The Compelling Need for a Cardiology and Oncology Partnership and the Birth of the International CardiOncology Society

Daniel J. Lenihan\textsuperscript{a}, Daniela Cardinal\textsuperscript{b}, Carlo M. Cipolla\textsuperscript{b,*}

\textsuperscript{a}Division of CV Medicine, Vanderbilt University, Nashville, TN, USA
\textsuperscript{b}Cardiology Unit, European Institute of Oncology, University of Milan, Milan, Italy

Abstract

Cardiac disease in patients with cancer is common and influences the longevity and quality of life both of patients in active treatment and of survivors of cancer. The disciplines of cardiology and oncology have increasingly recognized the benefits to patients of collaborating in the care of cancer patients with cardiac disease. This increased recognition arises from several factors: the aging population in which both cardiac and cancer diagnoses are common; the cellular and molecular therapeutic targets of newer medical treatments, and, in particular, the specific patient treatment choices and decisions that require careful, effective clinical interactions between these 2 disciplines. Responding to this need for an effective partnership between cardiology and oncology, the International CardiOncology Society was created and has set goals to develop and enhance our understanding and management of these clinical difficulties. (Prog Cardiovasc Dis 2010;53:88-93)

Keywords: Cardiotoxicity; Chemotherapy; Anti-angiogenesis; Cardiology and oncology

Scene 1:
December 1991, Venice, Italy.
City General Hospital, Medical Ward.
A 49-year-old man with a history of gastric lymphoma diagnosed several years previously and now in complete remission presents to the emergency room with typical angina during strong physical activity. He was diagnosed with an acute inferior myocardial infarction confirmed by electrocardiogram and serum enzymes. He was admitted for observation to the floor. No telemetry or cardiac catheterization was performed since “he is a cancer patient”.....

Scene 2:
April 1994, Milan, Italy.
University Cardiologic Center, Intensive Coronary Care Unit.
A 45-year-old woman with metastatic breast cancer has a recent onset of dyspnea not responsive to standard treatments. Echocardiogram demonstrates massive pericardial effusion with tamponade. It is then decided there is no need for intensive care, only palliation, because “neoplastic pericardial effusion tamponade is a typical end-stage manifestation of a cancer patient and there is nothing to do”.....

Scene 3:
June 1995, Milan, Italy.
European Institute of Oncology.
At the end of the first year of activity in this comprehensive cancer center, the percentage of cancer patients admitted who had a cardiac consultation: 7%.

Scene 4:
December 2008, Milan, Italy.
European Institute of Oncology.
At the end of the 15th year of activity in one of the most important cancer centers in the world, the percentage of
cancer patients admitted who had a cardiac consultation: 77%.

Scene 5 and 6: January 2009: The International CardiOncology Society is born.

September 2009: More than 100 international experts meet in Milan for the third international cardio-oncology congress.

Flash forward to 2025: All the cardiologists and oncologists of the world will have learned that for the optimal care of cancer patients, they enjoy working together.

It is this dream, hatched more than 15 years ago, that occurred to a group of cardiologists after noticing many discrepancies in the cardiac care of cancer patients. Convincing cardiologists that patients with cancer are, in many cases, patients with a chronic comorbidity to be managed, more like diabetes, as opposed to a terminal disease, can be challenging. This change in focus arises from well-established data showing the survival rate of patients with cancer, as well as those with cardiovascular (CV) disease, has greatly increased over the past 3 decades. This increase in survival is explained by improvements in pharmacologic treatment, enhanced surgical approaches, more detailed and sophisticated procedures, and presumably the reduction and control of major risk factors for both cancer development and atherosclerosis. At the same time, as the population ages, the incidence and prevalence of cancer and CV disease rise simultaneously and frequently patients may present with both oncologic and cardiologic comorbidities. In fact, cardiac disease and cancer together make up more than 70% of disease-related mortality in the developed world.

In the future, an emphasis on “personalized” therapy will continue to make collaboration between cardiologists and oncologists important. For instance, the targets of therapy at the cellular and molecular level are sometimes identical in cancer therapeutics and in CV treatments. One example is vascular endothelial growth factor (VEGF). To control and limit tumor growth, oncologists have developed drugs, such as bevacizumab, which inhibit VEGF creating an antiangiogenic effect. Although the target of therapy is the tumor, it is clear that systemic effects are likely with any new drugs and many will have important CV effects. Already this has been observed and each new drug may have specific characteristics that result in unique toxicities. In cardiology, over the past decade, VEGF has been given in clinical trials through a number of techniques to promote angiogenesis in the myocardium and in other tissues affected by ischemia. Although VEGF has been identified in connection with angiogenesis in ischemic tissues, the therapeutic trials with VEGF failed to show meaningful improvement in coronary ischemia. A second example is stem cells. Stem cell therapy, a vital component of treatment of certain hematologic-based malignancies, is being aggressively investigated in cardiac disease as a method of restoration of cardiac function after damage primarily from ischemic heart disease. A partnership between the cardiologists and oncologists is essential to bring stem cell engraftment into this arena.

However, the most compelling reason for the effective integration between the disciplines of cardiology and oncology comes from everyday patient care and decision making. Trastuzumab, an extremely effective anticancer therapy for breast cancer targeting the Her2-neu receptor, had an initial signal of substantial cardiac-related toxicity. Over the next decade, studies were carefully done with input from cardiology that helped refine the best target population for treatment with minimal toxicity and strategies were developed for dealing with individual patients to optimize their cancer treatment.

Anthracyclines, a class of drugs known to cause substantial cardiac-related toxicity, are still widely used therapies. It had previously been generally believed that detection of toxicity was difficult and treatment of left ventricular dysfunction was not very successful. Over recent years, because of active research, primarily from cardiologists, paradigms have been developed to manage these problems, with a notable impact on patient outcomes. Newer anti-VEGF-based therapies have a common clinical characteristic in which hypertension is induced, sometimes to alarming levels. Partnership with cardiologists in the patient management has improved outcomes in these situations.

To provide optimal treatment in situations involving patients with problems in both arenas, a coordinated effort by experts in both disciplines is required. When a cardiac patient develops an oncologic problem, the treating cardiologist often loses interest and tends to assume a defeatist attitude that may exclude the patient from other intensive treatment and/or intervention possibilities. Conversely, when a patient with cancer develops a cardiac problem, the patient is too often excluded from first-line, more aggressive (and therefore, more effective) chemotherapeutic strategies with a major impact on the cancer outcome. The patient moves “beyond the jurisdiction” of both the cardiologist and the oncologist, without getting comprehensive care from either discipline. As a consequence, the management of such patients is limited, disjointed, and often inadequate and most importantly the patient feels left alone and unprotected. Thus, a new discipline, CardiOncology, was created to meet these needs. A primary goal of this working group is to investigate innovative strategies, to collaborate and provide evidence-based recommendations, and to develop interdisciplinary expertise that will allow optimal management of this new and growing category of patients.
The elements mentioned above drove the development of the International CardiOncology Society (ICOS) in January 2009 (www.cardioncology.com). During the international meeting in Milan, a consensus document was presented that included several recommendations representing input from all that participated. The consensus document is summarized below:

Goals of ICOS:

- Eliminate cardiac disease as a barrier to effective cancer therapy
- Prevent the development of heart failure wherever possible
- Establish a multiinstitutional and international database
- Promote productive involvement of all important stakeholders in the development of clinical decisions with optimal patient outcomes as the focal point
- Develop web-based educational tools and interactive case study questions to provide ongoing clinical feedback to providers
- Develop the Common Terminology Criteria, version 4, to include sophisticated cardiac-based diagnostic tools and ultimately extend this common reporting criteria to CV clinical research
- Disseminate practical multidisciplinary guidelines, which are lacking at the moment, for cardiac monitoring of cancer treatments

These goals are laudable and optimistic, but certainly questions remain.

How can we achieve integration between cardiology and oncology with the best practice of medicine?

I. Collaborate at the outset with ongoing research

A. Define CV risk assessment at the beginning of research protocols

There is burgeoning evidence that CV risk factors may have a substantial impact on the cardiac toxicity of cancer chemotherapeutic agents and the preventive treatment of CV-related comorbid conditions can have a significant benefit on all-cause mortality and cardiac-related outcomes. Because many easily modifiable CV risk factors are not routinely measured in oncology treatment trials, these efforts must improve and be followed over the course of any carefully done clinical trial.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>CV toxicity: overall definition</th>
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<td>New symptomatic arrhythmia and conduction disturbances</td>
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<tr>
<td>Acute coronary syndrome</td>
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<td>Symptomatic heart failure</td>
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<td>Newly developed asymptomatic left ventricular dysfunction</td>
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<td>Sudden cardiac death</td>
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<td>Development of hypertension</td>
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<td>Pericardial disease</td>
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<td>Thromboembolic events (arterial and venous)</td>
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<th>Table 2</th>
<th>Definition: cardiac dysfunction</th>
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<td>Severity Grade</td>
<td>Adverse Event</td>
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<tr>
<td>Left ventricular systolic dysfunction</td>
<td>–</td>
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<td>Ejection fraction decreased</td>
<td>–</td>
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<tr>
<td>Heart failure</td>
<td>Asymptomatic with laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities</td>
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Definition: a disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations may include dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.

Definition: the percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present before the contraction.

Definition: a disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or the ability to do so only at an elevation in the filling pressure.
B. Integrate necessary sophisticated cardiac testing during oncology research into reported findings

Improving the standard of cardiology-based data critical to the conduct of a clinical study is essential.

C. Explore optimal screening techniques being mindful of practical issues (such as cost, feasibility, and effect on cancer or cardiac-related outcomes)

Screening for undiagnosed CV disease can be an extensive process and has to be viewed in the context of cancer treatment and the underlying cancer diagnosis. Screening for asymptomatic cardiac disease in patients with previous cardiotoxic therapy, including mediastinal radiation, requires the cardiologist to have knowledge of previous cancer therapy and its potential impact on the heart. Thus, international collaboration to help define these CV risks in cancer patients and report evidence-based screening strategies is needed.

D. Standardize definitions for cardiac-related events during chemotherapy or other cancer therapeutics in a clinically relevant manner

A standardized definition of cardiotoxicity is essential for the conduct of meaningful research. There have been a variety of definitions of “cardiac toxicity” over the past 2 decades of oncology clinical trials and the majority, if not all of them, are based largely on the measurement of left ventricular ejection fraction. Furthermore, different thresholds for the determination of cardiac toxicity have been used, which makes it difficult to establish the true incidence of “cardiac toxicity” over time. To eliminate such difficulties, a common definition needs to be established and one that incorporates clinical findings, not just laboratory tests, into the determination is necessary. The recently updated Common Terminology Criteria for Adverse Events, version 4, groups specific cardiac-related toxicity into clinically relevant categories that enhance the nature of cardiac issues that may occur in the course of cancer clinical research and treatment. An all-inclusive grouping used to broadly define cardiovas-

cular toxicity is described in Table 1. Cardiac dysfunction should include left ventricular systolic dysfunction, reduced ejection fraction, and heart failure by the criteria described in Table 2. Acute coronary events/myocardial infarction will incorporate acute coronary syndrome, myocardial infarction, and the rare diagnosis of myocar-
ditis in a clinically meaningful group that would allow an accurate detection of true acute coronary events (Table 3). Cardiac laboratory events will incorporate QTc interval measurements and troponin testing together as these are primarily laboratory findings and minor changes are not usually indicative of detectable and actionable clinical events (Table 4).

E. Contribute to the creation of an international database with cardiac end points in cancer patients to enhance the potency and relevance of post-marketing surveillance

It is recognized that detailed observation of outcomes of patients in clinical trials is already being done, but the accurate reporting of outcomes of patients excluded from trials or never enrolled is completely inadequate. There is a need to provide “post-marketing” surveillance for all
treatments to capture low frequency but important events, and there is a recognized essential need to do this for newer anticancer therapies that will likely have a myriad of CV effects when used in a broad unselected aging population. With the sophistication of the Common Terminology Criteria for Adverse Events criteria and the organization of oncology treatment groups, there is a clear and obvious opportunity to actually achieve this goal. The ICOS will strive to establish a method to follow important outcomes of all patients in an organized and data developing manner to understand patient safety issues better and more accurately.

2. Promote the prevention of heart failure and other major cardiac events by active cardiology involvement in high-risk clinical scenarios

A. Prevention and early detection are principles of cancer therapy that directly apply to the management of cardiac disease encountered in cancer patients

Proactive involvement by cardiology in the management of patients with cancer can be critically important. Examples of this vital integration includes the management of hypertension during anti-VEGF or antiangiogenic therapy18 and the detection and treatment of serious arrhythmias in high-risk populations such as those with amyloidosis undergoing stem cell therapy.23

Active management of preexisting cardiac disease by a cardiologist can promote the most effective cancer therapy

Patients who develop major cardiac issues during cancer therapy can be managed and still continue ongoing chemotherapy with appropriate monitoring and treatment.7,9,14

B. Understanding expected clinical outcomes for each discipline to have shared decision making is crucial

Effective communication between the disciplines of cardiology and oncology in the management of patients can have a profound effect but may not be done consistently. The scenes 1 to 4 at the outset of this article are examples of poor communication. Most importantly, focused education about these overlapping concerns to all providers is an essential step toward effective communication. In this manner, ICOS will commit substantial effort to medical school, residency, and fellowship training programs to incorporate these topics in the curriculum.

Conclusions

Cardioncology is a new, interdisciplinary area that is evolving rapidly, based on a comprehensive approach for the management of cancer patients with cardiac diseases. Because there are a lack of evidence-based indications to guide treatment choices and an urgent need for experts in this setting, cardioncology represents a new, largely unexplored clinical field of topical research. The clinicians and researchers involved in this effort have the ambitious task of investigating these scenarios and outlining new evidence-based guidelines. All this represents a big challenge and stimulating incentive for both the cardiologist and the oncologist.

Statement of Conflict of Interest

All authors declare that there are no conflicts of interest.
References