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IMMUNOTHERAPY AND CARDIOTOXICITY: DIAGNOSTIC AND TREATMENT STRATEGIES

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ABSTRACT

Immunotherapy of malignant neoplasms, primarily with immune checkpoint inhibitors, has transformed the landscape of oncology care over the past ten years, including in the Russian Federation.

As indications for and the number of patients receiving immuno-oncology drugs expand, the problem of cardiotoxicity, including myocarditis, pericarditis, acute coronary syndromes, arrhythmias, and heart failure, has come to the forefront.

This article summarizes data from international and Russian studies conducted in 2022–2024 on the incidence and structure of cardiotoxic complications of immunotherapy. The mechanisms of myocardial injury are discussed. Modern approaches to diagnostics and monitoring are presented, including the role of biomarkers (troponin, natriuretic peptides), imaging techniques (echocardiography, cardiac MRI), and risk stratification. Particular attention is paid to the Russian context: the rising incidence of cancer (624,835 new cases of malignant neoplasms in the Russian Federation), the expansion of the network of centers using antitumor immunotherapy (more than 135 clinics in 52 Russian cities offer these treatments), the development of cardio-oncology services, and expert documents on the prevention and treatment of cardiotoxicity.

Based on a literature review, optimal strategies for managing patients receiving immune checkpoint inhibitors are discussed, focusing on early detection of cardiotoxicity, treatment algorithms (glucocorticosteroids and other immunosuppressants), and the organization of oncologist-cardiologist collaboration.

KEYWORDS: immunotherapy, immune checkpoint inhibitors, cardiotoxicity, myocarditis, cardio-oncology, Russia, immune-mediated adverse events, diagnosis, treatment.

INTRODUCTION

Immunotherapy of malignant neoplasms is a set of systemic cancer treatment methods based not on direct cytotoxic action on tumor cells, but on modulating the antitumor immune response. Immune checkpoint inhibitors (ICIs)—monoclonal antibodies that block regulatory molecules such as CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), PD-1 (programmed death-1), and PD-L1 (programmed death-ligand 1)—play a key role in modern immuno-oncology. Blockade of these signaling pathways eliminates the physiological mechanisms of T-cell inhibition, enhancing the recognition and destruction of tumor cells [5].

The expansion of ICT use has been accompanied by the emergence of a specific group of complications referred to as immune-related adverse events (irAEs). These are based on the loss of immunological tolerance and the development of autoimmune-like inflammation in various organs: skin, intestines, liver, endocrine glands, lungs, muscles, and nervous system [8].

A specific area stands out against this background: cardio-oncological toxicity, or cardiotoxicity, which refers to structural and functional damage to the cardiovascular system caused by antitumor therapy. In immunotherapy, cardiotoxicity most often manifests as ICT-associated myocarditis, pericarditis, new or worsening arrhythmias, acute coronary syndrome, Takotsubo syndrome, and acute or chronic heart failure [3].

The term "ICT-associated myocarditis" is used to describe inflammatory myocardial damage associated with the use of PD-1/PD-L1 and/or CTLA-4 inhibitors and not explained by other obvious causes (ischemia, infection, toxic effects) [2]. The clinical picture may include symptoms of heart failure, arrhythmia, elevated cardiac biomarkers (troponin, natriuretic peptides), ECG and echocardiography changes, and, when imaging, signs of myocarditis based on cardiac MRI. In a broader sense, the group of immunotherapeutic cardiotoxicity also includes immune-mediated vasculitis of the coronary arteries, thromboembolic complications and combined lesions of the heart and skeletal muscles (myocarditis + myositis/myasthenia) [4].

In the context of oncology care in the Russian Federation, immunotherapy is gradually assuming an increasingly prominent place in tumor treatment standards, driven both by the accumulation of evidence and the expansion of the list of registered indications. This leads to an increase in the number of patients potentially susceptible to cardiotoxic complications. To

correctly select a management strategy for these patients, it is important to use a unified terminology: distinguishing between the concepts of "cardiotoxicity" (as a general umbrella term), "immune-mediated myocarditis," "immune-mediated pericarditis," and "immune-mediated arrhythmias," and specifying the severity of complications and their relationship to the immunotherapy line and regimen [6].

In the evolving practice of cardio-oncology, standardization of terminology and diagnostic criteria is of particular importance. This is necessary for the comparability of data from various clinics and registries, accurate reporting of adverse events, healthcare resource planning, and the development of coordinated national guidelines. This review article, drawing on modern terminology and conceptual frameworks in cardio-oncology, examines immunotherapy as a class of antitumor methods, cardiotoxicity as a complication of this therapy, and emerging strategies for the diagnosis and treatment of immune-mediated cardiovascular injury in the Russian and international context [1].

The introduction of immunotherapy, particularly immune checkpoint inhibitors (ICIs), has become a key development in oncology over the past decade. Drugs blocking PD-1/PD-L1 and CTLA-4 have demonstrated the ability to significantly prolong the survival of patients with previously unfavorable tumors, including non-small cell lung cancer, melanoma, renal cell carcinoma, a number of hematological malignancies, and other tumors.

In the Russian Federation, according to oncology care reviews and specialized reference resources, antitumor immunotherapy is available in at least 135 clinics in 52 cities across the country, primarily in federal and regional oncology centers and large multidisciplinary hospitals. However, official registries do not yet contain detailed information on the number of patients receiving specific classes of immuno-oncology drugs, so estimates of the scale of immunotherapy use rely on indirect data [7].

The increase in immunotherapy use is occurring against a backdrop of rising cancer incidence. In 2022, 624,835 new cases of malignant neoplasms were diagnosed in Russia (283,179 in men and 341,656 in women), which is 7.6% higher than in 2021. According to the Ministry of Health's 2023 report, the incidence of cancer detection in the country continued to grow, increasing by another 7.6%, and the cancer mortality rate increased by 1.8% compared to the previous year.

At the time of writing, only preliminary estimates are available for 2024, but they confirm a trend of increasing cancer incidence and a growing need for modern treatment methods, including immunotherapy.

At the same time, the safety of anticancer drugs is becoming increasingly important. Cardiotoxicity has long been known with anthracyclines, HER2-targeted therapy, some multikinase inhibitors, and radiation therapy. The advent of immune checkpoint inhibitors has created a new profile of cardiovascular complications: immune-mediated myocarditis, pericarditis, arrhythmias, acute coronary syndromes, and Takotsubo syndrome are described as rare but often severe complications, with mortality rates for ICT-associated myocarditis reaching 30–50%, according to several reviews.

Cardio-oncology as an independent field is also rapidly developing in Russia. Separate reviews and consensus documents by Russian experts are devoted to the prevention, early diagnosis, and treatment of cardiotoxicity associated with antitumor therapy, including immunotherapy. In 2021–2023, the Cardio-Oncology Section of the Russian Society of Cardiology published a consensus statement on these issues and is actively developing educational programs [10].

Given the rapid accumulation of data on the cardiotoxicity of immunotherapy and the need to implement standardized approaches to monitoring and treatment, this review summarizes key publications from 2022–2024, with an emphasis on Russian sources and practices.

RESEARCH MATERIALS AND METHODS

The research methods used in this study included analytical-synthetic, comparative, and content analysis of published data. Sources were searched in international (PubMed, Scopus, Web of Science) and Russian (eLIBRARY, CyberLeninka, specialized domestic journals) databases using combined keywords reflecting the topics of immunotherapy and cardiotoxicity.

Comparative analysis methods were used to compare data on the incidence of cardiotoxic complications and the specifics of their diagnosis and treatment, highlighting common trends and discrepancies between international and Russian sources. Epidemiological data for the Russian Federation (incidence of malignant neoplasms, volume of oncological care provided) were subjected to descriptive statistical analysis to assess the scale of the potential cardiotoxicity problem in the national context.

RESULTS AND DISCUSSION

According to cancer registries and analytical reviews, 624,835 new cases of malignant neoplasms were registered in the Russian Federation in 2022, with a crude incidence rate of 425.9 per 100,000 population, and a prevalence rate of 2,742.4 per 100,000 population. In 2021, there were 580,415 new cases, representing a 7.6% increase in incidence over the year.

According to the Ministry of Health's 2023 report, the cancer detection rate in Russia increased by another 7.6%, and cancer mortality by 1.8% compared to 2022. Complete data for 2024 has not been published at the time of writing, but preliminary information indicates a further increase in cancer incidence and the need for modern treatment methods. Immunotherapy, including PD-1/PD-L1 and CTLA-4 inhibitors, is registered in Russia for a number of indications and is actively used in major oncology centers. According to the aggregator RussianHospitals, more than 135 clinics in 52 Russian cities offer immunotherapy to patients, confirming the widespread adoption of this method.

Table 1. Selected indicators of oncology care in the Russian Federation and the spread of immunotherapy (2022–2024)

Indicator	2022	2023	2024 (according to the Ministry of Health report)

New cases of malignant neoplasms, absolute	580 415	624 835	+7.6% by 2022 (absolute value not specified)
"Crude" incidencerate, per 100,000	397,9	425,9	7.6% increase
Prevalence of malignant neoplasms, per 100,000	2 048,0*	2 742,4	2023 dataisbeingrevised
Number of Russian clinics offering immunotherapy	н/д	≥135	≥135 (accordingtoreferencedata)

* Based on 10-year cancer prevalence dynamics, estimated.

Figure 1 is presented to visualize the increase in cancer incidence in Russia in recent years.

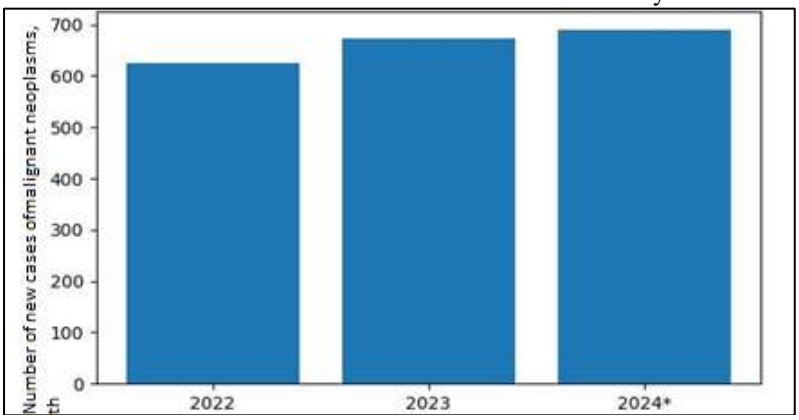

Figure 1. New cases of malignant neoplasms in Russia, 2021–2022.

The growing number of cancer patients, coupled with expanding indications for immunotherapy, inevitably leads to an increase in the number of people potentially susceptible to immune-mediated cardiotoxic complications. Consequently, the issue of immunotherapy cardiotoxicity is acquiring not only clinical but also organizational and public health significance. Cardiotoxicity of anticancer therapy is traditionally associated with anthracyclines, HER2-targeted therapy, and mediastinal radiation therapy; their contribution to the development of chronic heart failure and coronary artery disease has been well documented in numerous studies and reviews.

The advent of immune checkpoint inhibitors has expanded the spectrum of cardiotoxic phenotypes. According to international reviews and meta-analyses, ICT-associated myocarditis is relatively rare (approximately 0.3–1% of patients receiving ICT), but has a high mortality rate (30–50%) [11]. Other forms of cardiotoxicity include pericarditis, acute coronary syndrome, arrhythmia, takotsubo syndrome, progressive left ventricular dysfunction, and heart failure.

Russian review of ICT-associated myocarditis emphasizes that most cases develop in the first 3–4 cycles of treatment, more often with combination immunotherapy (CTLA-4 + PD-1/PD-L1), and are often accompanied by damage to other organs (myositis, myasthenia gravis, multiorgan irAEs) [9].

Table 2. Estimated frequency of clinically significant cardiotoxicity with various types of antitumor therapy

Type of therapy	**Maincardiotoxiceffects**	**Estimated incidence of clinically significant cardiotoxicity***
Anthracyclines	Left ventricular systolic dysfunction, CHF	5–9% (dose-dependent, higher at cumulative doses >300 mg/m²)
HER2-targeted therapy (trastuzumab, etc.)	Reversible left ventricular dysfunction, CHF	2–4% with monotherapy, higher in combination with anthracyclines
ICT (PD-1/PD-L1, CTLA-4) – myocarditis	Immune-mediated myocarditis, severe heart failure, arrhythmias	0.3–1% ofpatients, mortality 30–50%
ICT – othercardiotoxicity	Pericarditis, acute coronary syndrome, Takotsubo syndrome, arrhythmias	~1–2% (according to individual registries and case series)

*Ranges are based on data from international reviews; actual incidence rates may vary in specific centers.

A summary figure is provided to compare the cardiotoxicity profiles of different drug classes.

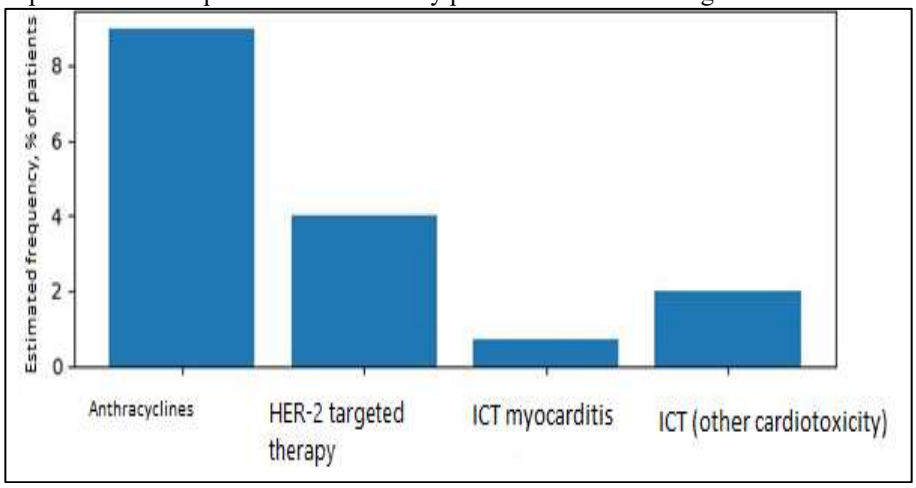

Figure 2. Estimated Frequency of Clinically Significant Cardiotoxicity with Various Types of Antitumor Therapy

The diagram in Figure 2 shows that the frequency of cardiotoxicity with ICT is significantly lower than with anthracycline therapy. However, its clinical significance is determined by the severity and high mortality rate of myocarditis, as well as the fact that lesions can occur in relatively young patients with an initially intact cardiovascular system.

Current guidelines and expert documents in cardio-oncology recommend stratifying all patients planned for immunotherapy based on their baseline cardiovascular risk, as well as the expected intensity and duration of treatment [12]. The basic diagnostic algorithm can be summarized in several key elements [13]:

- initial assessment (anamnesis, ECG, echocardiography, troponin, natriuretic peptides, cardiac MRI if necessary);
- regular monitoring of symptoms and biomarkers during the first 3–4 cycles of ICT therapy;
- A low threshold for in-depth cardiac examination in the presence of dyspnea, chest pain, syncope, new troponin elevation, or arrhythmia.

Russian guidelines on myocarditis and cardiotoxicity emphasize the role of cardiac MRI and, if necessary, endomyocardial biopsy in confirming the diagnosis, especially in cases of atypical presentation or mixed myocardial disease [6].

Table 3. Key elements of diagnosis and monitoring of cardiotoxicity during immunotherapy

Stage	Recommended measures	Comments
Beforestartingimmunotherapy	History, assessment of cardiovascular risk factors; ECG; echocardiography; troponin and BNP/NT-proBNP; cardiac MRI if necessary	Forming a "baseline" for comparing dynamics; especially important in patients with high CV risk.
During the first 3–4 cycles of ICT	Examination and interview before each cycle; ECG and troponin in intermediate- and high-risk patients; urgent echocardiography and/or MRI if symptoms are present	Most cases of myocarditis develop in the first months of treatment; more frequent monitoring is recommended.
Ifsuspicioussymptomsappear	Immediate assessment of troponin, ECG, and echocardiography; consideration of cardiac MRI; endomyocardial biopsy in severe cases	Early diagnosis is critical for prognosis; if ICT myocarditis is suspected, ICT therapy should be suspended.
Furthermonitoring	Long-term monitoring of LV function, HF symptoms, and arrhythmias; periodic repetition of echocardiography and biomarkers	Necessary due to potential late complications and recurrence of cardiotoxicity.

From a practical perspective, a key challenge for Russian centers is integrating these algorithms into existing patient workflows, ensuring access to laboratory diagnostics (especially high-sensitivity troponins) and imaging modalities (echocardiography, cardiac MRI) in oncology facilities, and establishing sustainable channels of interaction with cardiology departments [1].

Treatment of ICT-associated myocarditis and other serious forms of cardiotoxicity is based on the early initiation of immunosuppressive therapy, primarily systemic glucocorticosteroids. International and national guidelines recommend

initiating therapy with high doses of prednisolone (1–2 mg/kg/day) or equivalent, and in severe cases, intravenous pulse therapy with methylprednisolone, followed by transition to an oral regimen and gradual dose reduction.
If the response to glucocorticosteroids is insufficient, the use of other immunosuppressants (calcineurin inhibitors, mycophenolate mofetil, anti-TNF agents, etc.) is considered, although the evidence base for these approaches is limited and based primarily on case series and observational studies.
For ICT-associated myocarditis of most severity, discontinuation of this line of immunotherapy and discussion of alternative antitumor options are recommended. In some cases with a mild course and complete recovery of myocardial function, reinitiation of therapy under the supervision of a cardio-oncologist is possible; however, general recommendations are quite conservative [3].
For other types of cardiotoxicity (pericarditis, arrhythmias, acute heart failure, Takotsubo syndrome), treatment approaches combine standard cardiac therapy (LMWH/anticoagulants, antiarrhythmics, diuretics, inotropes, and interventions if necessary) with immunosuppression if immune-mediated damage is confirmed or suspected.
An important part of the strategy is the organization of cardio-oncology teams, including oncologists, cardiologists, imaging specialists, and, if necessary, rheumatologists and immunologists. The 2021–2023 report of the RKO Cardio-Oncology Section notes the active formation of such teams in federal centers and major regional institutions, which significantly improves patient routing and decision-making speed in cases of suspected cardiotoxicity.

CONCLUSION

Immunotherapy for malignancies, particularly immune checkpoint inhibitors, has become an integral part of oncology practice in the Russian Federation, as evidenced by the growing number of centers using these drugs and the overall increase in cancer incidence in 2022–2024. Against this backdrop, the problem of cardiotoxicity has become a major concern: although the incidence of ICT-associated myocarditis and other cardiac complications is relatively low, their severity and potentially high mortality require special attention.
A review of data from 2022–2024 shows that understanding of the mechanisms of cardiotoxicity of ICT and other immunotherapeutic approaches has advanced significantly; however, most recommendations still rely on retrospective case series and expert opinions. Nevertheless, several key elements of a modern strategy can be identified: mandatory initial cardiovascular risk stratification, regular monitoring of biomarkers and ECG during the critical period of the first cycles of therapy, a low threshold for in-depth cardiac diagnostics, and early initiation of immunosuppression if myocarditis is suspected.
For Russian practice, the development of cardio-oncology services, the integration of diagnostic algorithms and treatment for immunotherapy cardiotoxicity into local cancer center protocols, and the availability of high-tech imaging methods (cardiac MRI) and laboratory tests (high-sensitivity troponin, natriuretic peptides) are of particular importance. A key objective in the coming years is the creation of unified national registries of cardiotoxicity of anticancer therapy, including immunotherapy, which will allow for more accurate data on the incidence, structure, and outcomes of cardiac complications in the Russian conditions.

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