

## Cardiooncology - cancer treatments and cardiovascular toxicity

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### Abstract

During Second Congress of the 34th American College of cardiology consortium chapter of Serbia and Republic of Srpska, PRactical aspects and comparative analysis of ACC/AHA and ESC guidelines In Serbia 2017 (PRACSIS 2017) in collaboration with the Project and Campaign "25 by25" Of World Heart Federation, Cardiooncology session- treatment of malignant tumors and cardiovascular toxicity was held. The 2016 ESC Position paper on cancer treatments and cardiovascular toxicity developed under the auspice of the ESC Committee for Practice Guidelines were then presented illustrated with our examples from everyday practice. Further in the text below we present parts of this Guidelines with presentation of our cases and comments from the expert.

### Cardiovascular complications of cancer therapy (pathophysiology)

**T**reatment of malignant diseases by applying conventional radiotherapy, chemotherapy, as well as the so-called, innovative drugs from the group of monoclonal antibodies and small molecules, has led to significant progress in terms of prognosis of patients with hemato-oncological diseases. However, more complex therapeutic approaches have led to the emergence of increased morbidity and mortality rates related to adverse effects of applying different chemotherapy agents.<sup>1,2</sup> Cardiovascular diseases (CVD) are considered to be more frequent adverse events as the result of cardiac toxicity of chemotherapy and radiotherapy with concomitant presence of risk factors that predispose their formation.<sup>3</sup>

Cardiovascular complications occur after treatment of malignant tumors, divided into nine major groups, namely<sup>4</sup>:

1. Myocardial dysfunction and heart failure
2. Coronary artery disease
3. Valvular disease
4. Arrhythmias, especially those with QT prolongation
5. Arterial hypertension
6. Thromboembolic disease
7. Peripheral vascular disease and stroke
8. Pulmonary hypertension
9. Pericardial complications

Myocardial dysfunction and heart failure that is applied termin cardiotoxicity are the most common cardiovascular complications of treatment of malignant disease, and the cause of the increase in morbidity and mortality rates. Cardiotoxicity may be manifested immediately after drug administration, or months or years

later. Predicting the degree of cardiovascular damage is very important, because patients receive prolonged polychemotherapy, often combined with radiotherapy.

The dysfunction of the left ventricle (LV) and heart failure are common, so the monitoring of patients in whom they appear is necessary. For example, patients treated for aggressive non Hodgkin lymphoma have the incidence of heart failure, which is 17% after 5 years of treatment of malignant disease.<sup>5</sup>

Drugs that are most commonly responsible for this complication are anthracycline cytostatics, which also represent unique agents in the treatment of hematologic malignancies and solid tumors. They can cause the progressive myocardial remodeling, as a late complication of early myocyte damage and can lead to late cardiomyopathy, but on the other side, the effects can be transient. The most common pathophysiological mechanism for anthracycline – induced cardiotoxicity is a result of hypotheses of oxidative stress with the generation of reactive oxygen species and the process of lipid peroxidation of the cell membrane of cardiomyocytes.<sup>6,7</sup>

The degree of cardiotoxicity is connected with the cumulative dose of the drug, for example, in the case of doxorubicin 400mg/m<sup>2</sup>, the incidence of heart failure is 5%, which is growing exponentially and the amounts to as much as 48%, when a cumulative dose of drug is 700 mg/m<sup>2</sup>.<sup>8</sup>

According to the time of onset, anthracycline cardiotoxicity may be: acute, early and late. Acute toxicity occurs in <1% of the patients immediately after infusion of the drug, and is usually reversible. Most common is the phenomenon of supraventricular arrhythmias, transient LV dysfunction and ECG changes. Acute toxicity reflects damage to cardiomyocytes and can evolve into early or late cardiotoxicity.<sup>4</sup> Unfortunately, it can not be determined with certainty whether it is reversible or

progressive cardiac toxicity, but still an increase in serum biomarkers (troponin, BNP, NT-proBNP) can identify patients who are candidates for long-term myocardial damage. Early toxic effects on the myocardium usually occur within the first year of treatment, while late appear after several years.<sup>9,10</sup> Risk factors for anthracycline cardiotoxicity include: cumulative dose, dosing regimen (fast infusion with rapid peak serum concentration vs. long-term infusion of the drug), existing cardiac co-morbidities, arterial hypertension, concomitant use of other chemotherapeutics, mediastinal radiation, age > 65 years, female gender, renal failure.<sup>4,11</sup>

Other conventional cytotoxic drugs that can lead to myocardial dysfunction and heart failure are cyclophosphamide and ifosfamide - in high doses, as alkylating agents, cisplatin, and antitubular cytostatic agents: paclitaxel and docetaxel.

Immunotherapy with monoclonal antibodies and target molecules from the group of tyrosine kinase inhibitors (TKI) and other molecular signaling pathways inhibitors, despite of significant progress in the treatment of malignancies, was exhibited a degree of toxicity on various organs and tissues, including cardiotoxicity.

An example of such effects is drugs that act in the HER2 (human epidermal growth factor receptor 2) signaling pathway, as antibodies (trastuzumab) or as TKI, such as lapatinib, that are used in the treatment of breast cancer in combination with chemotherapy.

The cumulative incidence of composite cardiac dysfunction when trastuzumab is used in combination with anthracyclines was 6.2% and 20.1% after 1 and 5 year respectively.<sup>4,12</sup>

Also, the inhibition of other signaling pathways such as VEGF (vascular endothelial growth factor), by monoclonal antibodies (bevacizumab, ramucirumab), or drugs from the group of TKI to VEGF receptor inhibitors (sunitinib, sorafenib, cabozatinib, etc), may cause cardiotoxicity, when that drugs are used in the treatment of breast tumors, particularly in combination with anthracyclines.<sup>4</sup>

Small molecules, BCR-ABL kinase inhibitors (imatinib, dasatinib, nilotinib, etc) drugs for the treatment of chronic myeloid leukemia and gastrointestinal stromal tumors, may also lead to the occurrence of cardiac toxicity, as well as the proteasome inhibitors (bortezomib, carfilzomib) which are used in the treatment of multiple myeloma, as well as certain refractory lymphomas.<sup>4</sup>

Radiotherapy of the mediastinum and breast by applying high doses (> 30 Gy) and using the broader field of radiation (> involved field) also potentially cardiotoxic, especially when combined with anthracyclines.<sup>4</sup>

Coronary artery disease (CAD) as type of myocardial ischemia, myocardial infarction, arrhythmia caused by ischemia, can also be a consequence of chemotherapeutic attack. Mechanisms of CAD can arise due to myocardial ischemia, and range from direct vasospastic effects to endothelial lesions and acute arterial thrombosis, and finally may cause the long-term changes in the metabolism of lipids and consequent arteriosclerosis.

Previous mediastinal and breast radiotherapy may precipitate the effect of previously administered drugs to damaged coronary arteries, especially in correlation with the larger applied dose.

Fluoropyrimidines, like 5-fluorouracil (5-FU), and its oral form capecitabine may cause coronary vasospasm by various mechanisms, whereas cisplatin and anti-VEGF agents (monoclonal antibodies and small molecules), may lead to arterial thrombosis.<sup>4,13</sup>

As for the valve diseases, cytostatic agents can not damaged them directly, but radiation therapy can, in approximately 10% of cases, in terms of the fibrosis and calcification of the aortic root, aortic valve cusps, mitral valve annulus and the base and mid portions of the mitral valve leaflets, particularly at doses > 30 Gy.<sup>4,14</sup>

Cardiac arrhythmias can be diagnosed at 16-36% of patients with malignancies, which are: sinus tachycardia, bradyarrhythmias or tachyarrhythmias, and conduction defects which can be life-threatening.<sup>4,15</sup> Certain cytotoxic agents, such as arsenic trioxid, doxorubicin, histone deacetylase inhibitors and TKI, can cause QT prolongation, which can be a prelude to torsade de pointes as a life-threatening condition. Also, ventricular arrhythmia may occur with prolongation of the QT interval as part of chronic toxicity due to the application of chemotherapy and radiotherapy. Prolongation of the QT interval can appear due to electrolyte dysbalance, metabolic disorders, and usage of antibiotics, antifungal drugs, antipsychotics, and constitutional factors of patients with preexisting co-morbidities.

Arterial hypertension is often preexisting comorbid condition, but appearance of new hypertension during treatment can usually induce therapy with VEGF inhibitors, steroids and hormonal drugs such as erythropoietin.

Thromboembolic disease can be often caused by a variety of pathways, including procoagulant, antifibrinolytic and pro-aggregation, through the release of pro-inflammatory and pro-angiogenesis cytokines, as well as through the interaction of blood cells and vascular endothelium by means of adhesive molecules.

Arterial thrombosis is rare and occurs in about 1% of patients, while venous thrombosis is present in about 20% of hospitalized patients with malignancy, which is unfortunately often unrecognized. Various clinical factors are associated with venous thromboembolism in patients with malignant diseases and are defined as: factors related to the tumor (type and histopathological type of malignant disease, clinical stage of disease), factors related to the patient (demographic factors, comorbidities, previous history of thromboembolism, performance status), as well as factors related to the therapeutic approach (major surgery, chemotherapy, hormonal therapy, hospitalizations, transfusions, presence of central venous catheter).<sup>16</sup>

Peripheral vascular disease in terms of severe atherosclerosis or non-atherosclerotic peripheral arterial disease of the lower limbs may occur in over 30% of patients on therapy with TKI<sup>4</sup>, while the risk of stroke doubles in patients who previously had radiotherapy of neck, head and mediastinum.<sup>17</sup>

Pulmonary hypertension is a rare but serious complication that can occur in patients treated with second-generation TKI, such as dasatinib, which can cause severe precapillary pulmonary hypertension, and in patients who underwent hematopoietic stem cell trans-

plantation.<sup>4</sup> Also, cyclophosphamide and other alkylating cytostatics may cause pulmonary veno-occlusive disease.

Based on the foregoing, it follows that it is essential to define the basic risk of cardiac toxicity of each patient with a malignancy that will be treated with chemotherapy with the possible application of radiotherapy. In this regard, after assessing comorbid status, it is necessary to take into account the cumulative dose of anthracycline cytostatics in particular, a combination of drugs that are precipitating adverse effect, the prevention of venous thromboembolism with low molecular weight heparin (LMWH), and by optimizing doses and fields of radiation therapy.

### Therapeutic options for prevention of myocardial dysfunction caused by malignant tumor therapy

These Guidelines<sup>4</sup> are given in order to prevent myocardial dysfunction caused by the treatment of malignant tumor.

Patients with high prior risk for cardiovascular disease (CVD) and were previously treated with the therapy that included anthracyclines, or the risk factor for CVD were poorly controlled the strict control of these risk factors is necessary together with the preventive use of cardioprotective drugs.

If the patient has heart failure (HF) or significant left ventricular (LV) dysfunction before the initiation of treatment, cardiooncological team should decide between the following options: non-cardiotoxic chemotherapy, dose reduction, and/or the use of cardioprotective drugs (beta blockers, ACE inhibitors, aldosterone antagonists, dexrazoxan) (Table 1).<sup>4</sup> Cardioprotection should be initiated also in the cases of elevations of troponin during a high dose anthracyclines therapy. If during therapy course LV EF decrease ensues, treatment according to HF guidelines should be initiated.<sup>18</sup> However, there is no evidence to guide specific cardioprotection if early signs of subclinical myocardial dysfunction are detected during echocardiography-based GLS surveillance.<sup>19,20</sup> Cancer patients presenting with clinical HF during or following chemotherapy should be treated according to current ESC guidelines for HF,<sup>21</sup> the therapy is discontinued, and if therapy continuation is considered, patients should be put on beta blocker and ACE inhibitors. Also, during cancer treatment a healthy lifestyle is recommended (smoking cessation, healthy eating habits, body weight control, and regular moderate exercise, etc).

Having in mind that chemotherapy, as well as malignancies, increases a risk for venous thromboembolism (VTE), anticoagulation therapy with low molecular weight heparin (LMWH) is recommended.<sup>22,23</sup>

### Strategies for attenuation of complications related to use of specific agents

For attenuating **anthracycline** toxicity, there is a possibility to use less cardiotoxic drugs, the reduction in the cumulative dose; use of continuous infusions to decrease peak plasma levels in adult patients.

**Table 1.** Strategies to reduce chemotherapy-induced cardiotoxicity<sup>4</sup>.

| Chemotherapy drug       | Potential cardioprotective measure  |   |               |
|-------------------------|---|---|---------------|
| <b>All chemotherapy</b> | Identify and treat cardiovascular risk factors  |   |               |
|                         | Treat comorbidities (CAD, HF, PAD, HTN)   |   |               |
| <b>Drugs</b>            | QTc prolongation and torsade de pointes:<br>- Avoid QT prolonging drugs<br>- Manage electrolyte abnormalities<br>- Minimize cardiac irradiation |   |               |
|                         | <b>Anthracyclines and Analogues</b>   | Limit cumulative dose (mg/m <sup>2</sup> ):<br>- Daunorubicin <800<br>- Doxorubicin <360<br>- Epirubicin <720<br>- Mitoxantrone <160<br>- Idarubicin <150 |               |
|                         |   | Altered delivery systems (liposomal doxorubicin) or continuous infusions  |               |
|                         |   | Dexrazoxane as an alternative   |               |
|                         |   | ACE-Is or ARBs  |               |
|                         |   | Beta blockers   |               |
|                         |   | Statins   |               |
|                         |   | Aerobic exercise  |               |
|                         |   | <b>Trastuzumab</b>  | ACE-Is        |
|                         |   |   | Beta blockers |

Co-administration of **anthracyclines and trastuzumab** markedly increases the incidence of HF, but cardiotoxicity can be reduced significantly by introducing a drug-free interval between the two agents. The National Cancer Research Institute<sup>24</sup> recommends that if LVEF decreases to 45% or 10 percentage points from baseline to a value between 45% and 49%, trastuzumab should be interrupted and ACE inhibitors should be started; trastuzumab may be reinitiated if the LVEF is restored to 49%. If the decrease occurs despite ACE inhibitor therapy, the patient should be referred to a cardio-oncologist.

Patients treated with **pyrimidine analogues** frequently present angina pectoris, ischaemia-related ECG abnormalities, arrhythmias and myocardial infarction, even in patients with normal coronary arteries. In cancer patients with pre-existing CAD receiving drugs that may produce myocardial ischaemia, aggressive control of CAD risk factors is necessary.

**VEGF signaling pathway inhibitors** can cause blood pressure elevation, so close blood pressure monitoring and treatment is recommended.

Heart-sparing **radiotherapy** techniques should be oriented towards lowering the dose of radiation and the cardiac volume exposed using modern techniques based on 3D treatment planning (CT and MRI). Despite these measures, irradiation of the heart is unavoidable when the target volume is close, such as in left breast cancer and some cases of Hodgkin lymphoma.

## Long-term surveillance programmes for cancer survivors

Over the past decade, the population of patients surviving for long periods after the diagnosis and treatment of cancer has substantially increased together with the risk of CVD development. It is imperative to raise awareness of possible cardiac disease among these patients. Patients should be informed of their increased risk of CVD at the outset of their Cancer treatment and should be advised and supported to make appropriate lifestyle modifications. They should also be instructed to promptly report early signs and symptoms of CVD.

Cardiovascular complications include myocardial dysfunction, vascular disease and valvular heart disease (VHD).

Both paediatric and adult survivors of anthracycline-based chemotherapy have a lifelong risk for the development of LV dysfunction and HF. The time lapse between treatment and the development of HF can be very long, longer than 10 years. Thus, periodic screening with cardiac imaging and biomarkers, such as BNP, should be considered, particularly in those patients who demonstrated reversible LV dysfunction during cancer treatment.<sup>25</sup> Task Force recommendation is to continue HF therapy indefinitely unless normal systolic LV function remains stable after cessation of HF therapy and no further cancer therapy is planned. Trastuzumab-induced cardiac dysfunction is frequently reversible, cessation of HF treatment after normalization of LVEF may be considered for these patients.<sup>26</sup>

Having in mind that high percent of cardiovascular disease is 'silent' screening for ischaemic heart disease is a recommended for patients with cancer who received mediastinal radiation.<sup>27</sup> This screening should start 5 years after irradiation treatment and repeat it every 5 years. Owing to the increased risk of stroke in patients with previous neck irradiation, ultrasound scanning of carotid arteries to rule out the presence of subclinical atherosclerosis could be included for a comprehensive cerebrovascular risk assessment.

Radiation-induced VHD occurs late after mediastinal radiotherapy, with a median time to diagnosis of 22 years.<sup>28</sup> For asymptomatic patients, the EACVI/ASE consensus document recommends a screening transthoracic echocardiogram (sometimes TEE, 3D ultra-sound and CMR in patients with suboptimal TTE) at 10 years post-radiation and serial exams every 5 years thereafter. The European Association of Cardiovascular Imaging and the American Society of Echocardiography (EACVI/ASE) recommend a focused yearly history and physical examination with echocardiography in symptomatic patients.<sup>29</sup>

## Conclusion

The advances in Oncology treatments have brought an increase in long-term survivors.

The primary success was achieved using aggressive protocols with nonspecific, toxic drugs that have brought great consequences on cardiovascular health. On the other hand, the advances in cardiological diag-

nostic procedures and therapy enabled a great number of patients to be treated for malignancies and to perceive overall cardiovascular risk in these treatments.

A close collaboration between oncologists and cardiologists is necessary as well as formation of cardiac-oncology centres, with well-structured service that includes several healthcare professionals (nurses, doctors, cardiologists, imaging specialists, oncologists, etc.) with expertise in this field.

The role of Cardiologist includes a careful initial evaluation before starting potentially cardiotoxic chemotherapy and optimal control of pre-existing cardiovascular risk factors, followed by ongoing cardiac safety monitoring for early signs of cardiovascular toxicity and timely implementation of preventive or therapeutic measures. Oncologists and haematologists are faced with uncertainty over whether to disqualify or qualify a patient from treatment that might be lifesaving, due to baseline CVD.

One of the most important unresolved issues is the choice between a primary vs. secondary prevention strategy (only relevant in patients at highest cardiovascular risk or when using therapy with a high cardiotoxic potential.) There is a lack of evidence on sensitivity of serial assessment of LVEF. Several circulating biomarkers (troponin I, BNP or NT-proBNP) have shown sensitivity for the early detection of myocardial dysfunction.

In order to better identify patients that would benefit from either primary or secondary prevention there is a need to consider several factors: defining the most reliable cardiac monitoring approach, evaluating the rate of subclinical LV dysfunction and its transition to overt HF, determining the clinical effect and outcome (in terms of morbidity and mortality) after cancer therapy.

This approach could provide data that would allow the construction of true evidence-based strategies and open a new era in cardio-oncology.

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