Cardio-Oncology: Between a Rock and a Hard Place

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Abstract
Heart disease and cancer are currently the two leading causes of death in the Western World, creating an intriguing scenario when these two diseases intersect. It is increasingly being recognized that cancer therapeutics have unintended cardiovascular toxicity. Cardio-oncology is a novel, interdisciplinary area of growing interest, based on a comprehensive approach for the management of cancer patients with cardiac diseases.

Keywords: Cardio-oncology; Cardiotoxicity; Chemotherapy; Biomarkers

Abbreviations: BNP: Brain Natriuretic Peptide; HTN: Hypertension; LVD: Left Ventricular Dysfunction; VEGF: Vascular Endothelial Growth Factor; HF: Heart Failure; ROS: Reactive Oxygen Species

Background
Heart disease and cancer are currently the two leading causes of death in the Western World, creating an intriguing scenario when these two diseases intersect. Cancer-related survival improvement is likely due to advancements in early recognition and novel treatment modalities; however it has been associated with an unexpected increase in premature cardiovascular events, including coronary artery disease, hypertension, arrhythmias, stroke, and the development of congestive heart failure [1].

Types of Cardiotoxicity
With respect to ventricular dysfunction, two categories have been previously proposed and conventionally accepted thus far. Type I cardiotoxicity, seen classically with anthracyclines, is thought to be irreversible, dose-related, and caused by free radical formation, oxidant stress, and myofibrillar disarray. Type II cardiotoxicity, seen traditionally with the use of trastuzumab, has been described as reversible and not dose-related, with no accompanied ultrastructural abnormalities. However, it should be noted that the distinction between the two types of cardiotoxicity may be more complicated than once perceived [2]. Radiation therapy induces a spectrum of cardiotoxicities that differ considerably from chemotherapy-related cardiotoxic effects and affect all layers of the heart [3].

Cancer Therapies with Potential Cardiotoxicity
A variety of chemotherapeutic agents are linked with cardiovascular injury after treatment for cancer. The agents most commonly associated with injury include anthracyclines (Doxorubicin, Daunorubicin, Idarubicin), alkylating agents (Cyclophosphamide), tyrosine kinase inhibitors (Sunitinib, Imatinib, Sorafenib, Lapatinib), monoclonal antibodies (Trastuzumab, Bevacizumab), antimetabolites (5-Fluorouracil), microtubule-targeting agents (Paclitaxel, Docetaxel), and proteasome inhibitors (Bortezomib) [4]. The cardiotoxic effects and the mechanism of toxicity are summarized in Table 1.

Diagnosing Cancer Therapy-Induced Cardiotoxicity
The cornerstone of cancer therapy-induced cardiotoxicity diagnosis is the myocardial biopsy, since it is still considered as the most accurate and specific method in detecting the ultrastructural alteration of cardiomyocytes [4]. Nevertheless its invasiveness limited its use in clinical practice. Imaging methods emerged in the last decades as the landmark in monitoring cardiotoxicity in cancer patients. Left ventricular ejection fraction (LVEF) is widely considered the most important parameter for the diagnosis of cardiotoxicity. Several criteria for the diagnosis of cardiotoxicity are established by the Cardiac Review and Evaluation Committee Criteria for Diagnosis of Cardiotoxicity [5]. Despite the usefulness of LVEF as an index of overall cardiac function performance, it should be noted that this represents a late phenomenon in the physiopathology of the chemotherapy-induced cardiotoxicity. Therefore, other imaging methods that evaluate cardiac function independently of cardiac volumes...
alterations, aiming to detect the earliest manifestation of cardiotoxicity have been in use in recent clinical practice.

### Table 1: Cardiotoxic effects of Cancer Therapy

<table>
<thead>
<tr>
<th>Cancer Therapy</th>
<th>Cardiotoxic Effects</th>
<th>Mechanism of Cardiotoxicity</th>
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<tbody>
<tr>
<td>Anthracycline</td>
<td>LVD, HF</td>
<td>Impairment of protein synthesis, ROS formation, inhibition of DNA repair</td>
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<tr>
<td>Alkylation agents</td>
<td>Pericarditis, LVD, HF</td>
<td>ROS production</td>
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<tr>
<td>Tyrosine kinase inhibitors</td>
<td>HTN, LVD, HF, Ischemia, QT prolongation</td>
<td>Impairment of cell signal transduction, cell cycle regulation, metabolism and transcription</td>
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<tr>
<td>Monoclonal antibodies</td>
<td>LVD, HF, HTN, LVD, HF</td>
<td>Inhibition or ErbB2 pathway and VEGF</td>
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<tr>
<td>Antimetabolites</td>
<td>Arrhythmia, Ischemia</td>
<td>Coronary vasospasm</td>
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<td>Microtubule-targeting agents</td>
<td>Arrhythmia, LVD, HF</td>
<td>Impairment of microtubule function and cell division</td>
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<td>Proteasome inhibitors</td>
<td>LVD, HF</td>
<td>Interference with cell cycle degradation proteins</td>
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<tr>
<td>Radiation</td>
<td>Accelerated atherosclerosis, pericarditis, HF, valvular dysfunction</td>
<td>Microvascular injury, macrovascular injury, valve endothelial injury and dysfunction</td>
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</tbody>
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These include two-dimensional echocardiography, real-time three-dimensional echocardiography, speckle tracking imaging, contrast echocardiography, nuclear medicine imaging, and cardiac magnetic resonance (CMR) [6].

Especially CMR has been proven useful, among others, for the detection of the pathological myocardial substrate, responsible for life-threatening ventricular arrhythmias [7]. Finally, there is optimism that the use of specific cardiac biomarkers (Troponin-cTn), hemodynamic markers (Natriuretic peptides) and oxidative stress/inflammation indices (High-sensitivity C reactive protein-hsCRP, Glycogen phosphorylase BB, Myeloperoxidase-MPO, Total antioxidant status-TAOS, Circulating microRNAs) can help identify patients undergoing treatment who are at high risk for cardiotoxicity [8].

### Prevention of Cancer Therapy-Induced Cardiotoxicity

Once evidence of cardiac toxicity is suspected through the use of biomarker, imaging, or clinical exam monitoring it becomes imperative to guide intervention to prevent further damage from occurring. Modulation of chemotherapy with dose and cycle reductions is one possible way of ameliorating cardiac toxicity but often comes at the expense of diminished antitumor effect. Another strategy aims to treat the current cardiac damage and/or prevent further injury through the administration of a variety of preventive agents, such as Dextrazoxane, Angiotensinogen converting enzyme inhibitors (ACE-I), Beta blockers, and Liposomal based doxorubicin [8]. Finally, special attention should be paid to the prevention of cancer-related thromboembolic events, with the use of classical and direct oral anticoagulants [9,10].

### Conclusion

Cardio-oncology is a novel, interdisciplinary area of growing interest, based on a comprehensive approach for the management of cancer patients with cardiac diseases. Because of the increasing number of long-term cancer survivors, the ageing of the population, as well as the increased incidence and prevalence of oncologic and cardiovascular diseases, the number of patients presenting with oncologic and cardiologic co-morbidities are increasing, thus emphasizing the necessity for a comprehensive and evidence-based management of patients in whom the two co-morbidities exist.

### References

