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LEADING ARTICLE

Cardiotoxicity of cancer therapy

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Summary

Nowadays cancer is the second leading cause of death in Europe and in Russia. Life expectancy and relapse-free survival in cancer patients have increased significantly due to advanced diagnostics and innovative pharmacological treatment and radiotherapy. In accordance with it, time, the number of patients suffering from various complications including cardiologic ones has increased proportionally. Many chemotherapy agents have cardiotoxic effects that often are refractory to treatment and that are mostly manifested as asymptomatic ECG changes up to myocardial infarction, as various rhythm and conduction disorders, or as toxic cardiomyopathy with signs of severe heart failure. Taking into account all above-mentioned points, well-timed detection, monitoring and treatment of complications arising during and after anticancer therapy become new relevant tasks in clinical practice.

Key words

Cancer, antitumoral drugs, chemotherapy, radiotherapy, cardiotoxicity, prevention.

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Introduction

Nowadays cancer is the main and one of the most significant healthcare problems in Russia and in the world [1–3]. According to the information collected by Hertsen Moscow Oncology Research Center, cancer morbidity has been increasing constantly during the last few years. 589 341 new cancer cases were diagnosed in 2015, and this number is 4,0 % higher comparing with the previous year (270 046 male cases and 319355 female cases) [4]. Cancer is the cause of each sixth death in the world. 8,8 mln people died due to cancer in 2015. According to the World Health Organization (WHO) prognosis, within the next 20 % this number will increase approximately by 70 % [5].

But cardiovascular diseases (CVD) take the leading position between the causes of lethality in the majority of countries. In particular, more than 4 mln cases of death registered in Europe each year occur due to CVD, and 1 mln of them happen in Russia [6–7]. In terms of percentage, 55.9 % of CVD lethal cases occur in Russia, and 47 % of them occur in Europe [6]. Cardiovascular mortality of men is 4,7 times higher than the one of women, whereas death due to coronary heart disease (CHD), myocardial infarction, and cerebrovascular diseases is 7.2, 9.1, and 3.4 times higher in men than in women, respectively (fig. 1) [8].

When looking at these data, the importance of cancer prevention and treatment becomes obvious. Chemotherapy is the most effective way to fight cancer, but it leads to several complications, and the most frequent ones affect cardiovascular system (CVS). The severity of appearing adverse effects may lead to disability and death between cancer survivors [3, 9]. These adverse effects can result from cardiotoxicity of antitumor therapy especially in case of pre-existent cardiovascular risk factors (RF) [10]. It's important to point out that many features of long-term cardiovascular consequences of radiotherapy or chemotherapy have not been studied enough. The complexity of prediction of antitumor treatment adverse effects leads to hyper-diagnostics of CVD in the majority of cases, and sometimes it may lead even to termination of life-saving cancer treatment.

Creation of national registers of cardiologic problems in cancer allows determination of the impact of single risk factors on complications development in comorbid patients.

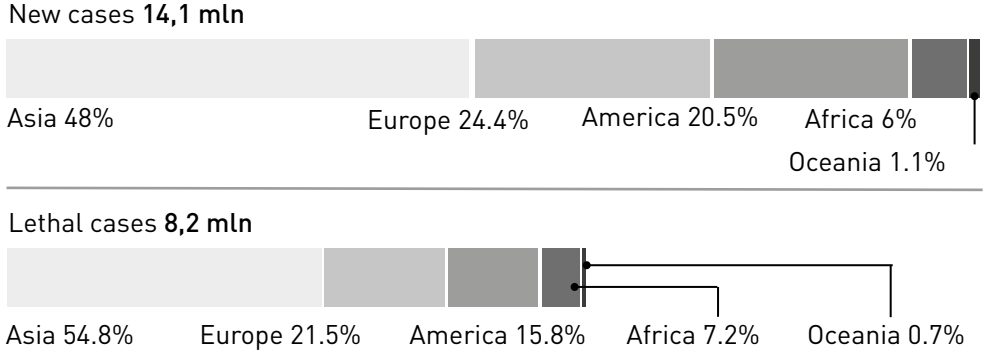
The first official document was published in 2016 by the European Society of Cardiology (2016) and it was dedicated to the cardiotoxicity of radio- and chemotherapy for cancer patients (The Task Force for cancer treatments and cardiovascular toxicity of the ESC) [11].

The risk factors of anticancer treatment include: total dose administered within one day or full course of chemotherapy; total dose of a drug (for example, cumulative dose of doxorubicin is 500–550 mg/m^2); drug order and velocity of administration; patient's history of mediastinal radiation, patient's age (below 15 and above 65 years); female gender; simultaneous administration of other antitumoral agents (cyclophosphamide, bleomycin, etoposide, cisplatin, vincristine, actinomycin, methotrexate); previous therapy with anthracyclin antibiotics; concomitant diseases of cardiovascular system; electrolyte disorders (hypokalemia, hypomagnesemia) [12–18].

Cardiovascular complications of cancer treatment

Nowadays there is no full classification of chemotherapeutic drugs' cardiotoxicity that would take into account the period of its appearance after the start of the therapy.

Time of cardiotoxicity manifestation can vary a lot. Adverse effects of several antitumor agents appear early and it has negative impact on general effective-



Source: Globocan

Figure 1. Prevalence of cancer in different parts of the world

ness of cancer therapy that complicates its management. Negative cardiovascular impact of other agents appears after a relatively long period.

Different chemotherapeutic agents may possess cardiotoxicity, but the anthracyclin antibiotics are particularly important from this point of view since there are numerous evidences of cardiologic complications (CVC) related to their administration.

Cardiotoxicity is subdivided into acute, chronic and subchronic forms [12–14, 19] (Table 1).

CVC caused by anticancer therapy can be divided into 9 main groups: myocardial dysfunction and heart failure (HF), coronary heart disease including myocardial infarction (MI), arrhythmias, arterial hypertension (AH), thromboembolism, peripheral artery disease and stroke, pulmonary arterial hypertension (PH); valvular heart disease (VHD), pericarditis.

It is necessary to highlight that tight interaction between oncologists and cardiologists is necessary to achieve the best possible result without negative effect on antitumor treatment, and to prevent and to control cardiotoxicity [20]. Systolic dysfunction of the left ventricle (LV) is the most threatening CVC of anticancer treatment and it is classified into two main types (Table 2).

It is important to keep in mind that the cardiotoxicity is not an indication for athracycline therapy withdrawal due to their high efficiency for the treatment of solid tumors and blood malignancies and possible negative impact on prognosis in case of treatment discontinuation. At the same time the ability of anthracyclines to cause irreversible myocardial changes and influence patients' lifespan and life quality has been proved. In 5% of cases patients who received doxorubicin had developed congestive HF after reaching cumulative dose of 400 mg/m^2, and the risk of congestive HF increases up to 48% in case of cumulative dose of 700 mg/m^2 [21]. It is necessary to take into account individual sensibility of patients since the standard anthracycline dose may result in no complications in some cases and cause them after the first administration in other patients.

Toxicity caused by administration of cytostatic drugs is related to damage of fast-proliferating cells in the majority of cases. Cells with restricted regenerative potential like cardiomyocytes are also suscep-

Table 1. **Cardiovascular complications of antitumor drug therapy**

	LV dysfunction/HF	AH	Myocardial ischemia	myocardial infarction	Arrhythmias	QT prolongation	Raynaud syndrome	Stroke	Peripheral artery disease	Pulmonary arterial hypertension	Deep vein thrombosis/ pulmonary embolism	Edema	Pericarditis/ pericardial exudation
Anthracyclines	x				x								
Bleomycin			x	x			x	x		x			
5-fluorouracil			x	x	x		x						
Capecitabine			x	x	x		x						
Gemcitabine			x	x			x						
Paclitaxel	x	x	x	x	x	x					x	x	
Cisplatin	x	x	x	x	x		x	x	x		x	x	
Cyclophosphamide	x		x		x					x			x
Vincristine		x	x	x	x		x						
Everolimus		x	x								x		
Temsirolimus		x	x								x		
Trastuzumab	x												
Bevacizumab	x	x	x	x				x			x		
Aflibercept		x		x				x			x		
Sorafenib	x	x	x	x	x	x		x			x	x	
Sunitinib	x	x	x	x	x	x		x			x	x	x
Pazopanib	x	x	x	x				x			x		
Axitinib		x	x	x				x			x		
Regorafenib		x	x	x									
Vandetanib		x						x					
Lapatinib	x		x		x	x							
Imatinib	x	x									x	x	x
Interferon-α	x	x	x	x	x		x	x	x	x	x		
Interleukin 2		x		x									

Table 2. **Comparison of two types of LV dysfunction related to antitumor therapy**

	LV dysfunction	
	Type I	**Type II**
Trigger prototype	Doxorubicin	Trastuzumab
Instrumental diagnostics	Reduction of LV ejection fraction (EF)	Reduction of LV ejection fraction (EF)
Period of manifestation	After the end of chemotherapy, most frequently within the first year	During therapy
Morphological changes of myocardium	Vacuolization Necrosis Abnormal position of cardiac muscle fibers	Absent
Dose-dependence	Yes	No
Risk factors	High cumulative dose of drug (≥250 mg/m^2 of doxorubicin, ≥600 mg/m^2 of epirubicin); Bolus drug administration; Combination with other cardiotoxic antitumor agents (cyclophosphamide, trastuzumab, paclitaxel etc.); Previous/simultaneous radiotherapy of mediastinal area/left part of the chest; CVD (CHD, moderate/significant valvular defects); initial LV dysfunction (LV EF <55 %); CVD RF: • AH • smoking • dyslipidemia • diabetes mellitus • hypodynamia • insufficient or excessive body weight • kidney failure • age <18 and >60–65 years • female gender	previous/simultaneous therapy with anthracyclines and other antitumor agents; CVD (CHD, cardiomyopathy, moderate/significant valvular defects); initial LV dysfunction (LV EF <55 %); CVD RF: • AH • smoking • dyslipidemia • diabetes mellitus • excessive body weight • alcohol consumption • age >60 years
Clinical course after discontinuation of the therapy	Stabilization is possible, but cardiomyocyte damage is irreversible	High probability of full recovery within the next months with good distant prognosis
Restarting therapy after discontinuation	High probability of LV dysfunction progression	Relatively safe if prescribed together with cardioprotective therapy

tible to permanent or transient effect of chemotherapeutic agents. According to Rickard J and colleagues, anthracycline cardomyopathy is the most malignant type of cardiomyopathy that may cause lethality in 50 % of cases within 2 years [22]. Long latent period, progressive course and resistance to cardioprotective treatment aggravate patients' prognosis. Early detection of drug-induced cardiotoxicity allows correcting dosage or velocity of drug administration and changing therapeutic regimens for less toxic drugs of new generation. Considering the importance of this problem, it remains relevant to study various methods of estimation of myocardial function for well-timed detection of cardiotoxicity-related pathologic changes [23]. There are other standard chemotherapeutic agents like cyclophosphamide, iphosphamide, cisplatin, and docetaxel that may cause cardiologic complications. Cyclophosphamide-induced cardiotoxicity is not frequent and it occurs in patients receiving high doses of the drug (>140 mg/kg) before bone marrow transplantation [24]. These patients develop HF within a few days after the treatment. Also alkylating agents similar to cyclophosphamide may cause HF. In case of treatment with platinum-based drugs it is necessary to dilute them in large volumes of appropriate solution for intravenous administration in order to avoid platinum toxicity. This volume overload often leads to HF manifestation or relapse. Docetaxel administration together with trastuzumab or other anthracyclines also increases the probability of congestive HF development. At the same time it is necessary to notice that often it is quite difficult to evaluate the impact of a single drug when they represent a part of a combined treatment.

Prognosis and treatment of cardiotoxicity

Cancer therapy is mostly combinative, and it complicates prediction of CVC. Taking into account the use of various combined regimens for cancer treatment and the possibility of early development of CVC, the use of combined therapy significantly complicates CVC prediction [25]. Nowadays liposomal forms of anthracyclines are actively developed. Design of such drugs is based on the idea that an active anthracycline is included in lipid-containing microscopic spheroids or as a part of their covering or inside them and then it is administered intravenously. The described form is less toxic and has the same therapeutic activity. It's possible to correct chemotherapy considering the susceptibility of patient's CVS to anthracyclines. It

Table 3. **Guidelines for treatment of patients with anthracycline-induced LV EF reduction (ESMO guidelines 2012)**

LV EF reduction	Strategy	Cardiac therapy
⩾ 15 % of initial levels if LVEF remains⩾ 50 %	Anthracycline therapy can be continued	Not required
<50 % during anthracycline treatment	Repeated echocardiography (EchoCG) evaluation 3 weeks after, if the same value is detected, anthracycline therapy should be temporally discontinued	Should be performed
<40 % during anthracycline treatment	Chemotherapy with this therapeutic regimen should be terminated	Should be performed, and other alternatives of pharmacological therapy should be discussed

explains the necessity of monitoring and continuous evaluation of myocardial function during all stages of patient's therapy, and correction or discontinuation of it in case of detected heart lesions. Troponin is the marker of anthracycline-induced myocardial damage. In rare cases troponin concentration can remain elevated several weeks after therapy termination. In adult patients high troponin I levels correlate with higher reduction of EF (by 16 %) comparing with patients without troponin elevation (⩽5 %) [26, 27]. Infradiaphragmatic radiotherapy is associated with high risk of CHD development due to atherosclerotic and non-atherosclerotic lesions of CVS complicated with plaque rupture, thrombosis and possible coronary spasm. Coronary ostium lesions are potentially fatal. After radiotherapy on the left breast atherosclerosis develops more frequently in the area of left anterior descending coronary artery and of left coronary, and atherosclerosis of circumflex branch of left coronary artery and right coronary artery are more frequent after Hodgkin's lymphoma treatment [28, 29]. Stress-test based on physical exercise revealed ischemic ECG changes in women who underwent radiotherapy of the left breast cancer comparing with the right breast cancer. CHD associated with cardiotoxicity can have different manifestations: acute coronary syndrome or sudden cardiac death, but more often CHD remains asymptomatic for a long time.

Carditoxicity after lymphoma treatment is more frequent in young patients and it manifests decades after the therapy. CHD development in patients with the history of Hodgkin's lymphoma is 4–7 times higher comparing with the other groups, and total risk of CVD development within the next 40 years after treatment reaches 50 % in this group of patients [30]. These patients have 2–7 times higher risk of myocardial infarction, and their total cardiovascular morbidity rate within the next 30 years is 10 % higher [30]. Taking into account this fact, it becomes reasonable to perform constant screening of patients who received antitumor therapy for detection of pathological changes of CVS during all their life after therapy initiation. Young age, lack of chest surface mould protection, high intensity of radiation, CV risk factors and CHD history are the risk factors of CHD development in patients who underwent radiotherapy together with anthracyclines treatment.

There is no specific treatment of anthracycline-induced cardiotoxicity. Cardiac glycoside have positive temporal effect; beta-blockers (metoprolol, labetalol etc) administration is reasonable for children with systolic dysfunction; angiotensin-converting enzyme (ACE) inhibitors (enalapril, captopril etc) are recommended in patients with increased afterload and asymptomatic LV systolic dysfunction, and diuretics are prescribed for treatment of patients with severe congestive HF. Combined use of bisoprolol and digoxin has positive effect (independently from cardiac rhythm). Bisoprol dose should be adjusted until reaching HR 58–60 beats per minute. Stabilization of patient's condition and optimal blood pressure levels allow addition of ACE inhibitors [31].

In order to prevent LV EF reduction and congestive HF development, it is reasonable to prescribe ACE inhibitors (enalapril) in patients with subclinical I type cardiotoxicity if elevated troponin levels are detected. LV HF requires treatment according to the guidelines of HF treatment (Table 3, Scheme 1).

Conclusion

The success of increased lifespan of cancer patients after introduction of new chemo-radiotherapy regimens is tightly connected with the high risk of cardiologic complications. The presence of various cardiotoxicity manifestations, relatively long period of asymptomatic course and disease progression require early and long dynamic monitoring of the condition of patients who underwent chemotherapy and radiotherapy. Patients' monitoring during all steps of cancer therapy is necessary for well-timed detection of pathological changes in myocardium, for the start of appropriate cardioprotective therapy and also for widening the knowledge of medical specialists about possible consequences of antitumor treatment. Joint work of cardiologists and oncologists is an important condition of patients'

Scheme 1. **Algorithms of diagnostics and treatment of anthracycline-induced cardiotoxicity (ESMO guidelines 2012)**

<table>
<tr><th colspan="4">EchoCG + ECG (QT interval) before the start of anthracycline therapy</th></tr>
<tr><td colspan="2">Anthracycline therapy</td><td colspan="2">Anthracycline therapy is finished and troponin I levels was not evaluated before therapy</td></tr>
<tr><td colspan="2">Troponin I levels evaluation before each chemotherapy cycle</td><td colspan="2">Immediately after the end of anthracycline therapy</td></tr>
<tr><td>Troponin I positive</td><td>Troponin I negative</td><td colspan="2">EchoCG</td></tr>
<tr><td>1) Cardiologist's consultation
2) Enalapril administration during 1 year</td><td>EchoCG should be performed 12 months after the start of anthracycline therapy</td><td></td><td>No LV dysfunction</td></tr>
<tr><td>After it EchoCG should be done after 3,6,9 months</td><td>After it EchoCG should be done once per year</td><td></td><td>EchoCG after 3 months</td></tr>
<tr><td>EchoCG should be performed 12 months after the start of anthracycline therapy</td><td></td><td rowspan="2">LV dysfunction</td><td>No LV dysfunction</td></tr>
<tr><td>After it EchoCG should be done once each 6 months during the next 5 years</td><td></td><td>EchoCG after 6 months</td></tr>
<tr><td colspan="2" rowspan="8"></td><td>1) ACE inhibitors
2) Beta-blockers</td><td>No LV dysfunction</td></tr>
<tr><td>3) Observation</td><td>EchoCG after 6 months</td></tr>
<tr><td></td><td>No LV dysfunction</td></tr>
<tr><td></td><td>EchoCG after 12 months</td></tr>
<tr><td></td><td>No LV dysfunction</td></tr>
<tr><td></td><td>EchoCG every year</td></tr>
</table>

management in the departments of radiotherapy and chemotherapy.

Numerous studies dedicated to the detection of pathological changes in myocardium and to the development of drugs with marked cardioprotective effect have been conducted during the last years.

«Make no harm» is the basic rule in all cases. It is important to explain to patients the importance of regular cardiologic visits and the use of drugs with well-proven efficacy.

Conflict of interest: None declared

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