CARDIOTOXICITY DURING AND AFTER ONCOLOGICAL TREATMENT
− ROLE OF CARDIO-MAGNETIC RESONANCE

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Abstract.
The purpose of this review article is to inform practicing cardiologists about the manifestations of cardiotoxicity in patients on or after antitumor therapy and about the potential of cardiac magnetic resonance imaging (CMR) in the diagnosis and follow-up of these patients. The definitions and classification of cardiotoxicity associated with antitumor treatment, the mechanisms of cardiac and vascular damage of some of the important groups of antitumor drugs, and the potential CMR findings are reviewed. The main clinical situations related to manifestations of cardiotoxicity in which CMR has or is expected to have a leading role are outlined.

Key words: cardiotoxicity, antitumor therapy, cardiac magnetic resonance imaging

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Introduction
Over the past two decades, we have witnessed remarkable advances in medical oncology. The introduction into routine clinical practice of new groups of drugs such as immune checkpoint inhibitors (ICIs), proteasome inhibitors, 2nd and 3rd generation tyrosine kinase inhibitors, endothelial growth
inhibitors, inhibitors on the endotelinia rasteghen factor and HER2平米lelne therapy avedo药材 to significa ently doobravanie on the prkevivemostta on the patienten със солидни и хематологичнi neoplasm. On the other hand, a significant proportion of these new therapies exhibit cardiotoxicity both in the course of clinical trials and in daily practice. This, against the background of the increasing frequency of cardiovascular and oncological diseases and together with the known cardiotoxicity of some of the already established antineoplastic drugs (for example, anthracyclines, tubulin inhibitors, some antimetabolites), leads to an increasing frequency of cardiovascular complications in the course of oncological treatment. There is an urgent need for early diagnosis and treatment of these potentially fatal complications, as well as a balanced approach to their prevention – an approach that maximizes the oncological benefits of treatment while minimizing cardiac risk. The relatively new interdisciplinary field in medicine – cardio-oncology – is tasked with modernizing existing and validating new algorithms for the follow-up of patients receiving potentially cardiotoxic treatment, taking into account cardiotoxicity events associated with new therapeutic strategies in oncology.

Imaging methods, together with cardiac biomarkers, are the basis of the diagnosis of toxic damage to the heart in the course of oncological treatment. 2D and 3D echocardiography, despite its undoubted advantages, also have significant limitations, especially when identifying and characterizing tissue changes in the myocardium. Given the endothelial toxicity of a number of antitumor drugs and the possibility of developing pulmonary hypertension during or after oncological treatment, it is important to monitor the function of the right heart, which is difficult with echocardiography only. Cardiac magnetic resonance imaging (CMR) with its multiparametric tissue contrast and proven capabilities in the assessment of the right heart is a valuable addition to the imaging specialist's arsenal in the initial evaluation and follow-up of cardiotoxicity, related to antineoplastic therapies and in a number of cases may be alternative to echocardiography. Moreover, the possibility of assessing microstructural changes in the myocardium using so-called "new" CMR techniques (T1, T2 and T1ρ mapping) and discrete changes in myocardial contractility using strain-CMR techniques (such as "feature tracking") promises to enrich our understanding of how antineoplastic treatment damages the myocardium and eventually of the myocardial physiology. The
aim of this review is to revisit the main groups of antitumor drugs and their mechanism of action, including cardiotoxicity, and try to outline the areas in which CMR brings or could bring “added value” to cardio-oncology.

**Definition and classification**

According to the position statement on behalf of the European Society of Cardiology (ESC) from 2016, a reduction in the ejection fraction (EF) below 50% or a reduction of the EF of more than 10% compared to the baseline examination is defined as cancer therapy-related cardiac dysfunction (CTRCD) [1, 2]. A number of studies have shown that change in global longitudinal strain (GLS) has a better prognostic value as a marker of left ventricular dysfunction compared to EF in patients both with and without oncological pathology [3, 4]. It should also be kept in mind that cardiotoxicity with some anticancer drugs can occur without a reduction in EF. For example, in 38% of patients with cardiotoxicity during ICI treatment, EF can be preserved for a long period of time [5]. Thus, GLS is also included in the definition of CTRCD, with the ESC defining a reduction of 15% from the baseline as indicative of cardiotoxicity. Of note, there is some variation in the criteria for cardiotoxicity in different guidelines and positions and in the criteria used in different studies. An attempt to harmonize criteria and definitions has been made in the current guidelines on cardio-oncology, published by the European Society of Cardiology in collaboration with the European Hematology Association (EHA), the European Society of Therapeutic Radiology and Oncology (ESTRO) and the International Society of Cardio-oncology (IC-OS) [6]. The criteria of some groups and organizations are listed in Table 1.

Recently, it has been questioned whether the widely used classification of CTRCD as type I (“myocardial injury”) and type II (“myocardial dysfunction”) makes sense [7, 8]. Proposed by Ewer in 2005, this classification aims to distinguish the now well-known, irreversible, and dose-dependent cardiotoxicity associated with anthracycline treatment (“myocardial injury”) from the relatively newly identified cardiotoxicity associated with HER-2 targeted therapies, primarily with trastuzumab [9]. The latter was initially thought to be rarer, dose-independent and reversible, with systolic function returning to baseline after discontinuation of treatment (“myocardial dysfunction”). However, subsequently accumulated data indicate that, although induced by a undoubtedly different mechanism, trastuzumab-induced car-
Cardiotoxicity is neither rare nor reversible in all cases [10, 11, 12]. With the expansion of the spectrum of anti-tumor drugs in the arsenal of medical oncology, CTRCD with a different clinic and mechanism will be observed. These include ICI-induced autoimmune myocarditis or vascular dysfunction caused by inhibitors of vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors, to name a few. There is no doubt that a deep revision of the classification will be necessary in the near future. In fact, the first steps in this direction have already been taken. For example, the European Society of Cardiology considers ICI-induced autoimmune myocarditis as a separate category of cardiotoxicity in its current guidelines [6].

<table>
<thead>
<tr>
<th>Граннична стойност на ФИ</th>
<th>ЕСК</th>
<th>EACVI/ASE</th>
<th>ESMO/CREC</th>
<th>ASCO</th>
<th>CTCAE</th>
<th>FDA</th>
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<tbody>
<tr>
<td>EF absolute reduction</td>
<td></td>
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<tr>
<td>&gt; 10% compared to baseline value</td>
<td></td>
<td>&gt; 10% from baseline</td>
<td>&gt; 5% to below 55% with symptoms and ≥ 10% to below 55% without symptoms</td>
<td>Grade 2: EF at rest 40-50%; 10-19% decrease compared to baseline value</td>
<td>3rd grade: EF at rest 20-39%; &gt; 20% decrease from baseline</td>
<td>4th degree: EF at rest &lt; 20%</td>
</tr>
</tbody>
</table>

| ГЛС | GLS | Намаление > 15% спрямо изходната стойност | Намаление > 15% спрямо изходната стойност | Намаление > 15% спрямо изходната стойност |
|     |     | Reduction > 15% compared to baseline value | Reduction > 15% compared to baseline value | Reduction > 15% compared to baseline value |

Съкрашения: // Abbreviations: ASCO – American Society of Clinical Oncology; ASE – American Society of Echocardiography; CREC – Cardiac Review and Evaluation Committee; CTCAE – Common Terminology Criteria for Adverse Events (US Departments of Health and Human Services); EACVI – European Association of Cardiovascular Imaging; ESC – European Society of Cardiology; ESMO – European Society of Medical Oncology; FDA – US Food and Drug Administration

Таблица 1. Разлики в използваните критерии за кардиотоксичност [1]

Table 1. Differences in cardiotoxicity criteria among various groups and institutions [1]
**ОЦЕНКА НА РИСКА ОТ КАРДИОТОКСИЧНОСТ**

Ред фактори влияят на вероятността за поява на СДСЛП [1] (табл. 2). От страна на пациента и с най-голяма тежест са на първо място възрастта и съществуващите сърдечно-съдови рискови фактори и заболявания (заседнал начин на живот, хипертония, инсулинова резистентност, диследемия, затъмяване, тютюнопушене, диабет, коронарна или периферна артериална болест, сърдечна недостатъчност). Пациентите с понижена (50-54%) ФИ преди началото на лечението, както и тези с анамнеза за по-висок риск от кардиотоксичност, в сравнение с други.

Факторите, свързани с терапията, имат относително по-малка тежест, като при пациенти на монотерапия рискът е най-низък. Рискът от кардиотоксичност се повишава при лечение с комбинация от препарации, особено при едновремено прилагане, както и при комбинирана лъче-химиотерапия. Някои медикаменти, особено при едновременно прилагане, както и при комбинирана лъче-химиотерапия, високодозови антрациклини, VEGF рецепторни и тирозинкиназни инхибитори, са свързани с по-висок риск от кардиотоксичност, в сравнение с други.

**Assessment of the risk of cardiotoxicity**

A number of factors influence the probability of the occurrence of CTRCD [1] (Table 2). On the patient side, age and concomitant cardiovascular risk factors and diseases (sedentary lifestyle, hypertension, insulin resistance, dyslipidemia, obesity, smoking, diabetes, coronary or peripheral artery disease, heart failure) are most important. Patients with a reduced (50-54%) EF before the initialization of the therapy, as well as those with a history of prior antitumor treatment, are also at increased risk [13, 14]. Factors related to therapy have relatively less weight, with monotherapy patients being exposed to the lowest risk. The risk of cardiotoxicity increases with treatment with a combination of drugs, especially with simultaneous administration, as well as with combined radiation-chemotherapy. Certain medications, for example VEGF-related tyrosine kinase inhibitors, are associated with a higher risk of cardiotoxicity per se, compared to others.

### Table 2. Risk factors for the occurrence of cardiotoxicity during antitumor treatment [1]

<table>
<thead>
<tr>
<th>Фактори, свързани с терапията</th>
<th>Фактори, свързани с пациента</th>
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<tbody>
<tr>
<td><strong>Нисък риск</strong></td>
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<tr>
<td>Ниска доза антрациклини (doxorubicin &lt; 200 mg/m², epirubicin &lt; 300 mg/m²), липозомни формули</td>
<td></td>
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<tr>
<td>Trastuzumab без антрациклини</td>
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<tr>
<td><strong>Среден риск</strong></td>
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<tr>
<td>Средна доза антрациклини (doxorubicin 200-400 mg/m², epirubicin 300-600 mg/m²)</td>
<td></td>
</tr>
<tr>
<td>Trastuzumab без антрациклини</td>
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<tr>
<td>VEGF тирозинкиназни инхибитори</td>
<td></td>
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<tr>
<td>Второ и трето поколение Bcr-Abl тирозинкиназни инхибитори</td>
<td></td>
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<tr>
<td>Протеазомни инхибитори</td>
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<tr>
<td>Комбинация от инхибитори на имунната контролна точка</td>
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<tr>
<td><strong>Висок риск</strong></td>
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<tr>
<td>Едновременно прилагане на Trastuzumab и антрациклини</td>
<td></td>
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<tr>
<td>Висока доза антрациклини (doxorubicin &gt; 400 mg/m², epirubicin &gt; 600 mg/m²)</td>
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</tr>
<tr>
<td>Средна доза антрациклини, комбинирани с облучване на левия хемиторакс</td>
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<tr>
<td>Повишени тропонии след лечение с антрациклини, преди HER2 таргетна терапия</td>
<td></td>
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<tr>
<td>Високодозови радиотерапия при включване на сърцето в полето на облучване</td>
<td></td>
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<tr>
<td>VEGF тирозинкиназни инхибитори след предходно лечение с антрациклини</td>
<td></td>
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</table>

**Patient-related factors**

| **Възрастът** | >18 и <50 години |
| **Възрастът** | >50-64 години |
| **Заболевания** | >1-2 сърдечно-съдови рискови фактори (хипертония, диследемия, затъмяване, тютюнопушене и т.н.) |
| **Заболевания** | >2 сърдечно-съдови рискови фактори |
| **Заболевания** | >2 кардиоваскуларни рискови фактори |

**Concomitant administration of Trastuzumab and anthracyclines**

| **Medium dose anthracyclines (doxorubicin 200-400 mg/m², epirubicin 300-600 mg/m²)** |
| **Trastuzumab after anthracyclines** |
| **VEGF tyrosine kinase inhibitors** |
| **Second and third generation Bcr-Abl tyrosine kinase inhibitors** |
| **Proteasome inhibitors** |
| **Combination of immune checkpoint inhibitors** |

**High risk**

| **Concomitant administration of Trastuzumab and anthracyclines** |
| **Medium dose anthracyclines combined with radiation to left hemithorax** |
| **Elevated troponin after anthracycline treatment, before HER2-targeted therapy** |
| **High-dose (≥30 Gy) radiotherapy when involving the heart in the field of irradiation** |

| **AGE 50-64 years** |
| **1-2 cardiovascular risk factors (hypertension, dyslipidemia, obesity, smoking, etc.)** |

| **AGE ≥65 years** |
| **>2 cardiovascular risk factors** |
| **Diabetes** |
| **Known cardiovascular disease (coronary artery disease, peripheral artery disease, cardiomyopathy, severe valvular disease, heart failure)** |
| **Reduced or subthreshold EF before initiation of treatment** |

**Prior treatment for carcinoma**
Antitumor Drugs, Suspected Mechanisms of Cardiotoxicity, MRI Findings

Anthracyclines

Anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin, etc.) are considered one of the most effective antitumor drugs and are used as first-line drugs in many solid and diffuse neoplasias. Anthracyclines intercalate between DNA bases, thereby inhibiting topoisomerase IIβ, preventing religation of the double helix, and leading to apoptosis; the anthraquinone component of their molecule in the presence of reductive enzymes generates free radicals that further damage DNA [15, 16].

Although anthracycline-related cardiotoxicity is the best studied, its detailed mechanisms are still not fully understood. Oxidative stress is thought to play a major role in cardiomyocyte damage; inhibition of topoisomerase IIβ, disruption of iron metabolism, and suppression of GATA4 expression also contribute [16, 17]. Recently, attention has also been paid to the damage to other cellular components of the heart during anthracycline therapy - primarily to the cardiomyocyte precursor population, but also to fibroblasts and endothelial cells.

The most frequently observed form of CTRCD in treatment with anthracyclines is early (up to one year after the start of therapy) or late (more than one year after the start of therapy), dose-dependent chronic cardiotoxicity [17] with a progressive, resistant to treatment dilated cardiomyopathy. In addition to reduced EF and reduced strain [16, 18], CMR demonstrates a progressive reduction in myocardial mass [16, 19, 20] that often precedes impairment of systolic function and is independently associated with worsening of heart failure and cardiac death [20]. Myocardial fibrosis that develops during the course of the disease is demonstrated by diffuse late enhancement in the myocardium [20], and native and post contrast T1 mapping show prolongation of T1 relaxation and an increase in extracellular volume [16, 21]. Rarely, acute cardiotoxicity with a reduction in myocardial contractility is observed, which occurs in the first two weeks of treatment, sometimes even after a single dose. The mechanism of myocardial injury in these patients remains unclear but possibly resembles stress-induced cardiomyopathy. In some of these patients, CMR demonstrated similar segmental disturbances in kinetics. Myocardial damage in this form of cardiotoxicity is usually reversible.
**HER2 Targeted Therapies**

HER2 receptor and the tyrosine kinase, bound to it activate multiple signaling chains in the cell; interestingly, at present no ligand for the receptor has been identified. Most of these chains suppress apoptosis, so blocking them has a pro-apoptotic effect. Blocking can occur at the receptor domain level or at the enzyme level; monoclonal antibodies (trastuzumab, pertuzumab) are used to block the receptor, and small molecules (e.g., lapatinib) to inhibit tyrosine kinase activity [15]. HER2 overexpression is observed in multiple neoplasms and its targeting is adjuvant/neoadjuvant, first-line or subsequent therapy in HER2-positive breast cancer, in gastric cancer, in lung adenocarcinoma, to name a few.

The cardiotoxicity of HER2-targeted therapies, primarily trastuzumab, is also well reported. The incidence of CTRCD with this treatment ranges from 4.0 to 18.6% for reduced left ventricular EF and from 0.4 to 4.1% for severe heart failure, when used in combination with anthracyclines. Cardiotoxicity with trastuzumab alone is significantly less frequent, with rates of decreased left ventricular systolic function and severe heart failure of 3.2 and 0.5%, respectively. It is believed that the cardiotoxicity of HER2-targeted therapies is not due to direct ultrastructural damage to cardiomyocytes, but to the exclusion of the cytoprotective cascades that are activated by the HER2-receptor [22]. This makes cardiomyocytes vulnerable to the toxicity of other drugs (eg, anthracyclines) or to increased tension loading. This hypothesis is consistent with the observations regarding the incidence of CTRCD with HER2-targeted therapies as monotherapy and in combination with other drugs, as well as with the observations regarding the higher incidence of cardiotoxicity of these drugs in patients with preexisting cardiovascular disease [13, 14].

According to initial observations, clinical manifestations of cardiotoxicity with treatment with trastuzumab, pertuzumab, or lapatinib – from asymptomatic reduction in left ventricular EF to severe heart failure – occur early and are reversible, resolving after discontinuation of treatment [14, 16, 23]. Along with the reduction in EF, MRI in these patients showed reduced longitudinal and circumferential strain. Jordan et al noted a reduction in circular strain assessed by CMR three months after initiation of antitumor therapy [24]. Of note, their prospective study (101 patients) shows a strong association of strain reduction with preload reduction (reduced end-diastolic volume) compared to baseline values. The authors...
tyrosine kinase inhibitors (TKIs)

Inhibitors of receptors for vascular endothelial growth factor (VEGF) and associated tyrosine kinases – inhibitors of angiogenesis

VEGF (VERF-A, VERF-B, VERF-C, VERF-D and PIGF) are a group of homodimers-glycoproteins, secreted by various cells in the human body, including tumor cells, and are ligands for a family of receptor-dependent tyrosine kinases (VEGF-receptors) [27]. Activation of the receptors triggers biochemical cascades that stimulate proliferation and migration, suppress endothelial cell apoptosis and increase vessel permeability (VEGFR2) or can, depending on the conditions, suppress or stimulate angiogenesis (VEGFR1 and VEGFR3). Blockade of these metabolic circuits leads to suppression of neoangiogenesis in tumors, ischemia and, ultimately, cell death. As with HER2, inhibition can occur both at the ligand and receptor level (monoclonal antibodies and pseudoreceptors) and at the level of tyrosine kinase activity (small molecules) [15]. A number of drugs are currently approved (e.g., anti-VEGF antibody, anti-receptor antibody bevacizumab, receptor-trap aflibercept, and the tyrosine kinase activity inhibitors ramucirumab, sorafenib, sunitinib, vatalanib and others) and are used as first- and subsequent-line therapy in carcinomas of the gastrointestinal tract,
The mechanisms of cardiotoxicity associated with VEGF-TKIs are diverse. Blockade of the VEGF-related metabolic cascade is thought to suppress myocardial contractility due to inhibition of phosphorylase C, linked along the metabolic chain. Another mechanism is cardiomyocyte apoptosis due to "collateral" inhibition of other kinases. Damage to coronary arteries and myocardial microcirculation due to vasospasm, in situ thrombosis, acceleration of atherosclerosis and rarefaction of capillaries is also of great importance, as is damage to peripheral and pulmonary vessels with arterial and pulmonary hypertension.

The incidence of CTRCD in treatment with angiogenesis inhibitors remains unclear. In a meta-analysis that included more than 10,000 patients, Ghatalia and collaborators found subclinical left ventricular systolic dysfunction in 2.4% of patients and symptomatic heart failure in 1.2%. However, the results of the included 21 studies varied widely, with some showing cardiotoxicity in up to 19% of cases [28]. Another large meta-analysis (72 studies) showed an increased risk of myocardial infarction with VEGF-TKI treatment, up to 3.54 times higher than in the control group, though the absolute incidence remains low [29]. A more commonly observed side effect is arterial and pulmonary hypertension, with new onset or worsening of already diagnosed hypertension occurring in up to 80% of cases [29]. VEGF-TKI-related CTRCD are believed to occur early in the course of treatment, often during the first cycle, and are reversible [30].

In patients treated with angiogenesis inhibitors, along with the reduction of EF, CMR can show intriguing tissue changes in the myocardium. A recent study observed diffuse tissue hypoperfusion; according to the authors, resting myocardial blood flow decreased by 18% from the baseline, while stress-perfusion blood flow (adenosine) remained unchanged. Another interesting observation in this study was the decrease in T1 relaxation time and extracellular volume compared with baseline values [31]. This is in agreement with the results of endomyocardial biopsy in patients with CTRCD treated with sunitinib, published in an earlier study; they have myocardial hypertrophy, but no edema or fibrosis [32]. The capabilities of CMR in the evaluation of the right ventricle determine its leading role in the initial evaluation and follow-up of VEGF-TKI induced pulmonary hypertension [33].
Mechanisms of cardiotoxicity with Bcr-Ab1-TKIs are similar to those with VEGF-TKIs. Off-target inhibition of other kinases (eg, AKT and ERK) and their associated anti-apoptotic signaling chains leads to cardiomyocyte apoptosis [35, 36]. A similar mechanism also explains the observed vascular toxicity, and here an increased expression of proatherogenic surface adhesive receptors is also involved [37, 38]. It is believed that third-generation Bcr-Ab1-TKIs (ponatinib) directly suppress myocardial contractility [34, 38].

The frequency of CTRCD during treatment with Bcr-Ab1-TKI varies by drug, being highest with ponatinib. During the 5-year follow-up of patients from the PACE study (phase 2), the cumulative incidence of arterial occlusion episodes with ponatinib treatment was 26%; 12% of patients had coronary artery occlusion with subsequent myocardial infarction and, occasionally, heart failure [35, 39, 40]. In addition, at least 25% of patients developed arterial hypertension or experienced worsening of existing hypertension. This led to early termination of the follow-up (phase 3) study (EPIC) [41].
При пациенти на лечение Bcr-Abl1-TKI КМРТ идентифицира миокардния инфаркт и демонстрира развитието на постисхемична дилатативна кардиомиопатия. Порядко се наблюдава неисхемична дилатативна кардиомиопатия, свързана с апоптоза на кардиомиоцитите. При тези пациенти Т1 картирането преди и след апликация на контрастна материя демонстрира нарастване на обема на интерстициалното пространство. Често усложнение е перикардиалната излив, понякога хеморагичен, който може да заплашва с тампонада и да изисква перикардиоценеза [42].

**Инхибитори на имунната контролна точка**

Ефектът на инхибиторите на имунната контролната точка (ИКТИ) се основава на блокиране на по-върхностните рецептори на Т-лимфоцитите, които потискат имунния отговор, както и на техните лиганди. Това са например цитотоксичният, асоцииран с Т-лимфоцитите, протеин-4 (CTLA-4) и протеинът на програмираната клетъчна смърт 1 (PD-1) и съответният лиганд, който се експресира от туморните клетки (PD-L1) и представлява важен механизъм за имунна "мимикрия" на карцинома. Блокирането на тези лифоцитоподобни рецептори и на лиганда им води до отключване на Т-медииран имунен отговор срещу неопластичните клетки. За целта се използват моноклонални антитела – ipilimumab срещу CTLA-4, nivolumab и pembrolizumab срещу PD-1 и atezolizumab, avelumab и durvalumab срещу PD-L1 [5]. ИКТИ се използват в адювантен план или за лечение от първа или последваща линия при метастатичен меланом и ред други тумори, най-вече адвансирали (бъбречноклетъчен карцином, уротелен карцином, недребноклетъчен бъбречен карцином и т.н.).

Кардиомиоцитите, както и останалите клетки в човешкото тяло, експресират PD-L1, което обуславя и кардиотоксичността на ИКТИ. Наред с директната Т-медиирана цитотоксичност възможен механизъм е блокирането на цитотоксични метаболитни каскади, свързани PD-L1, особено при предварително увреждане на кардиомиоцитите. В подкрепа на тази хипотеза е наблюдаваната сърцекспесия на PD-L1 лиганда при миокардна увреда (исхемична или неисхемична), както и при увеличено обемно или тензизно обременяване на миокарда. При мнозинството пациенти на лечение с ИКТИ се наблюдава системно възпаление, с повишаване на нивата на фактора на туморна некроза α. Тези екстра-кардиални ефекти също върху допират за увеличаване на миокардния стрес [5]. В-медиираната автомимнона реакция към експресираните от кардиомиоцитите лиганди е рядка [5, 43].

Честотата на СДСПЛ при лечение с ИКТИ остава неясна. Първоначалните данни от клиничните проучвания идентифицират относително ограничен брой – под 0,01% от 20 594 пациенти – случаи с инхибитори на имунната контролна точка.

In patients treated with Bcr-Abl1-TKI, CMR will identify myocardial infarction and demonstrate the development of post-ischemic dilated cardiomyopathy. Less commonly, non-ischemic dilated cardiomyopathy associated with cardiomyocyte apoptosis will be seen. In these patients, T1 imaging before and after contrast material administration will demonstrate an increase in the volume of the interstitial space. A frequent complication is pericardial effusion, sometimes hemorrhagic, which may threaten tamponade and require pericardiocentesis [42].

**Immune checkpoint inhibitors**

The effect of immune checkpoint inhibitors (ICIs) is based on blocking the surface receptors of T-lymphocytes, which suppress the immune response, as well as their ligands. These are, for example, the cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and the programmed cell death protein-1 (PD-1) and the corresponding ligand that is expressed by tumor cells (PD-L1). The latter represents an important mechanism for immune "mimicry" of carcinoma. Blocking these lymphocyte receptors and their ligands leads to the unlocking of a T-mediated immune response against the neoplastic cells. To achieve this, monoclonal antibodies are used – ipilimumab against CTLA-4, nivolumab and pembrolizumab against PD-1 and atezolizumab, avelumab and durvalumab against PD-L1 [5]. ICIs are used as adjuvant, first-line and subsequent treatment in metastatic melanoma and in a number of other tumors, especially advanced ones (renal cell carcinoma, urothelial carcinoma, non-small cell lung carcinoma, etc.).

Cardiomyocytes, like the rest of the cells in the human body, express PD-L1, and this is the main cause of the cardiotoxicity of ICI. Along with direct T-mediated cytotoxicity, a possible mechanism is the blockade of cytotoxic T-lymphocyte metabolic cascades associated with PD-L1, especially in the setting of a pre-existing cardiomyocyte injury. In support of this hypothesis is the observed overexpression of the PD-L1 ligand in myocardial damage (ischemic or non-ischemic) and in increased volume or tension load of the myocardium. In the majority of patients treated with ICI, systemic inflammation was observed, with increased levels of tumor necrosis factor α. These extracardiac effects also likely contribute to increased myocardial stress [5]. B-mediated autoimmune response to ligands expressed by cardiomyocytes is rare [5, 43].

The incidence of CTRCD with ICI treatment remains unclear. Initial data from clinical trials identified a relatively limited number – less than 0.01% of 20,594 patients – of cases with fulminant myo-
fulminant myocarditis [5, 44]. Inbreakeunently small, niskata честота, fulminant myocarditis следва да се разглежда като важно усложнение пореди високата – до 50% – смъртност [5]. По-късен метанаализ показа по-голяма част от случаите на кардиохирургия, като установява съществена недостатъчност при 2% и миокарден инфаркт при 1% от пациентите, лекувани с ИКТИ за недробно克莱тчен белодробен карцином [45]. Описват се и други прояви на кардиохирургия, свързани с ИКТИ. Escudier и сътр. в група от 30 па- циенти с проявя на СДСЛП по време на лечение с ИКТИ наблюдават левокамерна систолна дисфункция по модела на стрес-индуцирана кардиомиопатия, ри- тъмните и проводни нарушения и перикарден излив [46]. Ка- то цяло проявите на кардиохирургия при тези меди- диументи се появяват рано, най-често след първата до третата инфузия, и са напълно реверзibili само в част от случайте [5, 46].

КМРТ има решаваща роля при пациенти с подози- рана ИКТИ индуцирана кардиохирургия [6, 47]. До- колко в значителна част от случаите със фулминантни автосуспензационни миокардиоди фракция на изплакване на лявата камера остава запазена за дълго време, характерираното на тъканните промени в миокарда е от критично значение [5, 6, 47]. Белезите на миокарден едем – сигнали на TIRM образите и удължаване- то на времето за T2 релаксация, заедно с късното усил- ване на имунносупресивно лечение. Следва да се отбе- лежи, че при първоначално докладваните от Johnson и сътр. пациенти с фулминантен миокардиоди аутоимун- та показва масивна Т-клетъчна инфилтрация на си- нусовия възел [44]. Това предполага, че поне част от наблюданияте ритъмните и проводни нарушения (ка- мерни тахиаритмии, предсърдно мъждене, AV блок), са всъщност израз на миокардит и биха могли да се идентифицират с КМРТ. КМРТ е от полза в случаите с левокамерна систолна дисфункция с невъзпалителна генеза, напр. при стрес-индуцирана кардиомиопатия или при миокарден инфаркт [47].

Протеазомни инхибитори (ПИ)

Протеазомните инхибитори (бортезомиб, карфи- зомиб, ixazомиб и т.н.) са група противотуморни меди- каменти, навлезли в практиката след 2000 г. Изпол- зват се като първа и последващи линии на лечение предимно при В-клетъчни лимфоми (мутателен ми- елом, мантиоклетъчен лимфом), но и при солидни тумори (недребно克莱тчен белодробен карцином, овариален карцином). Това са малки молекули, свър- зващи се обратимо (bortezomib, ixazomib) или необра- тимо (carfilzomib) с протеазомните β5 и β5i субединиции и потискащи нелизосомалите протеолиза. Това води до нарушение на предназначени за “рециклиране” протеини в клетката и в крайна сметка активира ред проапопототични сигнални вериги [48, 49].

cardiitis [5, 44]. Despite the relatively low incidence, fulminant myocarditis should be considered as an important complication due to the high – up to 50% – mortality rate [5]. A later meta-analysis showed a higher incidence of cardiotoxicity, finding heart fail- ure in 2% and myocardial infarction in 1% of patients treated with ICI for non-small cell lung carcinoma [45]. Other manifestations of cardiotoxicity associated with ICTs have also been described. Escudier et al. in a group of 30 patients with CTRCD during ICI treatment found left ventricular systolic dysfunction with stress-induced cardiomyopathy pattern, arrhythmias and conduction disorders, and pericardial effusion [46]. In general, manifestations of cardio- toxicity with these medications appear early, most often after the first to third infusion, and are completely reversible only in a number of cases [5, 47].

CMR has a crucial role in patients with suspected ICI-induced cardiotoxicity [47]. Since in a significant proportion of cases with fulminant autoimmune myocarditis the left ventricular ejection fraction remains preserved for a long time, the characterization of tissue changes in the myocardium is of critical im- portance [5, 47]. Signs of myocardial edema - high signal on TIRM images and prolongation of T2 relaxation time - along with late enhancement are suggesti- ve of myocarditis and warrant initiation of immuno- suppressive treatment. Of note, in the patients with fulminant myocarditis originally reported by Johnson et al., autopsy showed massive T-cell infiltration of the sinus node[44]. This suggests that at least some of the arrhythmias and conduction disorders (ventric- ular tachyarrhythmias, atrial fibrillation, AV-block) are actually an expression of myocarditis and could be identified by CMR. CMR is also useful in cases of left ventricular systolic dysfunction of non-inflammatory origin, for example in stress-induced cardiomyopa- thy or in myocardial infarction [47].

Proteasome inhibitors (PI)

Proteasome inhibitors (bortezomib, carfilzomib, ixazomib, etc.) are a group of antitumor drugs that en- tered practice after 2000. They are used as first and subsequent lines of treatment mainly in B-cell lymphomas (multiple myeloma, mantle cell lymphoma), but also in solid tumors (non-small cell lung carcinoma, ovarian carcinoma). These are small molecules that bind reversibly (bortezomib, ixazomib) or irreversibly (carfilzomib) to proteasomal β5 and β5i subunits and promote non-lysosomal proteolysis. This leads to the accumulation of proteins destined for “recycling” in the cell and ultimately activates a series of pro-apop- totic signaling cascades [48, 49].
Доколкото кардиомиоцитите, като неделящи се клетки, са силно зависими от "рециклизирането" на протеините, механизъмът на кардиотоксиността при лечението с ПИ е очевиден. Допълнителен кардиотоксинен ефект вероятно има и доказаното въздействие на ПИ върху експресията на NO-синтезазата, по-специално върху експресията на eNOS, с увеличаване на оксидативния стрес, потискане на ангиогенезата и намаляване на адаптивността на микроциркулацията към обемно натоварване [50]. Трябва да се има предвид, че пациентите с мултиплен миелом (основната група, лекувана с ПИ) са поначало изложени на значителен сърдечно-съдов риск предвид високата честота на бъбречна недостатъчност и хиперкалциемия, със съвързани с тях усложнения от страна на сърдечно-съдовата система. Това са и пациенти, при които често (до 15% от случаите) се наблюдава лековерижна амилоидоза [50]. Кардиотоксичността при лечение с ПИ обикновено е ранна, като в проучванията и в реалната клинична практика до 86% от сърдечно-съдовите странични ефекти настъпват през първите 3 месеца от лечението [48, 49].

Честотата на СДСПЛ при пациенти, лекувани с ПИ, варира в зависимост от използваните медикаменти. При carfilzomib, който се свързва необратимо с β5 (химотрипсин-подобна активност) и β5i (имунопroteаза), честотата на кардиотоксиността е значителна. Ранните проучвания показат, че до 22% от лекуваните с carfilzomib пациенти развиват СДСПЛ, от тях 13,3% са различни аритмии, 7,2% – сърдечна недостатъчност, 2% – неисхемична дилатативна кардиомиопатия, и 3% – исхемична болест [49]. При bortezomib и ixazomib, които се свързват обратимо с протеазните β5 и β5i субединиции, честотата на сърдечно-съдовите странични ефекти не се различава съществено от тази при стандартно лечение на мултиплен миелом (високи дози dexamethasone). Интересно, че в проучванията комбинацията ixazomib-dexamethasone показва добра ефективност и безопасност при лечение на рецидивна или първично рефрактерна лековерижна амилоидоза, включително със сърдечно застъпване [49, 50]. Директното сравнение на carfilzomib и bortezomib (проучването PROTECT) също показва значително по-висока честота на кардиотоксиността при лечение с първия [51].

При пациенти на лечение ПИ КМРТ може да покаже увеличаването на обема на интерстициалното пространство, което настъпва рано в хода на неисхемична дилатативна кардиомиопатия и предшества редукцията на ГЛС и на ФИ. КМРТ също така може да идентифицира евентуален миокарден инфаркт и демонстрира развитието на постихемична дилатативна кардиомиопатия.

Since cardiomyocytes, as non-dividing cells, are highly dependent on protein "recycling", the mechanism of cardiotoxicity in PI treatment is obvious. In addition, the impact of PI on the expression of NO synthases (NOS), in particular on the expression of eNOS, may also have cardiotoxic effect via an increase of the oxidative stress, suppression of angiogenesis and a decrease in the adaptability of the microcirculation to volume load [49]. It should be borne in mind that patients with multiple myeloma (the main group treated with PI) are a priori exposed to a significant cardiovascular risk given the high incidence of renal failure and hypercalcemia, with associated cardiovascular complications. These are also patients in whom light chain amyloidosis is frequently (up to 15% of cases) observed [49]. Cardiotoxicity with PI treatment usually appears early, with up to 86% of cardiovascular side effects occurring in the first three months of treatment in studies and in real-world clinical practice [48, 49].

The incidence of CTRCD in patients treated with PI varies depending on the medication used. With carfilzomib, which binds irreversibly to β5 (chymotrypsin-like activity) and β5i (immunoproteasome), the incidence of cardiotoxicity is significant. Early studies have shown that up to 22% of carfilzomib-treated patients develop CTRCD, of which 13.3% are various arrhythmias, 7.2% heart failure, 2% nonischemic dilated cardiomyopathy, and 3% ischemic disease [49]. With bortezomib and ixazomib, which bind reversibly to proteasome β5 and β5i subunits, the frequency of cardiovascular side effects is not significantly different from that of standard treatment of multiple myeloma (high doses of dexamethasone). Interestingly, in studies, the ixazomib-dexamethasone combination showed good efficacy and safety in the treatment of relapsed or primary refractory light-chain amyloidosis, including cardiac involvement [49, 50]. Head-to-head comparison of carfilzomib and bortezomib (the PROTECT study) also showed a significantly higher incidence of cardiotoxicity with treatment with the former [51].

In patients on PI treatment, CMR can show an increase of the interstitial space volume that occurs early in the course of nonischemic dilated cardiomyopathy and precedes the reduction in GLS and EF. CMR will also identify a possible myocardial infarction and demonstrate the development of postischemic dilated cardiomyopathy.
Кардиотоксичност в хода на и след онкологично лечение – роля на кардиомагнитния резонанс

Други

Кардиотоксичност е наблюдавана с варираща честота и при други групи противотуморни медикаменти, например неисемична дилатативна кардиомиопатия при платина, при антиметabolити, при алигиращи агенти и при микротубулни инхибитори, перикардни изливи и исхемични епизоди при антиметabolити и микротубулни инхибитори [52]. Механизъмът на СДСПЛ при тези лекарства не е напълно изяснен и поне в част от случаите, вероятно, не е директно следствие на въздействието им върху кардиомиоцитите. КМРТ е в състояние да демонстрира както структурното и микролетателно увреждане на миокарда рано в хода на заболяването, което ще позволява своевременно започване на кардипротективна терапия.

**КМРТ – кога и защо**

В актуалната позиция на научните организации водеща роля при идентифицирането, оценката и проследяването на СДСПЛ се отрежда на ехокардиографията. Това е напълно обяснимо предвид широката достъпност и относително ниската цена на изследването, а също и предвид възможността да се възпроизведат бързо – в условията на спешност – и при лекото на болния. КМРТ, от друга страна, е относително скъп, изисква подготовен персонал и подходяща апаратура и е относително по-трудно достъпен. Към момента КМРТ се провежда най-често при пациенти, при които ехокардиографското изследване е затруднено от лош акустичен прозорец или дава противоречиви и несигурни резултати, както и при пациенти, при които се подозира миокардна исхемия [1]. През последните години обаче значителен брой проучвания, метаанализи и обзори се фокусират върху “дабованата стойност” на КМРТ при пациентите с прояви на кардиотоксичност в хода и след на онкологично лечение; достатъчно е да се споменат работите на Thavendiranathan [23], на Jordan [16, 18, 20, 24], а в по-ново време и на Dobbin [27, 31] и сътрудниците им.

Един от клиничните контекст, в които КМРТ има решаваща роля, е поява на нови симптоми на страна на сърдечно-съдовата система в хода на лечение с ИКТИ. При значителна част от пациентите с сулфимиант миокардит на фон на лечение с ИКТИ функциите на лявата камера се уврежда късно и е напълно възможно ехокардиографската нахodka с оценка на ФИ и на стрейна да подценят степента на миокардно засягане [5]. КМРТ, с помощта на TIRM образи и на T2 картиране, идентифицира поява на миокарден едем, като позволява да се диференцира автоимунен миокардит от невъзпалителна СДСПЛ и да се започне своевременно и потенциално животоспасяващо имunosупресивно лечение (фиг. 1). Разпространението на огнищата на

**CMR – when and why**

In the current position of scientific organizations, echocardiography is assigned a leading role in the identification, assessment, and follow-up of CTRCD. This is completely understandable given the wide availability and relatively low cost of the examination, and also given the possibility to perform it quickly – in emergency conditions – and at the patient’s bedside. CMR, on the other hand, is relatively expensive, requires trained personnel and appropriate equipment, and, accordingly, is relatively more difficult to access. Currently, CMR is most often performed in patients in whom echocardiographic examination is hampered by a poor acoustic window or gives contradictory and uncertain results, as well as in patients in whom myocardial ischemia is suspected [1]. In recent years, however, a significant number of studies, meta-analyses and reviews have focused on the “added value” of CMR in patients with cardiotoxicity during and after oncological treatment; it is enough to mention the works of Thavendiranathan [23], Jordan [16, 18, 20, 24], and more recently Dobbin [27, 31] and their collaborators.

One of the main clinical contexts in which CMR plays a crucial role is the newly appeared cardiovascular symptoms on the background of ICI treatment. In a significant proportion of patients with fulminant myocarditis during ICI treatment, the deterioration of the ventricular function comes late, and it is quite possible that the echocardiographic finding with assessment of FE and strain will underestimate the degree of myocardial involvement [5]. CMR, with the help of TIRM images and T2 mapping, identifies the occurrence of myocardial edema, allowing the differentiation of autoimmune myocarditis from non-inflammatory CTRCD and the initiation of timely and potentially life-saving immunosuppressive treatment (Figure 1). The distribution of the foci of ede-
едем and най-вече засягането на септума с AV възела
и снопчето на Хис, има определена предиктивна
стойност по отношение на появата на животозас-
трашаващи аритмии, като дава възможност да се
предприемат необходимите терапевтични мерки [5,
43-46]. Според актуалните препоръки на Европей-
ското дружество по кардиология КМРТ е образен
метод от първа линия при пациенти с лечение с
ИКТИ, при които се появяват нови сърдечно-съдови
оплаквания или се наблюдава повишение на нива-
tа на маркерите на миокардна некроза [6].

Друга клинична ситуация, при която се очаква
ролята на КМРТ да нарасне, е оценката на посте-
пенно настъпващата миокардна увреда по време и
след лечение с антрациклини и HER2 инхибитори. Ред
прочувания показават, че миокардната маса и
обемът на интерстициалното пространство в ми-
окарда са ранни предиктори за поява на дилататив-
на кардиомиопатия и увреда на левокамерната сис-
tолна функция при тези пациенти [18-22, 52] (фиг. 2).
Включването на КМРТ с оценка на миокардната
маса и T1 и T1ρ картиране в протокола за просле-
dяване на тези пациенти ще позволи своевременно
започване на кардиопротективно лечение.

Фиг. 1. Фулминантен миокардит при пациент с метастатичен меланом, на лече-
ние с nivolumab и atezolizumab. TIRM (A), T2 картиране (B), късно гадолини-
ево усилване (C) и нативно T1 картиране (D). Обширни зони на сигнали на
TIRM образите в дълбочина на левокамерния миокард, най-изразени по
свободната стена надолу, кореспондират с огнища на миокарден едем. T2 карта-
tата показва също и по-умерено усилване на времето за T2 релаксация по
цялата циркумференция на лявата камера и демонстрира действителното
разпространение на едема, докато петнистите огнища на късно усилване в
левокамерния миокард, включително в зоната на максимално усилване на
времето за T2 релаксация говорят за миокардна некроза.

Fig. 1. Fulminant myocarditis in a patient with metastatic melanoma treated
with nivolumab and atezolizumab. TIRM (A), T2 mapping (B), late gadolinium
enhancement (C) and native T1 mapping (D). Extensive areas of high signal on
the TIRM images in depth of the left ventricular myocardium, most pronounced
along the free wall downwards, corresponding to a marked prolongation of the T2
relaxation time and representing foci of myocardial edema. The T2 map also shows
a moderate prolongation of the T2 relaxation time along the entire circumference
of the left ventricle, depicting the actual spread of edema, while the patchy foci of late enhancement in the left ventricular myocardium, including
in the area of maximum prolongation of the T2 relaxation time, suggest myocardial necrosis.

Фиг. 2. Пациентка с карцином на гърдата, лекувана последователно с
epirubicin (500 mg/m²) и trastuzumab. TIRM (A), T2 картиране (B), късно гадолини-
ево усилване (C) и нативно T1 картиране (D). Дилатирана и ремо-
dелирания левая камера и редуцирана миокардна маса, най-изразено по
септума. Дифузно удължено време за T1 релаксация, израз на миокарден
едем. Малък трансмурален инфаркт в апекса, като други огнища
на късно усилване не се наблюдават

Fig. 2. A patient with breast carcinoma treated with epirubicin (500 mg/
m²), followed by trastuzumab. TIRM (A), T2 mapping (B), late gadolinium
enhancement (C) and native T1 mapping (D). Dilated and remodeled left
ventricle and reduced myocardial mass, most pronounced along the septum.
Diffusely prolonged T1 relaxation time due to myocardial fibrosis. A small
transmural infarct at the apex, with no other foci of late enhancement are seen.

ma, mostly the involvement of the septum with the
AV-node and the His bundle, has a certain predictive
value regarding the occurrence of life-threatening ar-
rhythmias, making it possible to take the necessary
therapeutic measures [5, 43-46]. According to the
current recommendations of the European Society of Cardiology, CMR is an imaging method of choice
in patients treated with ICI, in whom new cardiovas-
cular complaints appear or an increase in the levels
of markers of myocardial necrosis is observed [6].

Another clinical situation where the role of CMR
is expected to grow is the assessment of progres-
sive myocardial injury during and after treatment
with anthracyclines and HER2 inhibitors. A number
of studies have shown that myocardial mass and
myocardial interstitial volume are early predictors of
the development of dilated cardiomyopathy and im-
pairment of left ventricular systolic function in these
patients [18-22, 52] (Figure 2). The inclusion of CMR
with assessment of myocardial mass and T1 and T1ρ
mapping in the follow-up protocol will allow timely ini-
tiation of cardioprotective treatment.
No conflict of interest was declared

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Last but not least, MRI makes it possible to evaluate tissue changes in the myocardium under the influence of various antitumor drugs. Interesting and, often, unexpected observations in a number of studies suggest that our knowledge in this area is still limited [31, 46]. Accumulation of data in this direction will lead to a clearer understanding of the mechanisms of cardiotoxicity and, ultimately, to an improvement of the therapeutic approach in CTRCD.

Conclusion

The expansion of the therapeutic arsenal in medical oncology not only led to an improved survival of patients with solid and diffuse neoplasms, but also presented the medical community with new challenges. One of them is the increasingly common and sometimes unexpected cardiotoxicity during and after antitumor treatment. Cardio-oncology – a relatively new but rapidly evolving interdisciplinary field – faces the task of defining the mechanisms of cardiac dysfunction associated with antitumor treatment, building workable patient monitoring schemes and developing effective and safe therapeutic approaches for these serious complications, without compromising the success of the antitumor treatment itself. Solving this task requires close cooperation between different specialists – medical oncologists, cardiologists, imaging specialists – and rational use of available resources, including cardiac magnetic resonance imaging.

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Reference

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