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Acute Coronary Syndrome During Chemotherapy

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ABSTRACT

The use of modern chemotherapeutic drugs in the treatment of cancer is associated with various side effects. Cardiovascular complications include various heart rhythm disorders, heart failure, arterial and venous thrombosis of various localizations. This review article describes the pathophysiological features of various groups of chemotherapeutic drugs that are actively used in everyday practice, which lead to the occurrence of acute coronary syndrome. It also describes the features of percutaneous coronary interventions in patients undergoing chemotherapy.

Keywords: Cardioncology, chemotherapy, metabolic syndrome, acute coronary syndrome, percutaneous coronary interventions

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INTRODUCTION

The development of modern medical technologies based on evidence-based medicine has significantly improved the outcomes of many types of diseases, in particular, diseases of the cardiovascular system and cancer. The introduction and improvement of approaches to the diagnosis and prevention of cancer at the outpatient stage significantly increased the detection of cancer cases at earlier stages, which made it possible to conduct timely treatment and improve the survival rate of this group of patients.

The number of cancer survivors continues to grow worldwide. This trend reflects an increase in the number of newly detected cases of malignant diseases as a result of the overall population growth and aging. According to the American cancer community, there were more than 16.9 million Americans living with cancer in the United States as of January 1, 2019. This number is projected to grow to 22.1 million by January 1, 2030. [1] The increased survival rate of cancer patients, in turn, leads to long-term effects, including those associated with the treatment received (radiation therapy, chemotherapy, surgery).

Cancer is a hypercoagulable condition, the presence of which, as is widely known, leads to an extremely high risk of venous thrombosis. There are studies in which the frequency of venous thrombosis in cancer patients reaches 40-50%. [2] Frequency of arterial thrombosis in this cohort of patients is significantly lower and accounts for about 5% of all cases [3].

In most cases, in cancer patients, acute coronary syndrome proceeds as a myocardial infarction without ST segment elevation, and in general, mortality in this group of patients is higher than in the General population of patients with STEMI [4]. In the multicenter BleeMACS study, cancer patients accounted for 6.4% of the total patient population, and the presence of cancer was the strongest independent predictor of death, recurrent heart attack, and bleeding [5]. The clinical manifestations of cancer and atherosclerosis complicate the distinction between the progression of a pre-existing risk of cardiovascular disease and the side effects of chemotherapy.

Some methods of cancer treatment, in particular, various chemotherapeutic agents, can lead to the progression of atherosclerotic changes, cause endothelial damage and have a direct vasospastic effect, together significantly increasing the risk of developing acute coronary syndrome. Many aspects of the mechanisms of this group of drugs are not fully understood. However, certain medications have a correlation between the pathophysiological mechanism of drug exposure and the risk of ischemic myocardial damage.

Special attention should be paid to the development of metabolic syndrome in patients undergoing chemotherapy. Metabolic syndrome includes abdominal obesity, hypertension, insulin resistance, dyslipidemia (decrease in high-density lipoproteins, increase in triglycerides) [6] and in general the risk of cardiovascular diseases significantly increases, including the development of acute coronary syndrome. The presence of a metabolic syndrome can be judged by the presence of 3 out of 5 syndromes. Various chemotherapeutic agents, in addition to direct damage to the coronary bed, indirectly increase the likelihood of adverse cardiovascular complications.

Platinum-based drugs, alkylating agents, and camptothecins cause DNA replication and transcription, disrupt protein synthesis, and interrupt cell growth and regeneration, especially in endocrine cells, thereby disrupting the normal functioning of hormonal systems [7]. The same groups of drugs lead to mitochondrial dysfunction through the production of reactive oxygen species. Tissue hypoxia leads to the activation of macrophages and pro-inflammatory cytokines, which in turn contributes to the development of obesity, insulin resistance and dyslipidemia.

Cyclophosphamide and platinum drugs cause the disruption of the functioning of the gonads [6]. In a study by Haas and co-authors, 44% of patients receiving chemotherapy for testicular cancer had low levels of high - density lipoproteins, and 29% had high levels of triglycerides [8]. In a prospective study, Diele-Conwright and co-authors studied the development of metabolic syndrome in patients with breast cancer [9]. It is important to note that patients with pre-existing metabolic syndrome were excluded from this study prior to the start of chemotherapy. They were treated with platinum (carboplatin) and alkylating agents (docetaxel,

doxorubicin, trastuzumab, cyclophosphamide). Within 4 months from the start of chemotherapy, metabolic syndrome was detected in 72.5% of patients.

Basic angiographic characteristics of the coronary bed in acute coronary syndrome, conducted by Sinha and co-authors, showed that lesions of the left coronary artery trunk, multivessel lesions, as well as complex coronary lesions (tubular, diffuse changes) prevailed in the group of metabolic syndrome [10].

Pathophysiological aspects of chemotherapeutic drugs

Drugs of the fluorouracil group (5-fluorouracil, capecitabine) are widely used in everyday practice. The pathophysiological mechanism in the case of 5-fluorouracil and capecitabine is coronary artery spasm, and the development of ACS is possible even in the absence of atherosclerotic damage to the coronary bed [11] 5-fluorouracil provokes the development of ischemic events immediately at the beginning of the infusion, as well as a few days after administration [12]. The world literature describes cases of successful use of nitrates in the event of typical chest pain and ST-segment elevation in patients receiving course treatment with 5-fluorouracil [13]. In addition, 5-fluorouracil is a radiosensitizing drug that increases the risk of radiation-induced thrombosis [14]. Capecitabine is an oral form of 5-fluorouracil. Capecitabine is metabolized to 5-fluorouracil in vivo, and it is assumed that this drug causes similar cardiotoxic effects [15]. Acute coronary syndrome in capecitabine therapy may occur as early as on the 2nd and 3rd days from the start of administration [16,17].

Paclitaxel is a widely used antitumor agent of the taxane group, used as a first-line medicine for ovarian, breast, lung, cervical, pancreatic, Kaposi's sarcoma. This drug is effective, but it has a number of side effects: alopecia, neuropathy, myelosuppression, and cardiotoxicity. During the use of paclitaxel, there were reports of the development of acute coronary syndrome in a number of patients, but no direct cardiotoxic damage to the coronary bed was stated in these studies, since many patients had significant risk factors for cardiovascular diseases (hypertension, smoking, previous atherosclerotic damage to the coronary bed) [18, 19] Mechanism of cardiotoxic action of paclitaxel remains not fully understood. It is assumed that paclitaxel can increase the intracellular calcium concentration, leading to spasm of the coronary arteries [20]. Other researchers suggest that the vasospastic effect is exerted by an auxiliary substance in the composition of paclitaxel-Cremophor EL (polyoxyethylated castor oil), increasing histamine-mediated spasm of the coronary arteries [21].

Gemici and co-authors reported a temporal relationship between paclitaxel and acute coronary syndrome, suggesting an allergic effect of this drug on the myocardium [22]. The term "allergic myocardial infarction" has been significantly expanded by Kounis and co-authors. Currently, Kounis syndrome is classified in three different variants. Kounis syndrome type I includes coronary vasospasm in patients with unchanged coronary bed and without risk factors for coronary heart disease, type II includes patients with previous atherosclerotic lesions of the coronary bed, in which an acute allergic reaction can lead to rupture or erosion of the atherosclerotic plaque, manifesting as a myocardial infarction. Type III is associated with thrombosis of a previously installed drug-coated coronary stent [23].

Cisplatin is a derivative of platinum, belongs to the alkylating agents. The mechanism of action of this drug is a violation of the function of DNA, caused by chemical damage to DNA by the formation of coordination bonds between the platinum atom and the two bases of DNA. It is shown to be used in ovarian, bladder, prostate, lymphoma, esophageal, lung, stomach, and colon cancers. The cardiotoxicity of cisplatin includes arrhythmias, myocarditis, cardiomyopathy, congestive heart failure. The cardiotoxicity of cisplatin is mediated by direct action on cardiomyocytes or the production of reactive oxygen species that cause oxidative stress, being a prothrombotic agent [24]. Elevated levels of total cholesterol, low-density lipoproteins, and triglycerides have been reported in several studies in patients receiving cisplatin [25,26]. There are also data on the occurrence of coronary vasospasm when taking cisplatin [27]. Despite the fact that the prothrombotic effect of cisplatin may decrease over time, there are still significant conditions for the development of accelerated atherosclerotic damage to the coronary bed. Numerous tyrosine kinase inhibitors (sunitib, sorafenib, paopanib) are representatives of "targeted therapy", adapting to the specific genetic characteristics of each type of cancer. This group of drugs, as well as many others, despite its high antitumor effectiveness, has a number of side effects, including cardiotoxicity. The greatest risk of acute coronary syndrome in this group of drugs occurs in gefitinib and sorafenib. Gefitinib is actively used in small cell lung cancer with EGFR mutations. The risk of developing acute coronary syndrome when taking gefitinib is associated with increased thrombocyte reactivity. Gefitinib has been shown to activate platelets via a mechanism associated with adenosine-5-diphosphate [28], and to significantly increase prothrombotic activity due to its increased ability to produce thromboxane A2. In addition to this mechanism, there is a hypothesis about direct damage to the atherosclerotic plaque described by Yamaguchi and co-authors [29]. Vasospasm is at the heart of the development of acute coronary syndrome when taking sorafenib. Increased calcium sensitization plays a crucial role in the genesis of coronary spasm [30]. The pathogenetic mechanism of the cardiotoxic action of sorafenib is the suppression of MAPK / ERK kinase activity, which causes activation of the Rho-activated protein kinase pathway and an increase in calcium sensitization, which leads to coronary artery spasm [31]. In addition, sorafenib inhibits the activity of RAF1 and BRAF kinases and may disrupt signal transmission through the ERK kinase cascade, which plays an important role in cardiomyocyte stability under stress [32].

Vincristine and rituximab are the drugs of the group of Vinca alkaloids. Their mechanism of action is associated with tubulin blockade and stopping cell division in metaphase. They are actively used in the Hodgkin's disease, non-Hodgkin's lymphomas, germinoma brain, etc. A study by Mikaelian and co-authors showed that tubulin-binding drugs cause cell cycle arrest of rapidly proliferating endothelial cells and lead to myocardial infarction [33]. Rituximab infusion is associated with the release of interleukin-6 and tumor necrosis factor-alpha. Such cytokine cascades can lead to spasm of the coronary arteries, increased thrombocyte activation, and rupture of the atherosclerotic plaque [34].

Carfilzomib and bortezomib are representatives of a group of proteasome inhibitors that block the work of proteasome-cell complexes by destroying proteins. Drugs of this group of drugs are used primarily for multiple myeloma. Cardiotoxic events include cardiomyopathy, heart failure, progressive hypertension, arrhythmias

(atrial fibrillation), and arterial and venous thromboembolism. Cardiovascular complications that occur when taking these drugs are multifactorial due to their occurrence. There is evidence of emerging endothelial dysfunction, oxidative stress of cardiomyocytes, and cardiorenal syndrome [35-37]. There are also reports of thrombotic microangiopathy when taking bortezomib and carfilzomib [38].

A retrospective study by Chen and co-authors showed that the presence of previous cardiovascular diseases (in particular, secondary insufficiency, atrial fibrillation/flutter) is associated with a high risk of adverse cardiovascular complications [39]. In a prospective study by Cornell and co-authors of 95 patients taking botezomib and carfilzomib, three cases of acute coronary syndrome were observed when taking carfilzomib, including a case of sudden cardiac death that occurred in the patient 24 hours after myocardial infarction after carfilzomib infusion [40].

Features of percutaneous coronary interventions in cancer patients.

Patients with a history of cancer should be considered a high-risk group during PCI (percutaneous coronary interventions). Taking into account the presence of possible thrombocytopenia characteristic of cancer patients, transradial access is the method of choice, since possible hemorrhagic complications at the access site are less critical and more manageable than with transfemoral access [41]. It is preferable to use introducers with a smaller diameter and hydrophilic coating to reduce injury to the target artery and reduce the risk of bleeding [42]. When using transfemoral access, it is not recommended to use devices for closing arterial access, since the risk of local infection in the access area is higher due to reduced immunity in patients of this category [43].

The use of intravascular imaging is the preferred option, which will optimize PCI (selection of the length and diameter of the coronary stent), as well as avoid stenting in some cases. A study by Varenne and co-authors demonstrated the use of optical coherence tomography, which showed the possibility of using only aspiration of thrombotic masses without further implantation of a coronary stent in certain cases [44].

The SENIOR study demonstrated successful results of using modern drug-coated stents with a short duration of double disaggregant therapy (1-3 months), superior results after implantation of holometallic stents with a similar duration of double disaggregant therapy [45]. Bifurcation stenting and overlapping stents should also be avoided if possible, to reduce the risk of thrombosis.

SCAI currently recommends aspirin monotherapy for thrombocyte number greater than 10,000, and dual disaggregant therapy including aspirin and clopidogrel for total platelet counts between 30,000 and 50,000. The minimum duration of dual disaggregant therapy is 4 weeks for holometallic stents and 6 months for drug-coated stents. P2Y12 receptor inhibitors such as prasugrel and ticagrelor are associated with a higher risk of bleeding and should be considered for thrombocyte number > 50,000. The initial dosage of unfractionated heparin should be reduced to 30-50 U / kg when the platelet count is < 50,000. If the index is > 50,000, bivalirudin and heparin can be used at the rate of 50-70 U / kg [41].

CONCLUSION

The optimal treatment of acute coronary syndrome in cancer patients undergoing treatment with various chemotherapeutic drugs currently remains poorly understood. Detection of the metabolic syndrome, including before starting a course of chemotherapy, constant monitoring and timely correction of its components (blood pressure, blood glucose, triglycerides, LDL, etc.) by specialized professionals will reduce the risk of developing cardiovascular complications. Further study of this field of cardioncology is required with randomized clinical trials using modern capabilities of intravascular imaging (optical coherence tomography, intravascular ultrasound), drug-coated coronary stents of the latest generations, as well as additional studies related to the in-depth study of the pathophysiological foundations of the metabolic syndrome and the cardiotoxic effects of chemotherapeutic agents used in everyday clinical practice.

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