



The rising tide of cardiotoxicity associated with cancer chemotherapy

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Editorial

Advances in cancer treatment over the last few decades have resulted in marked improvements in patient survival. Unfortunately, many of these new cancer therapies are also associated with toxic side effects on the heart. Consequently, the use of newer potentially cardiotoxic cancer drugs, combined with an improvement in patient survival from the cancer, has resulted in a sharp rise in the incidence of heart failure in cancer patients. In fact, in many cancer patients the risk of developing heart disease may be higher than the risk of cancer recurrence [1]. Indeed, the American College of Cardiology/American Heart Association guidelines define patients receiving chemotherapy as Stage A heart failure patients, since they have an increased risk of developing heart failure [2]. The cardiotoxicity associated with cancer chemotherapy can range from mild and temporary alterations in left ventricular ejection fraction (LVEF) to severe and irreversible life-threatening heart failure. Because of the importance of cardiotoxicity associated with cancer therapy, this edition of *Heart & Metabolism* addresses the important issue of cancer and the heart.

Many of the pharmacological approaches to treat cancer involve a mechanism of action that is actually toxic to the cardiomyocyte. This includes approaches to promote free radical production, promote apoptosis, prevent angiogenesis, inhibit metabolism, and promote ischemia. It is not surprising, therefore, that a number of these cancer cytotoxic agents have the potential for cardiotoxicity. This includes the use of agents such as the anthracyclines, alkylating agents, microtubule targeting agents, monoclonal antibodies, tyrosine kinase inhibitors, and cytokines to treat cancer. The potential for cardiotoxicity during cancer treatment is not confined to acute use of cancer chemotherapy, but can also manifest in the chronic setting. Chiara Lestuzzi nicely highlights this in the Case Report in this issue of *Heart & Metabolism*, which describes a case of late left ventricular dysfunction in a long-term survivor of cancer. This case highlights the need to closely monitor survivors of cancer and aggressively treat any risk factors for the development of heart disease. This type of patient should benefit from the many recent advances made in treating heart disease. One of these involves advances made in anti-coagulant therapy. The Hot Topics article by Alda Huqi describes how newer-generation compounds, which includes dabigatran, may replace the use of warfarin as standard anti-coagulant therapy.

The mechanisms by which cancer cytotoxic agents result in cardiotoxicity are multifactorial. The Basic Article by Christian Zuppinger describes potential mechanisms as to how some of these cytotoxic chemotherapies for cancer may exert their cardiotoxic effects. The Main Clinical Article by von Klemperer and Fox also nicely highlights what cardiac manifestations these cancer chemotherapies can exert on the heart. This includes both the acute and chronic cardiac dysfunction that can result from the use of these cancer therapies. In addition, this article also describes how to identify and detect this cardiac dysfunction.

Detecting and monitoring cardiac dysfunction in cancer patients can involve a number of diagnostic methods including the use of echocardiography, radionuclide ventriculography, cardiac magnetic resonance imaging, and the use of biomarkers. Positron emission tomography (PET) has long been an important tool in detecting cancers, particularly by monitoring glucose uptake by the cancer cell. Indeed, as described in the Refresher Corner article by Jagdip Jaswal, cancer cells display a phenomenon called the Warburg effect, in which rapidly proliferating cells have enhanced glycolytic rates, which is uncoupled from the subsequent oxidation of the glucose. This increased uptake of glucose by cancer cells has been successfully exploited using PET to detect tumors. Use of PET to image glucose uptake (using ^{18}F -deoxyglucose) is an important tool for detecting tumors. In addition, however, PET can also be used to image the heart, and potentially to diagnose cardiac abnormalities. The Metabolic Imaging article by Mukesh Pandey, Aditya Bansal, and Timothy DeGrado describes some novel fatty acid oxidation imaging agents that can be used to assess fatty acid oxidation in the failing heart. These authors also describe how these PET imaging agents may also be useful in detecting tumorigenic cells.

As mentioned above, rapidly proliferating cancer cells have a distinct switch in metabolism, away from mitochondrial oxidative metabolism and towards glycolysis. The decrease in mitochondrial oxidative metabolism may actually decrease apoptosis and promote survival of the tumorigenic tissue. The New

Therapeutic Approaches article by Peter Dromparis, Gopinath Sutendra, and Evangelos Michelakis describes a potentially exciting new approach to treating cancer, which involves promoting mitochondrial oxidation of the pyruvate derived from the accelerated glycolysis seen in tumorigenic tissue. These authors have pioneered a new metabolic strategy for treating cancer that involves the stimulation of pyruvate dehydrogenase (PDH), using the metabolic agent dichloroacetate [3]. By stimulating PDH, glycolysis is better coupled to glucose oxidation in the tumor cell, resulting in an effective decrease in tumorigenesis. Another approach to stimulating PDH is to inhibit mitochondrial fatty acid oxidation, which indirectly results in an increase in mitochondrial PDH activity. The Focus on Trimetazidine (Vastarel[®] MR) article by Alda Huqi describes the potential use of the fatty acid oxidation inhibitor trimetazidine to treat cancer. The potential advantage of this therapeutic approach is that trimetazidine may also decrease the severity of cardiac toxicity in cancer, as a number of studies have shown that trimetazidine has efficacy in treating heart failure.

In summary, cardiac dysfunction is an important consideration when deciding on the best therapeutic approach to treat cancer. This calls for new relationships to be developed between the oncologist and the cardiologist in detecting, treating, and preventing cardiac dysfunction associated with the new cancer treatments. The development of novel therapies to treat cancer that involve metabolic modulation of the tumor cell may be one approach effectively treating cancer, while lessening the possibility of cardiac dysfunction. •

References

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