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Cardio-oncology: preventing cardiac damage from mandatory cancer therapy?

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Abstract

Impressive progress has been made in anticancer therapies, allowing successful treatment of previously incurable tumors. However, cardiac side effects are increasingly acknowledged as a result of cancer treatments and they may occur early after initiation or even years after termination of cancer therapy. Cardiotoxicity is difficult to predict and its presentation is variable, ranging from electrophysiological alterations, to abnormal laboratory or imaging tests to the occurrence of arrhythmias, thromboembolism, myocardial ischemia, or heart failure. The extent of cardiac side effects depends not only on the type of cancer treatment (classic or novel drugs, mediastinal radiotherapy), but also on the presence of cardiovascular risk factors and comorbidities. Thus, there is a high need for prevention, detection, treatment, and long-term follow-up of cancer therapy–related toxicity, as well as cardiac monitoring of cancer patients with concomitant cardiovascular diseases. Balancing the potential for improved outcome of cancer therapies with short- and long-term cardiac adverse events requires novel tools for risk stratification and early recognition of cardiotoxicity, such as imaging modalities or biomarkers. A close interdisciplinary collaboration between oncologists and cardiologists allows establishing dedicated cardio-oncology services in order to appropriately address potential cardiovascular complications and improve clinical care of cancer patients. ■ *Heart Metab*. 2018;77:9-12

Keywords: cardio-oncology; heart failure

Classic and novel cancer therapies: the heart is frequently under attack

Many cancer patients have benefitted from improved cancer treatment modalities, such as surgery, chemotherapy, radiation therapy, or novel targeted anticancer drugs, which helped to turn previous fatal cancers into curable diseases with increasing numbers of long-term survivors.[1] However, despite progress in identifying risk factors for cardiac side effects of classic chemotherapy and improved cardiac surveillance of cancer patients, cardiotoxicity is still frequently observed and limits quality of life and long-term prognosis.[2-4] On the other hand, early

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discontinuation of or a reduction in cancer therapies as a consequence of cardiac side effects may significantly impair the oncology outcome. Particular combinations of drugs or additional radiation therapy can have synergistic effects on cardiotoxicity.[2,3] Moreover, an existing cardiovascular risk profile or concomitant cardiac diseases are associated with an increased risk for left ventricular dysfunction or heart failure.[4,5] Nevertheless, there is a considerable individual variation in cardiac side effects that could be at least in part attributed to genetic predisposition.[6,7] Besides heart failure, cardiotoxicity may also present as arrhythmia, endocardial or pericardial complications, myocardial ischemia, and finally vascular complications.[2,3]

Cancer as a comorbidity and vice versa

Besides cancer therapy–associated cardiotoxicity, there is increasing evidence that the cancer itself may influence cardiac function. For example, several preclinical models have linked cancer with cardiac cachexia, which is characterized by cardiac atrophy and remodeling.[8] Furthermore, impaired systemic glucose metabolism seems to link cancer to impaired cardiac function and cardiac wasting.[9] On the other hand, heart failure promotes cancer growth by increasing soluble factors.[10] Most of these data, linking cancer and cardiac dysfunction to direct intercellular communications, are coming from preclinical models. The impact on the individual clinical course needs to be further explored in the future. However, these data are important because they link two endemic diseases and add up a novel layer of complexity with a high potential for future therapeutic approaches.

Novel cancer therapies and their cardiotoxic effects

Beside the "classic" cardiotoxic cancer therapeutics, such as anthracyclines and HER2-antagonists, there are novel drugs that are used broadly with a potential of cardiotoxicity (ie, proteasome inhibitors, RAS/RAF/MEK inhibitors, and immune checkpoint inhibitors).

Proteasome inhibitors

Recently, a novel generation of irreversible proteasome inhibitors was developed. This family of drugs has a high potential for the treatment of distinct cancer subtypes, such as multiple myeloma. Cardiac side effects range from arrhythmias to heart failure, with a frequency of up to 22% and an early occurrence after initiating a therapy.[11] Based on preclinical data from the Center for Drug Evaluation and Research, carfilzomib, the most frequently proteasome inhibitor used in clinical practice, completely blocks the chymotrypsin-like activity of the 20S proteasome in the heart directly after administration.[11] So far, there are no clinical data available that have systematically assessed cardiac changes under a proteasome inhibitor therapy using state of the art imaging techniques and/or cardiac biomarkers. Therefore, with improved patient survival, a better understanding of how to identify high-risk patients and how to treat them is needed.

RAS/RAF/MEK inhibitors

This family of therapeutics is frequently used in patients with malignant melanoma. Preclinical data have already shown that members of the mitogen activated kinases, such as RAS, RAF, and MEK, play an important role in cardiomyocytes.[12,13] Many of these studies have shown that this signaling pathway is required for normal cardiac function and protects the heart from adverse remodeling. Consequently, pharmacological inhibition in patients with malignant melanoma can be expected to be cardiotoxic. In clinical studies, combination therapies led to a reduction in left ventricular function of up to 8%.[14] Based on single cases, a reduction in the left ventricular ejection fraction can be expected at an early time point (2 weeks after initiation).[15] Therefore, an early assessment of cardiac function by echocardiography should be considered to rule out potentially harmful effects of this promising cancer therapy. The role of cardiac biomarkers for the detection of cardiotoxicity in patients with RAS/RAF/MEK inhibitors needs to be determined.

Immune checkpoint inhibitors

This novel class of anticancer drugs has started to revolutionize the treatment of different cancers by restoring immune resistance against cancer cells. Immune checkpoint inhibitors comprise monoclonal antibodies against immune checkpoint molecules. The first substance, ipilimumab, is a monoclonal antibody against cytotoxic T lymphocyte–associated antigen 4, which strikingly improves prognosis in patients with

melanoma by doubling the likelihood of long-term survival.[16,17] Further antibodies have been developed and successfully used in different solid tumors and hematological malignancies in the last few years.[18,19] However, these substances do not only restore antitumor immunity, but may also result in immune-related adverse events, such as myocarditis.[20,21] Although cardiotoxicity was overall low in clinical trials and in a large safety database,[22,23] increasing amounts of new substances and combinations require careful cardiac follow-up in order to identify myocarditis early in patients who are at risk. Since the presentation of myocarditis ranges from elevated biomarkers to different clinical findings, such as fatigue, chest pain, heart failure, arrhythmias, heart block, cardiogenic shock, and sudden death,[24] physicians need to be alerted in the case of EKG alterations, troponin elevation, or cardiac morphological abnormalities in patients treated with immune checkpoint inhibitors.

Challenges for following up cardiotoxicity in cancer patients

The differentiation of left ventricular dysfunction or heart failure as an effect of the cancer from an independent preexisting cardiac disease is challenging. The impact of cancer therapy–induced cardiotoxicity can be detected by assessing cardiac function before cancer therapy and during the subsequent follow-up. A symptomatic or asymptomatic decrease in left ventricular ejection fraction of more than 10% to less than 50% is considered clinically relevant and should result in reassessment of the anticancer therapy.[2,3] If oncology therapy is continued, a close cardiological follow-up should be scheduled and heart failure therapy should be initiated.[2,3] In the case of anthracycline chemotherapy, the role of early diagnosis of impaired left ventricular function and initiation of heart failure therapy has been well shown.[25,26] Although the use of biomarkers, such as troponins or natriuretic peptides, in asymptomatic patients without previous cardiovascular diseases has not been generally established, a potential role could be in tracking subclinical changes that might influence anticancer therapy in individual patients.[2,3] In particular, patients on immune checkpoint inhibitors may benefit from regular measurements of troponin for early detection of myocarditis.[24]

Is there hope for the heart?

While many questions regarding diagnosis and prophylaxis of cancer therapy–induced cardiotoxicity remain open, there are also encouraging reports about cardiovascular mortality in breast cancer patients. In older studies, increased cardiovascular mortality was reported, which was potentially due to high cardiotoxicity of combination therapies.[27] Interestingly, more recent studies have shown that cardiovascular mortality is not increased in breast cancer patients any more,[28,29] which might be explained by an increased consideration of cardiac protection when applying potentially cardiotoxic therapies, an improved understanding of mechanisms causing cardiac damage, and the early involvement of cardiologists in following up patients who are at risk. Implementation of dedicated cardio-oncology service structures will further help to prevent, diagnose, or treat cardiovascular adverse events in cancer patients.[30] ■

Conflicts of interest: *Authors declare that there are no conflicts of interest.*

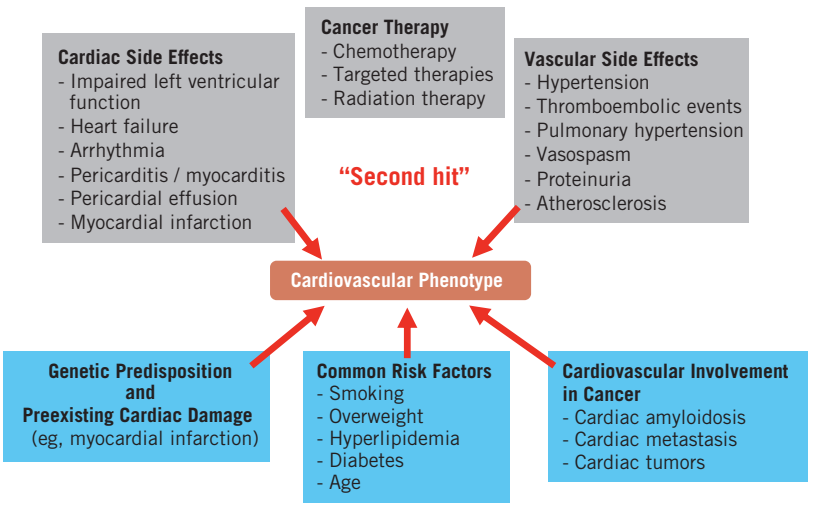

Fig. 1 *Concept of damage by cancer therapies as a second hit on preexisting cardiovascular conditions, such as genetic predisposition, previous cardiac damage, risk factors for cardiovascular diseases, and cardiovascular involvement in the cancer itself.*

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