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Editorial

Cardiac Disease in Cancer Patients: An Overview

There is a growing awareness of the potentially negative effects of cancer treatment on the heart and the management of cardiac disease during and after cancer therapy.[1,2] As newer chemotherapeutic agents are being developed with significant potential for cardiotoxicity,[3,4] as well as utilization of combinations of chemotherapy with known impact on the cardiac system,[5] the salutary effects resulting from cancer treatment, especially prolonged survival, allow persons to live long enough that cardiac toxicity can be the main determinant of quality of life and, in severe cases, can lead to "premature" mortality. In fact, for early-stage breast cancer, a person is more likely to die of heart disease than cancer.[6] This awareness is leading to new initiatives to develop cooperation and partnership between oncologists and cardiologists for the optimal management of these patients with cancer.[7]

The management of heart disease in all its forms in patients with cancer in all its forms presents special challenges to the cardiologist. In the war on cancer, the cardiologist is not in the front lines, directly confronting the enemy, but in the role of support and supply, providing the oncologist the ability to keep the warrior strong enough to defeat the enemy. In fighting the war on cancer, there is, like in any war, unwanted "collateral damage." There is no "silver bullet" but, in many ways, a refined shotgun, blasting the tumor while pellets hit other vital organs. The bone marrow, liver, and nervous system get their share of hits; but the heart and vascular system are certainly at risk depending on the weapon used, particularly because the vascular system and blood supply are intimately involved in any treatment delivery. Just as in a war, not only must the enemy be destroyed; but the damage must be contained to permit the rebuilding of the homeland.

The cardiologist's role in managing the cancer patient is not necessarily to protect the heart at the expense of undertreating the cancer, but rather to keep the heart and vessels from being so damaged that the patient's ultimate quality of life is not seriously impaired and/or life span is not shortened from cardiovascular causes. The cardiologist must use his/her expertise for the identification and management of the cardiac injury to maximize the potential for successful chemotherapy. New protocols to identify patients at risk for cardiac toxicity before clinically significant damage has occurred will benefit from the expertise of cardiologists familiar with chemotherapeutic agents and the latest imaging techniques.[8,9]

Managing cardiac disease in the cancer patient is unique and in many ways unlike managing cardiac disease in patients without cancer (Table 1) That is, the large seminal randomized trials of cardiac therapy upon which modern management of heart failure[10] or coronary disease[11-13] was developed uniformly excluded patients with cancer; so there are no true evidence-based guidelines that apply to the management of these patients. Thus, an important challenge to the cardiologist partner is to develop data that will allow the creation of evidence-based guidelines specific for the management of cardiac disease during and after cancer therapy. The challenge to the cardiologist is a modern version of the dilemma of Odysseus (Fig 1), who, to plot a course between Scylla and Charybdis, chose to avoid the whirlpool of Charybdis that would have led to the loss of the entire ship and all its crew by bearing close to Scylla where the many-headed monster would devour some of the crew, but the majority could pass by.* In typical cardiac patients, myocardial dysfunction and heart failure are caused by a variety of insults, some understood and some not understood: coronary ischemia and infarction, hypertension, viral infection, chronic inflammation, hereditary propensity, toxins (eg, cocaine, alcohol), and acute and chronic stress,

* Retrieved from Wikipedia April 9, 2010. Scylla was said to be a creature who was rooted to one spot in the ocean and regularly ate sailors who passed by too closely. Her appearance has varied in classical literature; she was described by Homer in *The Odyssey* as having 6 heads perched on long necks along with 12 feet, while in Ovid's *Metamorphoses*, she was depicted as having the upper body of a nymph, with her midriff composed of dogs' heads. Charybdis was depicted with a single gaping mouth that sucked in huge quantities of water and belched them out 3 times a day, creating whirlpools. According to myth, Odysseus was forced to choose which monster to confront while passing through the strait; he opted to pass by Scylla and lose only a few sailors, rather than risk the loss of his entire ship into the whirlpool. Crane, Gregory R. (ed). "Homer, Odyssey bk 12 l. 73." Homer, Odyssey. Tufts University.

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme

AICD = automatic implanted cardioverter defibrillator

BMS = bare metal (coronary artery) stent

CABG = coronary artery bypass graft surgery

DAPT = dual-antiplatelet therapy

DES = drug-eluting (coronary artery) stent

IVC = inferior vena cava

LMWH = low–molecular weight heparin

LV = left ventricle

NSTEMI = non–ST-segment elevated myocardial infarction

TEE = transesophageal echocardiogram

to name a few. In that situation, the cardiologist first aims to correct the inciting etiology if possible, that is, get the patient to stop drinking, stop smoking, lose weight, revascularize the ischemic myocardium, and treat the underlying inflammation. With the cancer patient, there is slightly different goal: to find ways to limit and/or modify the cardiac damage while permitting cancer therapy to continue.

The nature of the toxicities for the plethora of chemotherapeutic agents is just beginning to be carefully documented. An excellent overview of these problems is chronicled in this issue by Giuseppe Curigliano, MD, et al. Joanna Brell, MD, describes the difficulty of developing cancer drugs with potential cardiac toxicity and how regulation and oversight mechanisms protect and impede development. The capacity of defining prognosis with cessation of therapy or, more importantly to the patient, the prognosis with resumption of therapy[14-16] is just being developed. These data are presently available only from large single centers of excellence,[16] and multicenter studies are needed. The latest understanding of the effects of the major agents on direct toxicity to the cell, at the level of the subcellular systems, will be presented by a host of experts in the basic science of myocyte development and repair. These sections include the effects of tyrosine kinase inhibition by Thomas Force, MD; the strategies for protection during anthracycline administration by Douglas Sawyer, MD; and tratuzumab-related cardiotoxicity by Joseph Carver, MD. The translation of detailed cellular knowledge and understanding to the management of patients is just beginning. The potential cardiac toxicity of proinflammatory cytokines in cancer patients not only resulting from the chemotherapy, but as a result of the serious infections and other stressors these patients often endure, is another area of concern, which can result in serious arrhythmias, plaque rupture with infarction, and/or worsening left ventricle (LV) function.[17-20]

There needs to be agreement on measures of cardiac function to be used to guide therapy. For example, the oncologist defines cardiac toxicity by serial measurements of ejection fraction; and the criterion standard for many years has been the number obtained from the radionuclide multiple gated acquisition.[14,21] Cardiologists know that the correlation between symptomatic heart failure and ejection fraction is not reliable and that diastolic heart failure[22] carries a similar prognosis as heart failure with a depressed ejection fraction.[8,23] Advances in echocardiography with Doppler velocity measurements may provide information on ventricular function both in systole and diastole[24] as well as valve dysfunction and pericardial pathology. Measurements of only LV ejection fraction remain limited in the description of cardiotoxicity. The use of magnetic resonance imaging provides data on myocardial anatomy, ventricular structure, and hemodynamic based measurements but has not been validated in this setting and has not been a widely applicable test at the current time for several reasons, including expense, availability, expertise, and the length of time a patient has to cooperate to obtain adequate images.

The identification of troponin as a specific and extremely sensitive biomarker of ventricular damage has revolutionized the diagnosis of myocardial infarction,[25] as well as aided in the management of myocarditis and even pulmonary embolism.[26,27] B-type natriuretic peptide has simplified the diagnosis and management of heart failure and is a powerful predictor of outcome of cardiac patients[28] and cancer patients in a host of contexts.[29,30] These advances in biomarker detection and use have yet to be systematically introduced into the cancer patient population.[9] but early studies hypothesize an important surveillance role. The article by Cardinale and Sandri (p 120) provides an excellent overview of the current knowledge of cardiac biomarker utilization for the detection of cardiac toxicity.

Management of the patient with serious cardiac damage, including LV dysfunction, is extremely challenging in cancer patients. The major breakthroughs in long-term management of heart failure in the general cardiac population came from understanding the role of neurohormonal activation in heart failure[31] with management using angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and aldosterone antagonists.[27] However, it is not at all clear that these same mechanisms are activated to the same degree in chemotherapy-induced heart failure. Moreover, there is no information regarding the dose or dosing of these so-called neurohormonal antagonists in cancer patients. Finally, the arterial blood pressure is often low in these patients, which may lead to excessive fatigue and/or worsening renal function, such that different strategies may need to be devised for their treatment. The role for device therapy such as biventricular pacing has not been evaluated in cancer survivors with impaired systolic dysfunction, and the role of implantable cardiac defibrillators