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ARRHITHMIAS IN CANCER PATIENTS RECEIVING CHEMOTHERAPY

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Abstract. To date, the relationship between chemotherapy and arrhythmia has not been well studied. We have reviewed the existing literature in order to understand this issue in more detail. Arrhythmias have been reported as a side effect of many chemotherapy drugs. Anthracyclines are associated with atrial fibrillation (AF) in 2-10% of cases and rarely with ventricular tachycardia (VT)/fibrillation. Taxol and other antimicrotrubic drugs are safe from the point of view of proarrhythmic side effects and do not cause any permanent rhythm disturbances. Arrhythmias caused by 5-fluorouracil, including VT, are mainly of ischemic origin and usually occur in the context of a coronary spasm caused by this drug. Cisplatin, especially with intraperitoneal use, is associated with a very high frequency of AF (12-32%). Melphalan is associated with AF in 7-12% of cases, but apparently it does not cause VT. Interleukin-2 is associated with frequent arrhythmia, mainly with AF. We have studied the available data on arrhythmia caused by chemotherapy. Studies with the intended data collection and thorough analysis are necessary to establish a causal relationship between certain antitumor drugs and arrhythmia.

Keywords: chemotherapy, arrhythmia, atrial fibrillation, ventricular tachycardia

Introduction. Oncological diseases are a serious global problem. In the last few years, the scale and importance of the treatment of malignant diseases has increased significantly. One of the components of treatment that reduces the mortality of patients is chemotherapy, which in turn causes a number of complications, such as cardiotoxicity. The use of new anticancer drugs makes the problem of cardiotoxicity more and more urgent. Cardiotoxicity is a term that includes various pathological changes in the cardiovascular system that occur against the background of drug therapy of cancer patients.

Most often, consultations of cardiologists in cancer centers are held due to cardiac arrhythmias that occur in the postoperative period and after a course of chemotherapy. Complications after chemotherapy are associated with an extremely low therapeutic index of drugs. Many of the side effects of cytostatics can cause serious irreversible and sometimes fatal organ dysfunction. Therefore, the determination of the associated therapeutic risks based on the objective identification of potential organ toxicity is the task of the clinician.

The introduction of new anticancer drugs has led to an increase in the life expectancy of cancer patients. According to the American Cancer Society, from 1991 to 2017, the death rate from cancer decreased by 29%, including from 2016 to 2017 – by 2.2% (this is the most significant reduction in cancer mortality in one year). During the follow-up period from 2007 to 2017, the overall mortality rates

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from cancer decreased by an average of 1.5% per year [1]. The defeat of the cardiovascular system is a dangerous complication of cancer therapy and causes the cancellation of effective therapy regimens, early deaths, and a decrease in the quality of life of patients after successful recovery from cancer [2, 3].

Cardiotoxic effects can manifest themselves in the form of an asymptomatic decrease in the left ventricular ejection fraction (LVEF), acute myocarditis, pericarditis, transient heart failure, sudden cardiac death, myocardial infarction, toxic cardiomyopathy with a clinical picture of chronic heart failure, the development of rhythm and conduction disturbances, prolongation of the QT interval and ectopic heart activity recorded on an electrocardiogram (ECG) [4].

Cardiovascular side effects

As a result of the action of chemotherapeutic drugs, various types of heart damage can develop. T.M. Super, M.S. Ewer proposed to classify all cytostatics and targeted drugs according to the type of damaging effect on the cardiovascular system [5].

Type I is irreversible myocardial dysfunction due to the death of cardiomyocytes, an example of such an effect is anthracyclines. The degree of myocardial damage in this case depends on the cumulative dose.

Type II – reversible myocardiocyte dysfunction due to mitochondrial and protein damage. It is most characteristic of trastuzumab and does not depend on the cumulative dose.

However, this classification does not take into account all factors contributing to the development of cardiotoxicity. For example, trastuzumab belongs to type II, but in patients with concomitant cardiac pathology or cardiotoxicity from anthracyclines, it can contribute to the development of type I damaging effects.

As a result of the action of chemotherapeutic drugs, various types of heart damage can develop.

Heart dysfunction and heart failure

Cardiac dysfunction and heart failure (HF) are the most serious complications of chemotherapy. Frequently used chemotherapeutic drugs mainly affect the metabolism of the heart and contractile proteins, which leads to temporary contractile dysfunction, permanent damage to the myocardium, and eventually to remodeling of the heart [4, 5].

Arterial hypertension

This complication from chemotherapy is associated with the use of angiogenesis inhibitors. Hypertension can develop at any stage of treatment: complications include HF, proteinuria with renal thrombotic microangiopathy, intracerebral hemorrhages. In most patients, the condition improves when treatment with an angiogenesis inhibitor has ended, but in some cases severe hypertension persists [3, 6].

Myocardial ischemia

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Among the agents causing coronary artery spasm, pyrimidine analogues of 5-fluorouracil (5-FU) and oral analogues of capecitabine are the most common. Vasospastic angina has developed both in patients with prior coronary artery disease and in patients with normal coronary arteries, and is associated with coronary artery spasms during treatment with these drugs. Nitroglycerin and calcium channel blockers are successfully used for treatment and prevention [4-7].

Thromboembolic events

Given the fact that patients with malignant neoplasms are in a state of hypercoagulation, chemotherapy may increase the risk of venous or arterial thromboembolism. For example, the use of cisplatin was the cause of venous thromboembolism in 18% of patients. The reason for this effect is a direct endothelium-toxic effect and changes in the blood clotting system. A similar risk of arterial thromboembolism is observed when taking sunitinib, sorafenib, tamoxifen. Anticoagulant prophylaxis is recommended only for high-risk patients (hospitalized, after surgery, with multiple myeloma). Currently, low-molecular-weight heparins are being studied for the prevention of thromboembolism in cancer patients [6].

Rhythm disturbances

Arrhythmias associated with antitumor therapy are usually transient, caused by metabolic changes and resolved after the restoration of electrolyte homeostasis. The use of anthracyclines, for example, is associated with supraventricular arrhythmia and ventricular extrasystole during or immediately after administration. Taxa can cause sinus bradycardia during treatment, but it does not cause serious consequences and, as a rule, its treatment is not carried out.

Prolongation of the QT interval is associated with the use of a number of antitumor drugs and can pose a serious problem. A striking example is arsenic trioxide, which is used to treat leukemia, can prolong the QT interval in 40% of patients and increase the risk of life-threatening pirouette ventricular tachycardia (VT). The presence of concomitant diseases, including electrolyte disorders caused by diarrhea, vomiting, taking other medications (psychotropic and antiemetic agents) can additionally lead to an extension of the QT interval [4, 6].

Only in rare cases, arrhythmias are studied in a controlled manner before and after chemotherapy. On the other hand, they are usually reported as side effects in clinical trials. Cancer itself creates an arrhythmogenic environment. In a study on breast cancer, atrial fibrillation (AF) occurred in cancer patients 2 times more often than in the control group [7]. Since baseline studies reflecting the status of participants before the start of chemotherapy are often not available, it is difficult to determine whether these arrhythmias are related to the initial condition of the patient or whether this is a manifestation of side effects/toxicity of chemotherapeutic drugs. For example, in a study by C. Henninger et al. Holter monitoring was performed before and after chemotherapy by a number of agents of various classes. It was demonstrated that the proportion of patients with arrhythmias was high (64%) both

before and after chemotherapeutic treatment [8]. If the assessment of the relevant parameters of patients before treatment was not carried out, then these arrhythmias could be mistakenly associated with the adverse effects of chemotherapeutic agents.

Another difficulty is related to the fact that, as a rule, more than one chemotherapeutic agent is used in each patient. Several chemotherapeutic drugs are administered simultaneously, which makes it difficult to identify the drug agent that causes this adverse effect. For example, in the study of T.C. Tan, M. Scherrer-Crosbie, 2 out of 8 patients developed AF during treatment with an enhanced regimen of high doses of idarubicin, melphalan and cyclophosphamide, any of which could be associated with arrhythmia [9]. Similarly, in another study, AF developed in 3 out of 31 patients with malignant glioma. Patients received chemotherapy with "eight drugs in one day" (methylprednisolone, vincristine, procarbazine, hydroxyurea, cisplatin, cytosine arabinoside and imidazolcarboxamide). However, it is impossible to say which of the drugs caused the arrhythmia [10].

Drugs and their classification

Antitumor drugs are divided into: alkylating substances, antimetabolites, antibiotics, hormone agonists and antagonists (antitumor hormonal drugs and hormone antagonists), alkaloids and other herbal remedies, monoclonal antibodies, protein tyrosine kinase inhibitors, other antitumor drugs.

Anthracyclines

Anthracyclines (AC) are cytostatic antibiotics. They inhibit DNA and RNA synthesis by intercalating between DNA/RNA chain base pairs and preventing replication of rapidly growing cancer cells. Quinonoid anthracycline doxorubicin (adriamycin) is a widely used potent antitumor agent demonstrating a wide range of antitumor activity against various types of solid carcinomas, hematological malignancies and soft tissue sarcomas. Unfortunately, the clinical use of doxorubicin is associated with cumulative dose-limiting cardiac toxicity, manifested in the form of cardiomyopathy and congestive heart failure, which primarily involve mitochondrial damage. The formation of free radicals in and inside mitochondria, in particular an increase in the amount of reactive oxygen species, has long been considered a common mechanism by which doxorubicin causes serious cardiotoxicity [11].

The cardiotoxicity of AK has been well studied. Acute toxicity with transient effects developing during or immediately after the first dose manifests itself in the form of arrhythmias, pericarditis / myocarditis syndrome or acute heart failure. However, a few months after the start of treatment, cardiotoxicity most often develops, namely LV systolic dysfunction with possible arrhythmias.

The proarrhythmic effect of AK was observed in cardiomyocyte culture, where doxorubicin caused rhythm disturbances that could be prevented by beta-blockers [12]. In Purkinje fibers, adriamycin prolonged the action potential depending on the dose. The effect corresponded to a direct inhibition of the temporary incoming

current of sodium ions and/or an indirect decrease due to a decrease in the activity of sodium-calcium metabolism.

The effects of alternating current on the ECG of rats included the expansion of the QRS complex, an increase in voltage and an extension of the QT interval. Intravenous use of doxorubicin, depending on the dose, caused premature contractions of the ventricles and gastrointestinal tract in mice [13].

The frequency of ECG changes in patients treated with AK varied between 6-38.6%. They usually include nonspecific changes in ST-T and a moderate increase in supraventricular and ventricular ectopic contractions [14]. C. Henninger et al. a 3% incidence of arrhythmia was reported in the first hour after doxorubicin infusion and 24% in the first 24 hours after infusion [8]. However, in other observations, the increase in extrasystoles was insignificant.

Atrial fibrillation appears to be a fairly common complication of AK. In a study by T.C. Tan, M. ScherrerCrosbie, it was demonstrated that during the first course of doxorubicin-based chemotherapy, paroxysmal AF was registered in 16 (55.2%) patients out of 29. Pronounced prolongation of the QT interval with subsequent ventricular fibrillation (VF) was observed in 2 patients, 23 patients had repeated monomorphic VT once, causing cardiac arrest, 24 had cardiac arrest with documented VT/VF [9]. Arrhythmia was suspected but not documented in sudden death in 4 uncontrolled patients with AK. Other authors have reported sudden cardiac death as a result of VT/AF shortly after completion of AK therapy or a combination of AK+paclitaxel [14].

Thus, the relationship of the use of AK with the development of arrhythmia seems obvious. Prevention of damage to the cardiovascular system caused by anthracycline antibiotics begins with the identification of patients with a high risk of cardiotoxicity. The latter include: high total doses of anthracycline antibiotics, simultaneous use of other cardiotoxic agents, the presence of concomitant cardiac pathology (previous chemotherapy or mediastinal radiation in the anamnesis, diabetes mellitus, hypertension), female, age over 65 years [15].

Antimicrotubular agents

Antimicrotubular drugs include periwinkle alkaloids and taxanes (for example, paclitaxel and docetaxel). They block cell division by stabilizing microtubules. Paclitaxel is an extract of the rare Pacific yew. Poisoning from such extracts previously led to VT, FJ and sudden death.

Paclitaxel causes arrhythmia and bradycardia at doses approximately 10 times higher than therapeutic ones. In an isolated perfused guinea pig heart, paclitaxel caused conduction disturbances and decreased coronary blood flow, as well as systolic pressure in the LV [14]. In the hearts of frogs and rabbits, taxanes slowed down the heart rate, caused atrioventricular (AV) blockade, and then asystole. In dogs, ECG changes progressed with the expansion of the QRS and were eventually followed by VF and death [5].

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There are frequent cases of cardiovascular diseases among patients using paclitaxel. They include frequent asymptomatic sinus bradycardia (29%) and grade I AV block (25%). Later cardiac blockade and conduction disorders occur infrequently and are mostly asymptomatic [16].

In the database of the National Cancer Institute, only 4 patients out of about 3,400 experienced heart block of II and III degrees. There were also 9 cases of ventricular arrhythmias and 8 cases of atrial arrhythmias. Almost all patients with unstable VT received paclitaxel in combination with cisplatin. In general, VT and VF occurred only in 0.26% of patients, and atrial arrhythmias occurred even less frequently [17]. Therefore, for patients without a history of arrhythmia, routine cardiological monitoring is not required.

Antimetabolites

Antimetabolites provide antitumor effect by interfering with DNA synthesis. Methotrexate-related cardiotoxicity can manifest itself in the form of premature atrial contractions, ventricular extrasystole, gastrointestinal tract and sinus bradycardia [18].

5-fluorouracil

The overall frequency of cardiotoxicity of fluorouracil is mainly represented by ischemic phenomena caused by coronary vascular spasm or direct/mediated cytotoxic drugs, and varies between 1.2–18% [19]. Adverse effects on the heart are associated with ischemic manifestations, which are reflected in the form of ST segment changes with or without angina and rarely in the form of myocardial infarction, reversible myocardial ischemia, supraventricular and ventricular arrhythmias, as well as bradycardia.

Therapy with 5-fluorouracil (5-FU) was associated with prolongation of the QT interval and an increase in atrial and ventricular extrasystoles. In 2 out of 25 patients receiving 5-FU, the duration and dispersion of the P wave on the ECG increased, in 42% of patients transient asymptomatic bradycardia below 50 beats / min was observed. During treatment with 5-FU and cisplatin, 5 out of 72 patients developed arrhythmias, including 3 with AF and 2 with frequent supraventricular ectopic strokes [20].

D. Cardinale et al. patients were followed after treatment with 5-FU and cisplatin: 5 out of 76 (6.6%) patients had AF, which indicated the third most common manifestation of cardiac toxicity of this combination after chest pain and changes in the ST–T interval. They also reported frequent atrial extrasystoles, VF, and sudden cardiac death [21].

Since myocardial ischemia seems to dominate the picture of cardiac toxicity of 5-FU, many arrhythmias occur in conditions of ischemia and are more ischemic than chemotherapeutic complications, such as polymorphic ventricular extrasystoles, ventricular arrhythmias and cardiac arrest as a result of pronounced ST elevation [22]. Repolarization changes (ST segment deviation; T wave inversion) occurred in

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65%, and ST segment depression developed in 22% of patients with cardiac complications. So, patients receiving 5-FU are prone to coronary spasm, myocardial ischemia and myocardial infarction with all arrhythmias typical of this clinical condition. Arrhythmias without ischemic phenomena are extremely rare.

Capecitabine

Capecitabine is used in the treatment of breast and colon cancer. The cardiotoxicity of capecitabine and 5-FU is largely similar. Of the 153 patients treated with capecitabine and oxaliplatin, in 2 prospective studies for advanced colorectal cancer, 10 (6.5%) patients developed heart disease, 3 of whom had VF requiring defibrillation, VT, which spontaneously stopped after completion of intravenous administration of capecitabine, and 1 sudden cardiac death. The remaining patients had ischemic diseases [22].

Gemcitabine

Gemcitabine is used to treat solid tumors. The drug has a direct toxic effect on the sinus node and the AV conduction system. Cardiac arrhythmias, without further details, were reported in 12.2% of patients treated with gemcitabine, while the control group was absent [23].

Ventricular tachycardia with cardiac arrest and AF/atrial flutter (TP) were also detected in connection with gemcitabine. In 1 patient with pancreatic cancer, AF began after administration of gemcitabine in 6 cases. Episodes occurred within 18-24 hours after each infusion of the chemotherapeutic agent, despite prevention with amiodarone, which began to be carried out immediately after the second episode of AF [23].

When patients with metastatic non-small cell lung cancer received gemcitabine or gemcitabine+vinorelbin, 4 out of 49 patients had TP or AF. The combined regimen – carboplatin+paclitaxel and gemcitabine+amifostine – was associated with AF in 1 of 17 patients [24].

Cytarabine

Cytarabine is mainly used for chemotherapy of hematological malignancies. Cardiotoxicity is rare, but bradycardia may occur, which sometimes requires discontinuation of cytarabine infusion and administration of atropine [25].

Alkylating Agents

Alkylating agents include chlorambucil, cyclophosphamide, busulfan, cisplatin and melphalan. They cause DNA strands to cross-link, abnormal base pairing, or DNA strand breaks and thereby prevent cell division. They are usually used in the treatment of slow-developing cancers.

Cisplatin

Cardiotoxicity of cisplatin is more often associated with the development of rhythm disturbances – most often AF / TP and paroxysmal supraventricular tachycardia. Severe sinus bradycardia has been reported, including a patient with a

heart rate of 35 beats/min, which recurred during each of the six cycles of cisplatin therapy [25].

Intrapericardial and intrapleural administration of cisplatin in metastatic lesions led to AF in 12-32% of patients and nonparoxysmal supraventricular tachycardia in 8% of patients. The cause of all these cases is assumed to be direct irritation of the pericardium [26].

Melphalan

Atrial fibrillation is a known complication of melphalan. Among 40 patients over 60 years of age, AF after melphalan was present in 9 cases. In addition, melphalan, which was used before bone marrow transplantation, was associated with AF in 6.6–8.3% of 70 patients [27]. In a group of 36 patients after bone marrow transplantation without melphalan, AF did not occur. Echocardiography showed that all patients had structurally and functionally normal hearts, ischemia did not occur during stress testing. A study involving 17 patients over 65 years of age who received high doses of melphalan, as well as 17 younger patients (control group) who received the same treatment, showed that 2 patients in each age group developed AF. Thus, the connection of melphalan with AF is established – it occurs in a significant part of patients regardless of age [27].

Cyclophosphamide

Acute cardiotoxicity is a well-known, potentially fatal side effect of high-dose cyclophosphamide therapy. Nevertheless, arrhythmia usually develops as a result of perimiocytic inflammation and congestive heart failure, although isolated AF has also been reported. The use of high doses of cyclophosphamide (pentostatin), an adenosine deaminase inhibitor, increases the likelihood of acute cardiotoxicity and can lead to fatal arrhythmias and acute cardiomyopathy [28].

Ifosfamide is structurally similar to cyclophosphamide and may also be associated with arrhythmia. Therapy with high doses of cyclophosphamide is associated with early cardiac toxicity, usually in conditions of decreased kidney function, which manifests itself in malignant arrhythmias, for which antiarrhythmic drugs or cardioversion may be required. Arrhythmias associated with ifosfamide therapy included atrial and ventricular extrasystole, supraventricular tachycardia, AF/TP and VT. Most of these arrhythmias occurred in patients with cardiomyopathy [24].

Discussion

In clinical practice, an oncologist often has to deal with the appearance of cardiac arrhythmias and/or conduction disorders in his patient. The choice of therapeutic tactics and the need for further supportive therapy may directly depend on their etiology. Rhythm and conduction disorders in cancer patients are detected more often than in the general population of patients of the same age or with similar concomitant pathology of the cardiovascular system. The appearance of arrhythmias or heart blockades in an oncological patient is associated with electrolyte disorders

(hyperkalemia and hypocalcemia with the development of rapid tumor lysis syndrome, hypercalcemia with bone damage, hypokalemia and hypomagnesemia during infusion therapy with unbalanced solutions, etc.) or repeated pulmonary embolism. The reasons are diverse, but acute drug toxicity of antitumor drugs can also contribute to the development of rhythm and conduction disorders.

It is known that acute cardiotoxicity of antitumor drugs can be manifested by disturbances in the processes of ventricular repolarization, prolongation of the QT interval, supraventricular and ventricular arrhythmias, acute coronary syndrome, pericarditis, myocarditis and occurs up to 2 weeks after the use of chemotherapy [23].

Of particular interest is the frequency of arrhythmias associated with the direct proarrhythmogenic effect of specific antitumor drugs, especially since there are enough publications of individual observations of such effects in these drugs. However, conducting a controlled study is associated with serious methodological problems. First of all, the presence of a tumor disease (or even the patient's knowledge of its presence), apparently, in itself can be a proarrhythmogenic factor. Another obstacle to conducting a controlled study on the effect of antitumor treatment on the development of cardiac arrhythmias is the polyetiology of this disease; antitumor drugs, even with a high proarrhythmogenic potential, can help reduce the frequency of arrhythmias if they are able to influence the essential cause of their occurrence (for example, reducing the tumor mass in the mediastinum or tumor infiltration of the heart). An important factor complicating the analysis of the proarrhythmogenic effect of a particular antitumor drug is the combined nature of treatment (that is, the use of several different antitumor drugs at once) and often the simultaneous use of concomitant therapy drugs.

Atrial fibrillation is the most common type of arrhythmia in cancer patients: all other things being equal, the frequency of this arrhythmia in such patients is 3 times higher than in patients without malignant neoplasms. Chronic inflammation can play an important role in the development of AF in cancer patients, even in the absence of "traditional" risk factors: the level of one of the markers of systemic inflammation – C-reactive protein – is usually elevated both in malignant neoplasms and in patients with AF. However, the presence of chronic inflammation serves as nothing more than a predisposing factor for the development of AF in cancer patients [24].

Atrial fibrillation increases the risk of stroke by 5 times and causes the occurrence of every fifth stroke. Ischemic cerebrovascular accident in patients with AF often ends in death and, compared with strokes of other etiology, leads to the most pronounced disability, and also recurs more often. Accordingly, the risk of death in patients with AF-related stroke is 2 times higher, and treatment costs increase 1.5 times. In most patients, paroxysmal AF steadily develops into a long-lasting persistent or permanent form, which is associated with the progression of the underlying pathology [29].

Despite the fact that the data are limited, it was possible to identify the pattern of occurrence of various types of rhythm disturbances with the use of certain groups of antitumor drugs. AK, melphalan, are associated with the development of AF. It would be advisable to monitor the heart rate in patients receiving such drugs, especially with documented ECG disorders or arrhythmias that have developed against the background of a chemotherapeutic regimen.

Taxol and other antimicrotubular drugs are safe from the point of view of proarrhythmic side effects and do not cause any permanent rhythm disturbances, except for sinus bradycardia and mild conduction disorders, such as grade I AV block. Most likely, there is no need for routine monitoring of arrhythmias in such patients.

Arrhythmias caused by 5-FU, including VT, are most often of ischemic origin and usually occur in the context of a coronary spasm caused by this drug. In such cases, adequate prognosis and prevention of coronary spasms in the high-risk group undergoing chemotherapy is necessary.

Cisplatin, especially with intrapericardial administration, is associated with a very high frequency of AF, probably due to direct irritation of the pericardium and requires monitoring [23-29].

It can be concluded that the arrhythmia caused by chemotherapy exists as a phenomenon, but is poorly understood. It is necessary to conduct additional studies with data collection and their thorough analysis to establish a causal relationship between some antitumor drugs and arrhythmias. In this review, we have summarized the available data on arrhythmia after chemotherapy from the scientific literature to attract the attention of cardiologists and oncologists to this problem.

Conclusions

The introduction of new antitumor drugs has led to a decrease in mortality and an increase in the life expectancy of cancer patients. The defeat of the cardiovascular system is a dangerous complication of cancer therapy and causes the cancellation of effective therapy regimens, early deaths, and a decrease in the quality of life of patients after successful recovery from cancer. Therefore, the treatment of such a group of patients should be comprehensive and aimed at prevention and timely detection of signs of cardiotoxic damage to the cardiovascular system and the appointment of the necessary therapy for the development of complications. Modern medicine dictates a multidisciplinary approach, there is such a thing as cardioncology – a field of cardiology specializing in the detection, monitoring and treatment of cardiovascular diseases in cancer patients and/or arising as a side effect of antitumor drug therapy. Cardioncology defines extended examination and friendly observation by oncologists and cardiologists of patients with malignant diseases.

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