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Reversibility of Left Ventricular Dysfunction Resulting from Chemotherapy: Can This Be Expected?

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Abstract Recent advances in cancer management have improved long-term survival. Increased longevity has been accompanied by a rise in the frequency of age-related cardiovascular disease and treatment-related cardiotoxicity. Chemotherapy-related left ventricular dysfunction has historically been considered resistant to conventional therapy and to carry a poorer prognosis than other cardiomyopathies. However, these conclusions were drawn primarily from trials that predate contemporary heart failure therapy and where treatment was often initiated only after the development of symptoms. More recent data suggest that selected forms of chemotherapy-related cardiomyopathy are, to some degree, reversible, but response is dependent on early detection and prompt intervention. This challenges us to develop more sophisticated risk stratification and monitoring strategies that include symptom detection, noninvasive imaging, and carefully applied biomarkers. This paradigm also suggests that a multidisciplinary team of cardiologists and oncologists may provide more comprehensive care to this complex patient population. (Prog Cardiovasc Dis 2010;53:140-148)

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Over the past 2 decades, there have been significant advances in the diagnosis and management of cancer. Treatment options for patients with malignancies have expanded greatly and now frequently combine multimodal strategies including surgical resection, radiation therapy, and combination antineoplastic therapy. As a result, long-term survival from cancer has markedly improved. However, with greater longevity, there has been an increasingly recognized problem of treatment-related toxicities, with one of the most common being complications involving the cardiovascular system.[1] In addition, the aging of the US population has resulted in a concomitant increase in the burden of comorbid conditions within the population being treated for cancer.[2] Accordingly, cardiac disease is among the most important conditions affecting cancer survivors. In fact, for many survivors, the mortality risk from cardiac disease will be equal or greater than that from recurrent malignancy.[3,4] Not only does increased longevity expose cancer survivors to age-related cardiovascular disease, but also specific chemotherapies are associated with direct cardiotoxic effects including heart failure, myocardial ischemia, hypertension, and arrhythmias.[5-8] One of the most common manifestations of cardiotoxicity during or after chemotherapy is left ventricular dysfunction and heart failure. Myocardial dysfunction has been associated not only with a number of chemotherapeutic agents and classes, most notably the anthracyclines and tyrosine kinase inhibitors[9,10], but also certain alkylating agents, antimetabolites, proteasome inhibitors, and antimicrotubule agents.[8]

Situations where LV dysfunction occurs with chemotherapy

Left ventricular dysfunction and heart failure have been defined by the Common Terminology Criteria for Adverse

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Abbreviations and Acronyms

ACEi = angiotensin-converting enzyme inhibitor

ATP = adenosine triphosphate

BNP = brain natriuretic peptide

HF = heart failure

LVEF = left ventricular ejection fraction

PDGFR = platelet-derived growth factor receptor

TKI = tyrosine kinase inhibitor

VEGF = vascular endothelial growth factor

VEGFR = vascular endothelial growth factor receptor

Events (CTCAE) for the purposes of uniform reporting.[11] In general, adverse event are graded on a scale of 1 to 5 based on severity. Grade one adverse events are mild with no or minimal symptoms, whereas deaths related to an adverse event are graded as 5. Grades 2, 3, and 4 define events of moderate, severe, and life-threatening severity, respectively. Historically, LV dysfunction was defined by serial changes in left ventricular ejection fraction (LVEF) over the course of a clinical trial in oncology and reductions in LVEF were considered safety end points. For instance, a 10% absolute change was considered evidence for toxicity in many such trials. The CTCAE criteria have changed over the years; and in the recently updated version 4, heart failure (HF) and more specialized testing were introduced (such as echocardiography and biomarker testing) to provide a framework for a more sophisticated detection of toxicity with newer chemotherapeutic agents. Reflecting the importance of myocardial dysfunction as a safety end point, LV systolic dysfunction when detected is considered severe, grades 3 through 5, with the distinction between 3 and 4 based on whether symptoms respond to therapy. Regarding the reporting of HF, grade 1 signifies asymptomatic laboratory or imaging abnormalities and grades 2 to 5 indicate increasing severity of symptoms, culminating in death. It is important to note that all studies reported previously in the oncology literature used CTC version 3 or earlier; and as a result, only serial changes in LVEF were the primary safety end point reported. More sophisticated descriptions of HF or even cardiac biomarker testing are not considered in these analyses. As a result, the true incidence of HF as a safety signal may not be accurately known.

Anthracycline cardiotoxicity is well described, although the precise molecular mechanisms responsible remain controversial. A widely accepted mechanism involves cell loss due to free radical formation and oxidative stress. Other purposed mechanisms include sarcomere disruption, alterations in adenosine triphosphate (ATP) production, and alterations in the expression of the sarcoplasmic reticulum calcium-ATPase.[12,13] This topic will be covered in detail by Douglas Sawyer, MD, and his colleagues in this symposium. Anthracycline-associated cardiotoxicity has numerous clinical manifestations (Table 1). Rarely, patients experience an acute cardiomyopathy with a clinical picture associated with myopericarditis, arrthythmias, and left ventricular dysfunction that is typically transient and often reversible with discontinuance of the offending agent. More commonly, anthracyline cardiotoxicity manifests as either asymptomatic cardiac dysfunction or heart failure beginning with diastolic dysfunction later progressing to include systolic dysfunction.[23] This more typical pattern is recognized as either subacute (developing within 1 year of completion of chemotherapy) or late (>1 year after the completion of chemotherapy) and has largely been considered irreversible and refractory to therapy. These conclusions, however, are based on older data in which early detection was not used nor was early and aggressive treatment of left ventricular dysfunction.

The exact prevalence of anthracycline-induced cardiomyopathy is not clear, but it has been suggested to account for 1% of all cases of cardiomyopathy.[24] Long-term follow-up of patients after treatment with anthracyclines suggests that cardiac abnormalities are common in survivors and can become evident even 4 to 20 years after receiving chemotherapy. Abnormal cardiac function on noninvasive testing was present in 18% of patients followed up for less than 10 years and 38% of those followed up for 10 years or more (median, 12 years).[25] In children treated for leukemia with anthracyclines, increased afterload and/or decreased contractility was present in 65% of patients up to 15 years after the completion of treatment.[26] At 10 to 20 years after treatment, approximately 5% of patients will develop heart failure,[25] a serious concern because 60 000 patients per year are exposed to anthracyclines in the United States alone.[9]

Tyrosine kinase inhibitors (TKIs) are molecularly targeted anticancer drugs that inhibit aberrant tyrosine kinase signaling present in some malignancies. Current agents are either monoclonal antibodies targeting receptor tyrosine kinases or small molecules directed toward receptor and nonreceptor tyrosine kinases. Although generally having fewer side effects than many traditional chemotherapeutic agents, these targeted therapies have been found to have unforeseen consequences, including conduction abnormalities, myocardial injury, arterial thromboses, hypertension, left ventricular dysfunction, and heart failure.[10]

Tyrosine kinase inhibitors are thought to result in cardiotoxicity by both on-target and off-target mechanisms. On-target mechanisms refer to effects related directly to the kinase inhibiting activity of the agent. In malignant cells, TKIs target pathways that promote abnormal proliferation and survival. Some of these pathways are also involved in the survival, repair, and proliferation of normal tissues, which includes myocardium. In targeting the pathologic pathways of malignancy, these agents may also interfere with normal prosurvival