Chemotherapy-induced cardiotoxicity

Edin Begić1,2
Alma Sofo-Hafizović3
Buena Aziri1
Nirvana Šabanović-Bajramović4

1 Faculty of Medicine, University of Sarajevo, School of Science and Technology, Sarajevo, Bosnia and Herzegovina
2 General Hospital “Prim. dr Abdulah Nakašt”, Department of Cardiology, Sarajevo, Bosnia and Herzegovina
3 Clinic for Hematology, Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina
4 Clinic for heart, blood vessels and rheumatism, Clinical Center of the University of Sarajevo, Sarajevo, Bosnia and Herzegovina

Corresponding author:
Doc. dr Edin Begić
Katedra za farmakologiju, Medicinski fakultet Univerziteta Sarajevska Škola za nauku i tehnologiju, Hranička cesta 3a, Sarajevo, Bosna i Hercegovina
begic.edin@ssst.edu.ba

Abstract

Cardiotoxicity is one of the most important side effects of first-line chemotherapy medications. It is influenced by genetic variation, whereby the relationship between the chemotherapeutic dose and the risk of cardiotoxicity can be altered. The incidence of cardiotoxicity depends on the substance used in the therapeutic modality of cancer and can reach an incidence of 30% during a three-year follow-up. The main element of the clinical picture is systolic dysfunction of the left ventricle, with symptoms of heart failure, which can change or stop oncological therapy, along with pharmacological treatment of heart failure. These symptoms can occur during prolonged use of cancer therapies, monitoring the patient is advisable.

Considering the increasing success of oncology therapy and the extension of life, as well as the improvement of the quality of life, a multidisciplinary approach, as well as the symbiosis of the work of cardiologists and oncologists, is imperative. Patient stratification concerning oncological treatment modality is imposed as part of a cardiologist’s daily work from the beginning of cancer treatment.

Keywords: cardiotoxicity, chemotherapy, treatment, prognosis

Introduction

Cardiotoxicity is one of the most important side effects of first-line chemotherapy medications, which can result in a poor prognosis and a lower survival rate1. Cytotoxic agents can often directly or indirectly induce cardiovascular injury through various mechanisms, increasing the risk of cardiovascular disease1. Age, obesity, diabetes mellitus, and the underlying heart conditions hypertension, coronary artery disease, structural heart disease, and cardiomyopathy are risk factors for chemotherapy-induced cardiotoxicity2,3. Additionally, existing cardiovascular diseases and conditions, namely left ventricular ejection fraction < 50% or symptomatic heart failure, coronary disease, left ventricular hypertrophy, cardiomyopathies, arrhythmias (both supraventricular and ventricular rhythm disorders), classic cardiovascular risks, family history of early cardiovascular disease, arterial hypertension, diabetes mellitus, dyslipidemia, smoking, alcoholism, lack of physical activity, also play a role in the development of cardiotoxicity induced by such agents4.

Meanwhile, oncological cardiovascular risks include old age, chemotherapy in childhood, trastuzumab use in people over 50 years old, anthracycline use in people over 65 years old, previous use of anthracyclines, cumulative dose of anthracycline, combined chemotherapy, and prior mediastinal or chest therapy5. A further possible risk factor for the cardiotoxicity of cytotoxic agents is the concurrent administration of other medications exhibiting cardiac adverse effects6. Chemotherapy-related cardiotoxicity is also influenced by genetic variation, whereby the relationship between the chemotherapeutic dose and the risk of cardiotoxicity can be altered7,7. Clinical manifestations of cardiotoxicity related to cytotoxic agents range from arrhythmias or a decline in cardiac function to sudden death8. Furthermore, a constant risk factor for cardiotoxicity is cumulative chemotherapeutic exposure. The limit value of the cumulative anthracycline dose, which represents the limit of extremely high risk for the manifestation of complications, has yet to be precisely defined. In 2012, the critical cumulative dose of doxorubicin was 500 mg/m²; in 2016, it was 250 mg/m², while the American Society of Clinical Oncology recommends 250 mg/m² (there are also described cases of severe cardiotoxicity at lower doses)4.

It is well-recognized that common chemotherapy medications like anthracyclines display toxic effects on the cardiac muscle9. Following anthracyclines, fluoropyrimidines are considered the second most common cytotoxic agents resulting in cardiotoxic effects, though rare but potentially fatal side effects, with an incidence of up to 30%. Additionally,
immune checkpoint inhibitors (ICIs), as well as molecularly targeted antiangiogenic medications, including vascular endothelial growth factor (VEGF) inhibitors and tyrosine kinase inhibitors (TKIs), are available for the treatment of cancer; the cardiovascular effects of the later ones may start early and not be dose-dependent, while some can be significant and potentially fatal\textsuperscript{10,11}. Also, the human epidermal growth factor receptor 2 (HER2) trastuzumab has demonstrated a low to moderate risk of cardiotoxicity, as well as biologic response modifiers, topoisomerase inhibitors, alkylating agents, microtubule-targeting drugs, antimetabolites, antitumor antibiotics, monoclonal antibodies, among others\textsuperscript{12,13}. The prognosis of cancer patients is improved by cytotoxic drug-induced cardiotoxicity\textsuperscript{14}. The definitions regarding cancer therapy-related cardiac dysfunction (CTRCD) range from mild to severe, whereby symptomatic CTRCD referring to heart failure (HF) demands inotropic support, mechanical circulatory support, or consideration of transplantation, while asymptomatic CTRCD, when severe, is defined as a new left ventricular ejection fraction (LVEF) reduction to < 40\%\textsuperscript{4}. Thus far, cut-off values for cardiac biomarkers, such as natriuretic peptides (NP) and cardiac troponin (cTn) in patients receiving cytotoxic therapies have not been clearly defined, and it is essential to take into consideration age, sex, renal function, underlying atrial fibrillation or pulmonary embolism, obesity, and infections as factors that may alter their levels in these patients\textsuperscript{4}. Not only are cardiac biomarkers useful for CTRCD screening and diagnosis, but they also play a role in guiding therapy, as their release varies in different cancer treatments depending on the timing of treatment initiation and comorbidities\textsuperscript{4}. This article aims to provide an overview of cardiotoxic effects associated with different groups of cytotoxic agents, the mechanisms involved, as well as their treatment.

**Occurrence and the mechanism of cardiotoxicity**

The occurrence of cardiotoxicity, the mechanism of cardiotoxicity, the cumulative dose concerning the pharmacological agent, as well as the treatment, are displayed in table 1.

**Clinical presentation of chemotherapeutic toxicity**

Cardiotoxicity of chemotherapy can manifest itself through different clinical presentations: heart failure, myocarditis, pericarditis, arrhythmias, hypertension, ischemia and myocardial infarction, and various thromboembolic incidents.

**Heart failure**

Transient or permanent decline in left ventricular (LV) function is a manifestation of chemotherapeutic toxicity\textsuperscript{14,15}. Anthracycline-induced LV systolic dysfunction brought on as fatigue, dyspnea, orthopnea, edema, and cardiogenic shock in cancer survivors are comparable to those seen in individuals with other causes of heart failure and is linked to a significant early increase in serum troponin in 30-35\% of anthracycline-treated patients\textsuperscript{15,16}. In addition, patients may exhibit arrhythmias triggered by elevated filling pressures\textsuperscript{16}. Cardiotoxic effects of the anthracyclines are dose-dependent, and they are more common with mitoxantrone andidarubicin than with doxorubicin; these rates are fundamental concerning the recommended cumulative lifetime doses, which should not be exceeded to prevent clinically significant cardiotoxicity (table 1)\textsuperscript{16}. Furthermore, anthracycline chemotherapy should typically be avoided in patients with an LVEF ≤ 40\%; instead, other non-anthracycline-containing regimens should be considered. Before starting anthracycline-based chemotherapy, an LVEF assessment is performed to detect any preexisting LV dysfunction\textsuperscript{15,17}. For the primary prevention of anthracycline-related cardiotoxicity, dexrazoxane is an effective medication, which exerts its action by chelating intracellular iron, thereby preventing the generation of iron-assisted oxidative radicals and inhibiting topoisomerase II-beta (an enzyme linked to anthracycline cardiotoxicity)\textsuperscript{17}. Posttreatment monitoring is based on the differences in the ideal measurement of LV function, the threshold for testing, and the interval for testing\textsuperscript{15,17}. Additionally, echocardiographic assessment is performed throughout the treatment after each cycle of chemotherapy as well as annually after its completion in patients with acute cardiotoxicity who will undergo further anthracycline exposure or in those with preexisting LV dysfunction\textsuperscript{17}. The survival rates of patients with clinical HF triggered by anthracycline toxicity are comparable to those of individuals with HF caused by other factors\textsuperscript{15,17}. Dysfunction of the left ventricle has also been observed in patients treated with specific VEGFR tyrosine kinase inhibitors (axitinib, lenvatinib, pazopanib, rilretinib, sunitinib, and sorafenib) (table 2)\textsuperscript{18,19}.

Cardiotoxicity of the HER2-targeted drug trastuzumab manifests as a reduction in left ventricular ejection fraction, but this effect can be reduced by discontinuing the treatment (table 1)\textsuperscript{12}. In patients with LVEF of 40-50\%, age > 50 years, and hypertension, the risk of heart failure is slightly increased when trastuzumab is administered after anthracycline therapy\textsuperscript{12,14}. Moreover, lapatinib, an orally active tyrosine kinase inhibitor affecting both HER2 and the EGFR, has a more favorable cardiotoxicity profile than trastuzumab, according to preliminary results from clinical studies, while beneficial effects on left ventricular ejection fraction (with the recovery of LVEF up to a value of ≥ 50\%) were also reported in 87\% of patients on pertuzumab, a monoclonal antibody binding to a different epitome of HER2\textsuperscript{20,21}. Dilated cardiomyopathy can coexist with immune-checkpoint inhibitor-related impairment of left ventricular function\textsuperscript{22}. In addition, cardiac adverse events, especially new-onset HF, as well as coexistent cardiovascular comorbidities and an increased baseline CV risk, have been demonstrated to occur...
Table 1. Cytotoxic agents inducing cardiotoxicity\(^9\)\(^{-15}\)

<table>
<thead>
<tr>
<th>GROUP</th>
<th>CYTOTOXIC AGENTS</th>
<th>INDICATIONS</th>
<th>CARDIOTOXIC EFFECT</th>
<th>MECHANISM OF CARDIAC TOXICITY</th>
<th>RELATED TO CUMULATIVE DOSE</th>
<th>TREATMENT OF CARDIAC COMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>Doxorubicin, Daunorubicin, Idarubicin, Epirubicin, Mitoxantrone</td>
<td>Hodgkin lymphoma, non-Hodgkin's lymphoma, acute leukemia</td>
<td>HF, arrhythmias</td>
<td>Oxidative stress, topoisomerase-II mediated cell death, the time course of cardiotoxicity (with early (j) in cardiac troponin, (j) in LVEF)</td>
<td>Yes (with doxorubicin)</td>
<td>Limit the cumulative dose, administering the medication via infusion rather than bolus dose, liposomal formulations</td>
</tr>
<tr>
<td>Immune checkpoint inhibitors</td>
<td></td>
<td>Hodgkin lymphoma, various types of cancer</td>
<td>Myocarditis, pericarditis, HF, arrhythmias, vasculitis</td>
<td>Target cytotoxic T lymphocyte-associated antigen 4, programmed cell death receptor 1, and programmed cell death ligand 1</td>
<td>No</td>
<td>If elevated troponin levels or conduction abnormalities occur; immediate transfer to the coronary care unit or cardiac transplant</td>
</tr>
<tr>
<td>Fluoropyrimidines</td>
<td>Fluorouracil, Capecitabine</td>
<td>Head and neck, esophagus, stomach, colon, rectum, anus, and breast malignancies</td>
<td>Myocardial ischemia</td>
<td>Coronary vasospasm, a direct myocardial toxic effect due to the antimetabolite effects</td>
<td>No</td>
<td>If symptomatic: discontinue therapy</td>
</tr>
<tr>
<td>Molecular-targeting agents</td>
<td>Bevacizumab, Ramucirumab, Afibertcept VEGFR tyrosine kinase inhibitors - sunitinib, sorafenib, pazopanib, vandetanib, cabozantinib, axitinib, ponatinib, vandetanib, cabozantinib, bevacizumab</td>
<td>Metastatic non-small cell lung cancer, renal cell carcinoma, ovarian cancer, cervical cancer, glioblastoma multiforme</td>
<td>Hypertension, thromboembolic disease, left ventricular dysfunction, myocardial ischemia, prolongation of the QTc interval, thrombotic microangiopathy</td>
<td>Vasoconstriction mediated by endothelins, with reduced myocardial perfusion, disruption of endothelial cell homeostasis by a dose-dependent increase in mitochondrial superoxide generation and reduced nitric oxide availability myocyte necrosis, decreased cardiac repair, targeting the PDGF receptor</td>
<td>When combined with doxorubicin</td>
<td>If pericarditis: corticosteroid therapy</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Vinca alkaloids - vinblastine, vincristine, vinorelbine Taxanes - paclitaxel, nabpaclitaxel docetaxel Eribulin mesylate Ixabepilone</td>
<td>Acute lymphoblastic leukemia, Hodgkin lymphoma, non-Hodgkin's lymphomas, ovarian cancer, breast cancer</td>
<td>Hypertension, myocardial ischemia, infarction, AV conduction block, VT, bradyarrhythmia</td>
<td>Angina, decrease in ejection fraction, conduction abnormalities, cardiovascular collapse</td>
<td>When combined with doxorubicin</td>
<td>If impaired cardiac function during therapy or cardiac ischemic: discontinue therapy</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Fludarabine, Pentostatin, Cladrabine, Methotrexate, Cytarabine</td>
<td>Hematologic malignancies, bone marrow transplantation agent</td>
<td>Ischemia, HF, syncope, MI, SVT, VT, pericarditis, pericardial effusion, cardiac tamponade</td>
<td>Purine antagonist disrupt the normal metabolic processes of cardiomyocytes, leading to hypotension and chest pain</td>
<td>Yes</td>
<td>If symptoms are severe: close monitoring and supportive care (oxygen therapy), temporarily withhold or reduce the dosage</td>
</tr>
<tr>
<td>Alkylation agents</td>
<td>Cyclophosphamide, Ifosfamide, Cisplatin, Busulphan, Trabectedin</td>
<td>Lymphomas, leukemia, autologous hematopoietic stem cell transplantation, allogeneic hematopoietic cell transplantation, prophylaxis of graft-versus-host disease in patients undergoing haploidentical allogeneic HCT, testicular germ cell tumors, preparative regimen for bone marrow transplantation, soft tissue sarcomas</td>
<td>Acute cardiomyopathy, arrhythmias, HF, pericardial effusion, myocardial ischemia, LBBB, endocardial fibrosis</td>
<td>Oxidative stress and inflammation in the cardiac muscle</td>
<td>Yes</td>
<td>If symptoms are severe: close monitoring and supportive care (oxygen therapy), temporarily withhold or reduce the dosage</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Mitomycin C, Bleomycin</td>
<td>Solid tumors - breast, lung, ovarian cancer Lymphomas</td>
<td>HF, damage similar to radiation-induced cardiac injury, pericarditis, acute onset of chest pain, CAD myocardial ischemia, MI</td>
<td>Generation of free radicals, oxidative stress, and impairment of mitochondrial function in cardiac cells</td>
<td>Yes (at cumulative doses &gt; 30 mg/m(^2))</td>
<td>If the acute onset of substernal chest pain: supraventricular or atrioventricular rhythm, or if the cumulative dose exceeds the recommended limit</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biological Response Modifiers</th>
<th>Key Features</th>
<th>Side Effects</th>
<th>Management</th>
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<tbody>
<tr>
<td><strong>B-cell hematological malignancies / CD 20+</strong></td>
<td>Malignant and benign hematologic conditions. T-cell prolymphocytic leukemia, T-cell lymphomas (mycosis fungoides, Sézary syndrome)</td>
<td>Arrhythmias, angina, MI, ventricular fibrillation, and cardiogenic shock</td>
<td><strong>Yes</strong> (long-term cardiac toxicity with rituximab)</td>
</tr>
<tr>
<td><strong>Lymphomas, part of cisplatin-based regimens</strong></td>
<td></td>
<td>MI, vaso spas tic angina</td>
<td><strong>Generation</strong> of reactive oxygen species, DNA damage impairing heart function, mitochondrial dysfunction</td>
</tr>
<tr>
<td><strong>Chronic myeloid leukemia, melanoma, renal cell carcinoma</strong></td>
<td></td>
<td>Myocardial ischemia and infarction, atrial and ventricular arrhythmias, SCD, reduced ejection fraction, HF</td>
<td><strong>Inhibition</strong> of the HERG potassium channel, which regulates the electrical activity of the heart, inhibition of the L-type calcium channel and the sodium channel, alterations in calcium handling, generation of ROS, effects on the autonomic nervous system</td>
</tr>
<tr>
<td><strong>TK inhibitor - brigatinib</strong></td>
<td>Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer</td>
<td>Hypertension, AF, ventricular arrhythmias, brady cardia</td>
<td><strong>Inflammatory response</strong>, cytokine storm</td>
</tr>
<tr>
<td><strong>MAPK inhibitors - cobimetinib, trametinib, binimetinib</strong></td>
<td>Metastatic or unresectable BRAF-mutated melanoma</td>
<td>Left ventricular dysfunction, prolongation of the QTc interval</td>
<td><strong>Direct cytotoxic effects</strong> lead to necrosis and fibrosis, increased inflammation, disruption of cardiac mitochondrial function, inhibition of signaling (PI3K/AKT and MAPK) pathways critical for maintaining cardiac function, impairment of potassium channels resulting in arrhythmias</td>
</tr>
<tr>
<td><strong>ALK inhibitors - crizotinib, ceritinib</strong></td>
<td>Anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer, anaplastic large cell lymphoma, inflammatory myofibroblastic tumor</td>
<td>Bradycardia, QTc interval prolongation</td>
<td>Decrease in cardiomyocyte survival, increased production of ROS, interference with the calcium handling in cardiomyocytes affecting contractility and electrophysiological changes, mitochondrial dysfunction, inflammation in the heart</td>
</tr>
<tr>
<td><strong>BTK inhibitors - ibritinib, zanubrutinib, acalabrutinib</strong></td>
<td>B-cell hematological malignancies – chronic lymphocytic leukemia, Waldenström macroglobulinemia, and mantle cell, marginal zone lymphoma</td>
<td>Supraventricular and ventricular arrhythmias, HF, conduction disorders, hypertension, sudden death</td>
<td>Vascular toxicity impairing blood flow to the heart, ion channel dysfunction in the cardiac cells, apopsis of cardiomyocytes, mitochondrial dysfunction, off-target effects</td>
</tr>
<tr>
<td><strong>Gastrointestinal stromal tumors, chronic myeloid leukemia with a T3151 mutation, acute lymphoblastic leukemia</strong></td>
<td>Gastrointestinal stromal tumors, chronic myeloid leukemia, Waldenström macroglobulinemia, and mantle cell, marginal zone lymphoma</td>
<td>HF, ischemic heart disease due to arterial occlusive events, QTc prolongation, AF, brady cardia, syncope, VT, AV blocks</td>
<td>Inhibiting PI3K/AKT and ERK signaling pathways important for cardiac repair, increased oxidative stress, inhibition of c-KIT, mitochondrial dysfunction</td>
</tr>
<tr>
<td><strong>Non-small cell lung cancer with EGFR T790M mutation</strong></td>
<td></td>
<td>Reduced ejection fraction, HF, cardiomyopathy, prolongation of the QTc interval</td>
<td>Impaired cardiac contractility and relaxation by inhibiting EGFR signaling, oxidative stress, and mitochondrial dysfunction in cardiac cells, prolongation of QT interval increases the risk of arrhythmias</td>
</tr>
<tr>
<td><strong>Hormone-positive, advanced, or metastatic breast cancer</strong></td>
<td></td>
<td>Prolongation of the QTc interval</td>
<td>Prolonged QT intervals can lead to an increased risk of arrhythmias, reduced LVEF, vascular damage</td>
</tr>
<tr>
<td><strong>Gastrointestinal stromal tumors</strong></td>
<td></td>
<td>HF, acute left ventricular failure, left ventricular diastolic dysfunction, ventricular hypertrophy</td>
<td>Inhibiting enzyme activities, interfering with calcium balance in the heart, prolongation of the QT interval</td>
</tr>
<tr>
<td><strong>RET fusion-positive non-small cell lung cancer, medullary thyroid cancer</strong></td>
<td></td>
<td>Prolongation in the QTc interval</td>
<td>Direct toxicity to cardiomyocytes, inhibition of VEGF and PDGFR signaling, effect on ion channels</td>
</tr>
<tr>
<td><strong>Advanced renal cell carcinoma, hepatocellular carcinoma, several other types of cancer, pancreatic neuroendocrine tumors</strong></td>
<td></td>
<td>Hypertension, reduced LVEF, clinical HF</td>
<td>Direct toxicity to cardiomyocytes, generation of ROS, alteration of ion channels, inhibition of VEGF and PDGF factor signaling</td>
</tr>
</tbody>
</table>
with proteasome inhibitors (bortezomib, carfilzomib), which are the mainstay treatment for multiple myeloma (MM) (tables 1 and 2)6,13.

**Myocarditis**

Myocarditis, a rare but potentially life-threatening cardiotoxic effect, can be induced by immune checkpoint inhibitors (ICIs) evidenced by new left ventricular impairment, active myocardial inflammation as indicated by cardiac MRI or endomyocardial biopsy, as well as elevated serum levels of the cardiac biomarkers troponin T, troponin I, brain natriuretic peptide (BNP), or N-terminal prohormone of brain natriuretic peptide (BNP), or N-terminal prohormone of brain natriuretic peptide (BNP). Of these biomarkers, it is worth noting that troponin I has a high sensitivity, whereas NT-proBNP is less specific for myocarditis and can be increased due to cancer-related inflammation rather than heart failure in acute poisoning with anthracyclines 27. Particularly, atrial fibrillation can be more common than heart failure in acute poisoning with anthracyclines 27.

**Pericarditis**

Infrequent cardiac toxicity following immunotherapy is pericarditis, particularly with combined programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, while the predisposing factors are yet unknown (table 2)26. In addition, pericarditis has also been reported with immune checkpoint inhibitors (ICIs), which may also occur simultaneously with myocarditis, presenting with typical chest pain and dyspnea with rapid progression to respiratory failure12.

**Arrhythmia**

Anthracycline use may lead to sudden death or palpitations14,27. Particularly, atrial fibrillation can be more common than heart failure in acute poisoning with anthracyclines27. Arrhythmias arising due to anthracycline toxicity are treated by discontinuation of the therapy as well as management of arrhythmia in the acute and long term14,15,27. Also, dose-dependent prolongation of the QTc interval has been reported with VEGF TKIs, specifically sunitinib, vandetanib, and lenvatinib28. Individuals who experience an increase in their QTc interval during therapy should discontinue the medication until their QTc returns to 450 ms; dosing should then be resumed at a lower dose11,28. Importantly, concurrent use of potent CYP3A4 (Cytochrome P450, Family 3, Subfamily A, Polypeptide 4) inhibitors, which may raise plasma concentrations of TKIs that block angiogenesis, may necessitate lowering the TKIs dose28. CDK4/6 inhibitors such as ribociclib, which are the standard of care in adjuvant and metastatic breast cancer therapy, also prolong the QT interval,
and those patients are monitored during the first months\(^1\). Furthermore, cardiac conduction disease, including atrial fibrillation, ventricular tachycardia or fibrillation, and AV block, have been reported following treatment with ICIs, the highest incidence being with supra-ventricular arrhythmias\(^{10, 22}\). Furthermore, treatment with immune checkpoint inhibitors (ICIs) can lead to bundle branch block, complete AV, as well as a prolonged PR interval, all of which might result in cardiac arrest (table 1). Arrhythmia risk is time-dependent and is thought to be directly related to T cell-mediated cytotoxicity spurred by the use of ICIs. Finally, bradycardia and heart block have also been linked to taxanes (paclitaxel) (table 2)\(^{13}\).

**Hypertension**

Antiangiogenic agents have been associated with the onset of hypertension\(^{39}\). Therefore, blood pressure should be carefully monitored in all patients undergoing treatment with an angiogenesis inhibitor. Moreover, VEGFR tyrosine kinase inhibitors and bevacizumab have been reported to cause abnormal structural changes in arterial walls that can lead to aortic dissections and aneurysms; thus, it is imperative that patients undergoing treatment with these medications have their hypertension under control, and in the event of otherwise unexplained chest or abdominal pain, a high index of suspicion for aortic dissection is necessary. In addition, hypertension has been reported with microtubule-targeting drugs (vinca alkaloids) (table 1)\(^{10, 31}\).

**Myocardial ischemia and infarction**

Ischemic cardiac events are increased in patients treated with the antiangiogenic agent bevacizumab\(^{32}\). Additionally, specific VEGFR tyrosine kinase inhibitors (regorafenib, sorafenib) have been associated with myocardial ischemia and infarction\(^{11, 32}\).

Furthermore, fluoropyrimidines (5-fluorouracil) have also been linked to cases of myocardial ischemia, with vaso-pasm being a major contributing factor, typically following the inheritance of gene polymorphisms, specifically the rate-limiting enzyme in fluorouracil catabolism\(^{35}\). In addition, major adverse cardiac events are four times more likely to occur in patients receiving ICI treatment\(^{22}\). The myocardial infarction that occurs following ICI therapy is partly driven by ICI-associated inflammation and T cell activation-induced coronary vasculitis\(^{16, 22}\). Furthermore, the expression of the PD-1–PD-L1 doublet is upregulated in myocardial ischemia and infarction, and atherosclerosis is accelerated by PD-1 genetic deficiency\(^{22}\). Moreover, vinca alkaloids (microtubule-targeting drugs) induce myocardial damage and necrosis, thus leading to myocardial ischemia and infarction, and other vaso-occlusive complications (table 2)\(^{36}\).

**Thromboembolic events**

While a prior history of an arterial thromboembolic event (ATE) is not an absolute contraindication for antiangiogenic agent use, keeping a low index of suspicion for drug-related ATEs, including transient ischemic attacks, strokes, angina, and myocardial infarction, is imperative\(^{31}\). Of all the cytotoxic agents, the angiogenesis inhibitor bevacizumab, particularly, has been linked to a higher incidence of potentially fatal ATEs (table 2)\(^{37}\). Therefore, in high-risk patients with a previous thromboembolic event, concurrent anticoagulation with low-dose aspirin alongside bevacizumab is justified. Additionally, bevacizumab has been associated with an increased risk of venous thromboembolism (VTE) in cancer patients, as opposed to other VEGF-targeted therapy\(^{38}\).

**Echocardiographic evaluation in oncological patients**

Assessment of systolic function, which is based on measuring the amplitude and speed of movement or deformation of the myocardium by measuring strain and strain rate, is gaining more and more space in oncology patients themselves.

Oncology patients undergoing chemotherapy and radiation therapy can develop cardiomyopathy not only during treatment but also years after therapy\(^4\). Early detection of left ventricular dysfunction and early detection, prevention, and treatment of cardiotoxicity is crucial to reduce irreversible damage to the myocardium\(^{39}\). In this context, global longitudinal strain (GLS) is a more sensitive parameter than

<table>
<thead>
<tr>
<th>CARDIOTOXIC EFFECT</th>
<th>CYTOTOXIC DRUGS</th>
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<tbody>
<tr>
<td>Heart failure, myocardial ischemia, and cardiac arrest</td>
<td>antiangiogenic agents, osimertinib, mobocertinib, proteasome inhibitors, interferon, interleukin-2, asciminib</td>
</tr>
<tr>
<td>Myocardial necrosis leading to dilated cardiomyopathy and heart failure</td>
<td>sunitinib, alemtuzumab, imatinib, trametinib, taxanes combined with anthracyclines</td>
</tr>
<tr>
<td>Arterial occlusive events</td>
<td>bevacizumab, ponatinib</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>cytotoxic T lymphocyte-associated antigen 4 inhibitors, programmed cell death receptor 1 inhibitors, programmed cell death ligand 1 inhibitors, cytarabine, bleomycin</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>taxanes, vandetanib, vemurafenib, asciminib, ponatinib, crizotinib, nilotinib, histone deacetylase inhibitors</td>
</tr>
<tr>
<td>Prolongation of the correct QT (QTC) interval</td>
<td>vandetanib, osimertinib, mobocertinib, selpercatinib, eribulin, crizotinib, arsenic trioxide, BRAF inhibitors, histone deacetylase inhibitors, tyrosine kinase inhibitors targeting BCR-ABL1</td>
</tr>
</tbody>
</table>

Table 2. Summary of different cytotoxic agents linked with specific cardiotoxic effects
Conclusion

Chemotherapy has been associated with a variety of cardiotoxic effects, including heart failure, myocarditis, pericarditis, arrhythmias, hypertension, myocardial ischemia, and infarction, as well as thromboembolic events. Close monitoring for cardiac adverse effects is indispensable in patients treated with cytotoxic agents, and the risks and benefits of the specific therapies need to be carefully weighed in an individualized manner. The link between cumulative dose and cardiotoxicity is intricate and differs based on the specific medication, treatment duration, and individual patient characteristics.

Literature


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