Cardiotoxicity: a challenge for modern oncology

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Abstract

The article provides a modern vision of the problem of cardiotoxicity in oncology. Integrity and generality of nodal pathogenetic events in the body in case of carcinogenesis, antitumor therapy and cardiopathy are caused by similar mechanisms at different hierarchical levels. Identity of potential risk factors, including inflammation, aging, obesity, diabetes and smoking, has been noted. Similarly, in the development of metabolic syndrome and carcinogenesis, the level of growth factors (IGF-1), neoangiogenesis, hormones and other triggers of oncological and cardiovascular pathology is increasing. It is important that a variety of clinical manifestations of cardiotoxicity are due to the rapid expansion of the number of therapeutic options for effects. This thesis is illustrated by vivid examples of the use of anthracycline-based drugs whose mechanism of action is aimed at damaging genetic targets. The use of monoclonal antibodies - trastuzumab, is directed against HER2 / ErB2 receptors in breast cancer and is accompanied by distinct signs of cardiotoxicity especially in the elderly. A new strategy to enhance the targeted cytotoxic immune response to cancer cells (Ipilimumab, Nivolumab) has a chance to cause autoimmune myocarditis and myositis. Modern anti-angiogenic methods of cancer therapy, including inhibition of VEGF, significantly increase the risk of myocardial ischemia, hypertension and atherosclerosis. This indicates the need for monitoring of complications, a targeted selection of preventive and curative strategies, as well as attention to the mechanisms of tissue homeostasis in the implementation of the antitumor effect.

Keywords
Cardiotoxicity, Cardiopathology, Carcinogenesis, Trastuzumab, Tissue homeostasis, Antitumor effect

Imprint

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Presently much evidence has been obtained that cancer and cardiovascular diseases have a similar biological mechanism of their development. In a complex process of carcinogenesis, cells are exposed to effects of several genetic “shocks” before their complete neoplastic degeneration and initiation of the program of growth, invasion and metastasis [1]. In a like manner, the pathogenesis of cardiovascular diseases is organized as a multi-step process. Known are many existing potential risk factors common to cancer and cardiovascular diseases, such as inflammation, aging, obesity, diabetes mellitus, hypodynamia, diet and smoking. But it does not exclude that in addition there may be many other mechanisms that might also be classified as the same risk factors for cancer and cardiovascular diseases [2].

Inflammation

It has been long been known that there is a connection between inflammation and cancer available. Known are associations between some chronic infections and cancer diseases, that is, for example, human papillomavirus and cervical cancer [3], Helicobacter pylori and stomach cancer, Epstein-Barr virus and cancer [4,5]. With the passage of time, it has been recognized that inflammation in the tumor micro-environment promotes malignant transformation and carcinogenesis. Approximately 10-20% of the cancer cases occur at the site of chronic inflammation [6].

At present, it is also known that atherosclerosis was originally considered a disease associated with a disorder in lipid metabolism, characterized by inflammation. Many cardiovascular diseases risk factors (hypertension, tobacco use, hyperlipidemia and insulin resistance) cause atherosclerosis by stimulating the adhesion of endothelial cells and promoting the attachment of leukocytes to the blood vessels walls, that leads to inflammation [5,7,8]. Elevated levels of in
pro-inflammatory biological markers, such as C-reactive protein (CRP), is closely allied to cardiovascular diseases [9].

**Age**

It is known that the rate of the majority of the cancer types increases with age. In developed countries, 78% of all newly identified cancer types cover individuals aged over 55. In a similar manner, an increase in the cardiovascular disease risk is reported to be associated with age, too. Although 4.3% of individuals aged 18 to 44 years suffer from a heart disease, this occurrence increases to 12% for people aged 45 to 64 years, 24.6% for individuals aged 65 to 74 and reaches 35% in subjects older than 75 years [2].

**Metabolic syndrome**

Proven has been the relationship between obesity and many types of cancers, including adenocarcinoma of the esophagus, pancreas and liver, as well as colorectal, postmenopausal breast, endometrial and renal cancers [10]. In an extensive meta-analysis by Rennihan et al. [11], an increase in body mass index of 5 kg/m² was significantly attributed to a risk of esophageal adenocarcinoma (relative risk 1.52, P <0.001), thyroid cancer (RR 1.24, P <.001) and kidney cancer in male individuals (RR 1.24, P <.0001), and endometrial cancer (RR 1.59, P <.0001), gallbladder cancer (RR 1, 59, P = 0.04), adenocarcinomas of the esophagus (RR 1.51, P <0.0001) and kidney cancer in female individuals (RR 1.34, P <.0001).

Obesity is associated with an increased risk of cardiovascular diseases. The relative risk rate for cardiovascular disease is higher for those who have excessive weight (for male individuals on average RR 1.21, for female individuals RR 1.20) or obesity (male individuals RR 1.46, female individuals RR 1.64). Within the framework of the metabolic syndrome, obesity is associated with pro-inflammatory and pro-thrombotic conditions, insulin resistance and atherogenic dyslipidemia [12,13].

This is evidence that certain biological mechanisms associating the inflammatory condition and the metabolic syndrome both with cardiovascular diseases and cancers are available. One of the common factors is an elevated level of insulin-like growth factor (IGF-1) that is detected in metabolic syndrome and pathogenesis by tumor growth in experimental l models [14-17].

It is known that the development of breast cancer and endometriosis is associated with an elevated level of estrogens. An increase in the level of estrogen is usually observed under obesity. Biologically, estrogen is linked to tumor proliferation. Leptin, considered to be associated with cardiovascular disease [18], is correlated both with obesity and tumor growth. It is probable that it regulates the expression of cyclin D1 and Mcl-1 to stimulate the growth of malignant cells by activating the PI3K / Akt and MEK / ERK1 / 2 pathways in cancer [19]. Recent studies have provided a large amount of evidence in favor of the idea of the association of insulin resistance and cancer [20,21]. It has been established that breast cancer cells overexpress the insulin receptor, and insulin-associated IGF-1 promotes cell proliferation by stimulating the proliferation and metastasis of cancer cells [22]. Using this line of reasoning, it should be mentioned that arterial hypertension is one of the metabolic syndrome factors. In hypertension, the vascular endothelial growth factor (VEGF) increases, and the latter is also involved to provide neoangiogenesis in tumor growth [23]. Some studies show the relationship between hyperlipidemia, which is also a factor in the metabolic syndrome, and breast cancer [24,25]. The relationship between hyperlipidemia and cardiovascular diseases has long been known.

**Tobacco use**

Smoking cigarettes contributes to the development of cardiovascular diseases, including stroke, myocardial infarction and hypertension [26]. Obtained has been the evidence for the relationship between the use of nicotine and the pathogenesis both of cardiovascular diseases and cancer by inhibiting apoptosis and increasing angiogenesis [27].

**Correlation between the cardiovascular and oncological diseases**

Taking into account the common risk factors for cancer and cardiopathology, it is not surprising that many patients suffering from cancer also have cardiovascular diseases. Similarly, many individuals with cardiovascular diseases also have a history of cancer [2].

One more study [28] shows that 62% of patients with cancer of different locations had an excessive weight or obesity, 55% of patients suffered from hypertension, and 21% had diabetes of type 2. This study
is consistent with many other published papers [29]. It is often the case, when cancer patients have an increased cardiac risk already at the stage of diagnostics, before they begin to receive chemotherapy or radiation. Another study [30] demonstrates that patients with prostate cancer have a higher occurrence rate of elevated levels of blood pressure, hyperlipidemia and glucose resistance as compared with conditionally healthy subjects. Besides, it is reported metabolic syndrome is also more frequently found in the above cohort of this sort [31]. Thus, the results of an increase in cardiac risk factors, when giving a cancer diagnosis, if to compare with the respective reference groups of individuals, supply an additional evidence for the common biology triggering both cardiovascular diseases and cancer.

Cardiotoxicity in cancer treatment

The existing cancer treatment methods include conventional surgery, radiotherapy and standard approaches to chemotherapy; it should be mentioned that the other two new methods have been expanded over the last decades: molecular targeted therapy (MTT) and immunotherapy [32]. The rapid growth in the number of therapeutic options offered nowadays for the treatment of cancer, which may trigger the development of cardiovascular complications in patients, is an ever-increasing challenge both for oncologists and cardiologists. In this connection, it should be noted that the common risk factors for cancer and cardiovascular diseases play a significant role in this association [33]. Besides, an increase in the survival rate favored to identify the cardiac toxicity as a problem, which results from the antitumor therapy. Anti-tumor drugs of several classes affect the cardiac muscle leading to damages of the myocardial cells, that finally results in the appearance of a number of clinically significant effects, including electrophysiological abnormalities, symptomatic heart failure (HF), and even death [34]. Clinical peculiarities are represented by a large range of cardiovascular manifestations, or events, including bradycardia, tachycardia, cardiomyopathy, elevated pulse pressure, hypotension, arrhythmia, reduced left ventricular ejection fraction (LVEF), troponinemia, QT prolongation, myocarditis, myocardial infarction, pericarditis, acute coronary syndromes and congestive heart failure [35,36].

Cardiomyopathy after the use of anthracyclines is the most well-known and described kind of cardiotoxicity induced by chemotherapy. Therefore, accordingly, this mechanism has been studied most thoroughly. This type of cardiotoxicity causes the death of cardiomyocytes and is conventionally referred to as type I [37,38]. The mechanism of the action of anthracyclines initiates an interruption of the cell replication by intercalation with DNA, as well as the inhibition of topoisomerase II. Mechanisms of cardiac toxicity are not completely identified, but they are widely recognized in respect of the oxidative stress due to the formation of oxygen active forms. The interaction occurs both with the topoisomerase IIA, which is overexpressed in malignant cells and is one of the therapeutic targets, and the topoisomerase IIB, which is expressed in cardiomyocytes [34]. It is evidenced that the anthracyclines can reduce the proliferation of cardiomyocyte precursors, impairing the recovery from physiological and pathological stress factors and inhibiting the ErbB and NRG-1 signaling pathways [39,40]. Reasoning from some proposed concepts of the mechanisms of toxicity, many therapies, both new and those generally accepted in the treatment of cardiovascular diseases, are considered as preventing or reversing the cardiotoxicity induced by anthracyclines.

Despite the fact that anthracyclines have dominated among the clinical problems associated with the cardiotoxicity of anti-tumor therapy for many years, the widespread use of monoclonal antibodies, Trastuzumab, directed against HER2 / ErbB2 receptors for the treatment of breast cancer, has revealed clear signs of cardiac toxicity in their use [41].

The overall occurrence of Trastuzumab-related cardiotoxicity varies depending on the assessment of the population. In the main clinical trials, the incidence of symptomatic congestive heart failure (CHF) ranged from 0.8% to 5.1%, and the rate of the reduced left ventricular ejection fraction from 3.5 to 19% [42-45]. It has been noted that the cardiotoxicity indicators associated with Trastuzumab are significantly higher in the elderly individuals [46-48].

A certain success has been achieved in the treatment of several types of malignant tumors, including disseminated melanoma, when using the agents which inhibit immune control points. Ipilimumab is the first antibody against CTLA-4 approved by FDA in 2011, and Nivolumab is the second antibody against PD-1 approved by FDA in 2014. This revolutionized strategy of the anti-cancer treatment opened a new era [49,50]. Anticytotoxic T-lymphocyte-associated antigen 4
(CTLA-4) and protein-programmed protein-1 (PD-1) with cells are particularly useful for the treatment of diseases such as melanoma [51]. Typically, cancer cells can use these receptors to avoid the destruction due to the T cells by binding to CTLA-4, reducing and activating the naive T cells, or by expressing ligand protein-1 (PD-L1), mediating the regulation of the T-cells and apoptosis [52]. The inhibitors such as Ipilimumab (anti-CTLA-4 monoclonal antibody), Pembrolizumab and Nivolumab (anti-PD-1 monoclonal antibodies), bind and disable the inhibitory effects of the receptor sites, thereby enhancing the cytotoxic immune response to cancerous cells [49].

However, in this case, the therapeutic effects vanish due to the appearing cardiotoxic effects [53-55]. It has been established that the T cell responses can be non-specific to cancer cells, and can also target the normal tissue that leads to frequent, immune-related side effects. It has been recently reported on the cardiotoxicity in the form of a potentially fatal myocarditis, especially in case of Ipilimumab and Nivolumab combination therapy [56]. Known are at least several cases of the cardiotoxicity associated with the immune control point inhibitors with manifestations such as myocarditis and complete heart block, although these data probably underestimate the true picture of the complications [53-56]. Based on biopsy of tumor, as well as the heart and skeletal muscle in two patients who experienced acute myocarditis, Johnson et al [56] suggested that the activated T cells can be targeted at an antigen that is shared by the tumor and the myocytes in the skeletal and cardiac muscles. This “target” effect eventually leads to autoimmune myocarditis and myositis.

In a similar way, the chimeric antigen receptor (CAR) -T therapy had valuable advantages for treatment of the B cell lymphoblastic leukemia (B-ALL). Mechanically, the functions of CAR-T are reduced to the fact that the native T cells are designed to express the chimeric antigen receptor at the cell membrane. The receptor is linked to an external binding domain to specifically recognize and bind to tumor antigens. CAR-T also has an internal activation domain, which subsequently activates the T cell, when CAR-T is bound to its target. In patients with B-ALL the CAR-T therapy is effective in 70-90% of cases [Jackson Johnson et al., 2016]. However, the occurrence of IRAE also increased along with the combination therapy, reaching 96% in patients, who received Ipilimumab and Nivolumab [58]. The CAR-T therapy and ACT are both associated with risks of cardiotoxicity. The CAR-T-therapy, in particular, is connected to cytokine release syndrome (CRS), an inflammatory response that correlates with the activation of the CAR-T cells. CRS manifestations include arrhythmias, decreased LVEF and QT prolongation [59].

The vascular endothelial growth factor and its corresponding receptors, VEGFR, are one of the most important pathways of tyrosine kinase. VEGF-A is the most representative component, and the VEGF signaling pathway plays a central role in influencing the vascular system [60]. It is demonstrated that modern anti-angiogenic methods of therapy, including inhibition of VEGF, have an adverse effect on the cardiovascular system [36,61,62]. In case of the anti-VEGF therapy with tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib, sunitinib, sorafenib, axitinib, and ponatinib), known are cases of hypertension, ischemic damage to the heart muscle and rapid progression of atherosclerosis [63]. Inhibition of the VEGF pathway can lead to endothelial dysfunction resulting from the disorder of the normal endothelial homeostasis mediated by nitrogen oxide [60]. A meta-analysis conducted after the use of sunitinib showed an increased relative risk of cardiovascular complications. The risk of myocardial ischemia caused by sunitinib was 3.03 times higher if to compare with placebo [64]. Ponatinib was associated with significant cardiovascular toxicity, reported to have 10% of the cardiovascular, 7% of the cerebrovascular and 7% of the peripheral side effects within 28 months after the treatment. Hypertension was diagnosed in 26% of the patients received this drug [64].

Both conventional chemotherapeutic agents and the most advanced methods of treatment of malignant neoplasms have an important effect on the myocardial tissue, provoking arrhythmia, ischemia, and even death of patients. The mechanism of this toxicity refers to the “target” therapeutic mechanisms of anti-tumor medication that indicates a possible inevitable relation between these vital chemotherapeutics and the cardiovascular toxicity. As new treatment methods are developed and introduced in practice, especially when they are used in treatment in the elderly patients showing a depleting heart reserve, it is of great importance that oncologists work closely with cardiologists to monitor and control complications of this sort. It is also vital to recognize the multi-factor featured processes that lead to the development of cardiovascular
diseases in patients suffering from malignant tumors [34]. Considering the above, several strategies have been proposed to prevent the appearance of cardiovascular complications after the use of anti-tumor agents. However, none of them can be recognized as completely safe and meeting all applicable standards of treatment, that is connected with the complexity of various types of cardiac complications. Besides, it should be noted that cardiac dysfunction can also manifest itself many years after the completion of anti-cancer therapy that makes it difficult to properly evaluate preventive and curative strategies. What counts for the implementation of the best suited treatment tactics, it is the proper understanding of the biochemical and molecular mechanisms involved, which are initiated by anti-cancer agents and which may affect the cardiomyocytes and the immune cells [65].

Statement on ethical issues
Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest
None declared.

Author contributions
All the authors read the ICMJE criteria for authorship and approved the final manuscript.

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