this treatment are systematically diagnosed for cardiovascular diseases. Table 2 shows methods recommended for monitoring these patients by cardiologists.

Cardiological biopsies and modern imaging techniques suggest that myocardial damage may already have occurred at the start of exposure to the anthracyclines, regardless of whether it had been diagnosed using standard non-invasive techniques. Data obtained from biopsies and charts showing dose-response relationships provide strong evidence that the damage occurs at the beginning of the exposure, despite the fact that cardiac reserve does not allow them to be diagnosed until it is completed [19]. Thus, there is no specified period for the onset of pathological post-anthracycline changes in the circulatory system. Therefore, three types of post-anthracycline cardiotoxicity have been distinguished: acute, chronic and delayed.

Acute cardiotoxicity (not related to the dose of the drug) can occur during or immediately after a single dose of an anthracycline. It can be characterized by transient arrhythmia or electrocardiographic changes (nonspecific ST- and T-wave changes) and pericardial effusion. In some cases it can cause pericarditis, myocarditis and heart failure. It is believed, however, that cardiac toxicity is not a serious therapeutic problem, but it should be noted that it is often asymptomatic. It is probably the consequence of direct damage caused by anthracycline and excessive discharge of catecholamines and histamine caused by these drugs.

However, the most serious type of cardiotoxicity is the chronic type (associated with drug dose), as it causes irreversible changes in the circulatory system. This type of cardiotoxicity usually occurs within a year after treatment with anthracyclines, and can result in development of congestive heart failure (CHF), refractory to medical therapy.

If the lesions show up years or decades after exposure to the drug, they are referred to as delayed cardiotoxicity [7, 21–23] and are characterized by arrhythmias such as paroxysmal ventricular tachycardia and paroxysmal supraventricular tachycardia, and atrioventricular block. Exacerbation of chronic heart failure, *de novo* CHF or sudden cardiac death can also occur [21].

The pathomechanism (Table 1) of post-anthracycline cardiotoxicity is controversial and still not completely understood. It is believed, however, that anthracyclines may become cardiotoxic immediately after the reduction of one or two electrons. One-electron reduction (of the quinone moiety of anthracyclines and the subsequent semiquinone redox cycling) leads to the formation of reactive oxygen species (ROS), which cause oxidative stress and loss of energy in the cells of the myocardium. Two-electron reduction (of the side-chain C-13 carbonyl group) leads to the creation of secondary alcohol metabolites that are responsible for the disruption of homeostasis of calcium and iron in the organism [9, 22, 24]. The best known mechanism of cardiotoxicity is the one concerning conventional doxorubicin. It is worth noting that ROS are responsible for the occurrence of early cardiac abnormalities, including impairment of DNA repair pathways. This leads to irreversible changes in the myocardial cells, which have limited capacity for regeneration due to a low level of antioxidant enzymes in the myocardium. Secondary alcohol metabolites, however, may have a key role in the progression of cardiomyopathy-causing cardiotoxicity and CHF [6, 22, 25]. Post-anthracycline cardiomyopathy may occur in the form of severe myocardial damage or be asymptomatic. The prognosis for post-anthracycline cardiomyopathy is significantly worse than in infarct heart failure or idiopathic cardiomyopathy [26].

The primary cause of impaired intracellular metabolism is free radicals, as they cause DNA, cell membrane and endoplasmic reticulum damage, among others [21]. The mitochondria also become impaired, and changes occurring within them are responsible for the release of cytochrome c, AIF protein (apoptosis inducing factor) and intramitochondrial caspases from the inter-membrane space. Free radicals induce lipid peroxidation. Cell membrane structure, its transport properties and transport enzyme activity may be modified as a result [27].

The mechanism of damage to the structure and impaired cardiac function by anthracycline is multifactorial. It consists of processes such as inhibition of the synthesis of nucleic acids and proteins, reducing the amount of GSH, ATP and creatine phosphate, pathological adenine, amino acids and glucose absorption, inhibition of enzymatic activity of the Na^+ and K^+ ATPase, inhibition of ion pumps (with consequent disruption of the metabolism of iron), myocyte calcium overload, inhibition of ion exchange of sodium/calcium, inhibition of adenylate cyclase, impairment of oxidative phosphorylation, blocking the activity of topoisomerase II, abnormal metabolism of sphingolipids, a sudden release of catecholamines and histamine, disturbance in the sympathetic system, activation of signaling pathways and gene expression alteration [14, 28, 29]. Kaczmarek-Borowska and co-authors emphasize that the activity of coenzyme Q10 in the respiratory chain may be impaired – its inhibition may result in shortage of energy. All metabolic and ultrastructural changes in the cardiac muscle lead to its pathological mechanical and electrical activity [21].

It is worth noting that doxorubicin, through the generation of mediators of oxidative stress, not only causes apoptosis of cardiomyocytes, but can also have a damaging effect on the endothelium of blood vessels. This leads to reduction of vasomotor activity. Przybyszewski and co-authors believe that the pathology of the endothelium may result in the early stage of development of post-anthracycline atherosclerosis of coronary arteries [14]. Galderisi and co-authors state that treatment with these substances may also cause cardiac muscle valvular pathologies [10].

Summary

Nowadays, the high efficiency of anticancer therapy increases the rate of survival in patients treated for breast cancer. It should be emphasized, however, that these treatments damage not only the affected tissue, but also the healthy tissue. Consequently, with the increase of the survival rate in these patients, the number of patients with complaints concerning many organs and systems also increases, which is the result of earlier treatment. Pathologies caused by anticancer therapy may contribute to disorders of the cardiovascular system. It seems appropriate at this moment to ask whether the reduction in the risk of relapse is tantamount to prolonging overall survival in these patients.

In patients with cancer, the principle of *primum non nocere* should be of particular significance, and therefore the number of studies on the effects of cancer treatment on the human body is constantly increasing. This issue is not to be underestimated, as the pathology of the cardiovascular system leads to reduction in the quality of life in these patients. The awareness of the need to balance the oncologist's objectives (maximum elimination of cancer cells or inhibiting their division) with the objectives that impact the quality of life is of paramount importance.

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