We will discuss the old problem of anthracycline cardiotoxic effects with new insights, the new challenge of anti-HER2 cardiotoxic effects, the off-target effect of targeted therapies, and the development of a new clinical discipline, oncocardiology.

New Insights in Anthracycline Induced Cardiotoxic Effects

Daunorubicin, the first anthracycline isolated from cultures of Streptomyces peucetius, was reported in 1963 by French and Italian researchers (Table 1). An early clinical study showed that pediatric patients with leukemia could achieve partial or complete hematologic remission from a single dose of daunorubicin; moreover, prolonged remission could be obtained by maintenance therapy. However, patients often developed heart failure with maintenance daunorubicin therapy (Table 2). In a retrospective analysis, the cumulative probability of congestive heart failure (CHF) was shown to be dependent on the cumulative dose of doxorubicin. Long-term follow-up data from adult survivors of childhood cancer showed that up to 30% of patients treated with doxorubicin had signs of cardiac dysfunction when more sensitive detection techniques were used.

Doxorubicin targets topoisomerase II to block DNA replication. Because cardiomyocytes were considered to be terminally differentiated, researchers believed that doxorubicin could not cause cardiotoxic effects by inhibiting DNA replication. Therefore, the reactive oxygen species (ROS)/iron hypothesis was proposed because doxorubicin is capable of causing redox changes in an iron-dependent manner to produce highly toxic hydroxyl radicals. Thus, inhibition of ROS formation and iron chelation were tested as strategies to prevent doxorubicin-induced cardiotoxic effects. Although N-acetylcysteine was effective in quenching ROS in tissue cultures, it was not effective in preventing doxorubicin-induced cardiotoxic effects. Furthermore,
Table 1. Milestones in Oncocardiology

<table>
<thead>
<tr>
<th>Year</th>
<th>Milestones</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963</td>
<td>Discovery of daunorubicin (1st anthracycline)</td>
</tr>
<tr>
<td>1966</td>
<td>Early report of anthracycline-induced cardiotoxic effects</td>
</tr>
<tr>
<td>1977</td>
<td>Anthracyclines cardiotoxic effects is dependent on the cumulative dose</td>
</tr>
<tr>
<td>1980</td>
<td>Efforts to reduce anthracycline-induced cardiotoxic effects through dose limitation, chemical protection, change in formulation, or change in delivery schedule</td>
</tr>
<tr>
<td>1998</td>
<td>Early report of trastuzumab (herceptin)-induced cardiotoxic effects</td>
</tr>
<tr>
<td>2007</td>
<td>Reports of multidisciplinary inhibiting cancer progression, heart failure, vascular occlusion</td>
</tr>
<tr>
<td>2012</td>
<td>Discovery of Topoisomerase IIb as the molecular basis of anthracycline-induced cardiotoxic effects</td>
</tr>
</tbody>
</table>

Iron chelation failed to prevent doxorubicin-induced cardiotoxic effects in an animal model. Remarkably, dexrazoxane, the only effective protectant against doxorubicin cardiotoxic effects, was shown to be a catalytic inhibitor of topoisomerase II. There are 2 topoisomerase II isozymes. Topoisomerase IIα, highly expressed in cancer cells and required for cell division, is the target for anthracycline's antitumor effect. However, adult cardiomyocytes express only topoisomerase IIβ, which is not required for cell division. Since dexrazoxane binds to topoisomerase IIβ and inhibits doxorubicin-induced DNA double-strand break, it is likely that doxorubicin causes cardiotoxic effects by targeting topoisomerase IIβ. We generated a mouse model in which topoisomerase IIβ could be genetically deleted in adult cardiomyocytes and showed that both doxorubicin-induced DNA double-strand breaks and apoptosis were blunted.

Doxorubicin also causes a profound change in the transcriptome of cardiomyocytes because topoisomerase IIβ is required in cardiomyocytes with intact topoisomerase IIβ. This explains why doxorubicin-induced ROS production is dependent on topoisomerase IIβ. Interestingly, peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α) and PGC1β, 2 key transcription factors important to mitochondrial biogenesis, are also decreased in the doxorubicin-treated cardiomyocytes. As a result, mitochondrial electron transport proteins are decreased. Electron microscopy of heart samples showed classic histological changes in the mitochondria of cardiomyocytes treated with doxorubicin, but not in topoisomerase IIβ-depleted cardiomyocytes. Together, these findings show that topoisomerase IIβ is the molecular basis of anthracycline-induced cardiotoxic effects. This new paradigm retains the old observation of doxorubicin-induced ROS generation and mitochondrial biogenesis but explains them in terms of topoisomerase IIβ (Figure). The identification of topoisomerase IIβ as the molecular basis of anthracycline-induced cardiotoxic effects leads to 3 useful predictions. First, a new anthracycline specific for topoisomerase IIα, but not for topoisomerase IIβ, should have antitumor activity but no cardiotoxic effects. Second, determining a patient's topoisomerase IIβ expression level may be useful in predicting the patient's susceptibility to anthracycline-induced cardiotoxic effects before chemotherapy is initiated. Finally, inhibition of topoisomerase IIβ should be the most effective strategy to prevent anthracycline-induced cardiotoxic effects. However, an early clinical trial showed that patients who received dexrazoxane and doxorubicin had reduced objective response rate, but time to progression and survival were not different compared with placebo and doxorubicin. Thus, the US Food and Drug Administration limited the use of dexrazoxane to metastatic breast cancer patients who have already received 300 mg/m² of doxorubicin. Since doxorubicin causes subclinical cardiac damage even at low doses, the use of dexrazoxane in patients who have received more than 300 mg/m² of doxorubicin is clearly too late. With the new understanding of the pathogenesis of anthracycline-induced cardiotoxic effects, further clinical trials of dexrazoxane in cardioprotection are warranted.

Harnessing the Cardiotoxic Effects of Anti-HER2 Therapy

Cancer treatment underwent a remarkable revolution in 1998 with the approval of trastuzumab (herceptin) for the treatment of metastatic ERBB2 (HER2)-positive breast cancer. ERBB2 belongs to the family of human epidermal growth factor receptors (EGFRs). In cancer cells, amplified ERBB2 binds to ERBB3 to form an oncogenic ERBB2/ERBB3 complex. Trastuzumab inhibits ERBB2/ERBB3 dimerization by binding to domain 4 of ERBB2 to block phosphatidylinositol-3-kinase signaling. However, ERBB2 is also expressed on cardiomyocytes and deletion of ERBB2 gene in the cardiomyocytes led to development of dilated cardiomyopathy in the mouse model. In cell cultures, adult rat ventricular myocytes (ARVMs) treated with doxorubicin showed a concentration-dependent increase in myofilament disarray. Concomitant treatment of myocytes with anti-ERBB2 and doxorubicin caused a significant increase in myofilament disarray compared with doxorubicin treatment alone.

In the pivotal trastuzumab trial, New York Heart Association class 3 or 4 heart failure was observed in 27% of patients receiving anthracycline, cyclophosphamide, and trastuzumab; in 8% of patients given an anthracycline or cyclophosphamide alone; in 13% of patients given combined paclitaxel and trastuzumab; and in 1% of patients given paclitaxel alone. Thus, trastuzumab can induce cardiotoxic effects by itself, and the severity of these effects is compounded by concomitant use of anthracycline. The alarming incidence of cardiotoxic effects prompted a call to more cautious use of trastuzumab. The high incidence of heart failure in the metastatic breast cancer trial prompted institution of intensive cardiac monitoring in the subsequent adjuvant trials. Newer clinical trials avoiding concomitant use of anthracycline and trastuzumab had much lower incidences of heart failure. The manifestation of cardiotoxic effects is different between anthracyclines and trastuzumab. Cardiac biopsy of trastuzumab-treated patients did not reveal the classic changes of myofibril disarray and mitochondriopathy associated with anthracycline cardiotoxic effects. Clinically, trastuzumab-induced cardiotoxic effects also differ from anthracycline-induced cardiotoxic effects. In contrast to cardiotoxic effects induced by anthracycline, trastuzumab-induced cardiotoxic effects is not dose-related; it is often reversible with cessation of therapy and initiation of conven-
rechallengewithtrastuzumabisgenerallywelltolerated.26Furthermore,otheranti-HER2therapieshavebeendevelopedthat
showedlesscardiotoxiceffects.T-DM1istrastuzumablinkedto
anantimicrotubuledrug,emtansine.27Nosignificantcardiotoxic
effectswerenotobservedwithT-DM1inpatientspreviouslytreated
withtrastuzumabandtaxanes.28Pertuzumabisanmonoclonal
antibodybindingtoumbrelladomain2ofERBB2toinhibitligand-
dependentERBB2dimerization.29Pertuzumabprolongsthesur-
vivalofpatientsdiagnosedwithmetastaticbreastcancerwhen
addedtostrastuzumabandanthracyclines.30Inclinicaltrials,
pertuzumabhasemergedasa“safedrug,”withlittleor nocardiactoxic
effects.31Thus,wehavelearnedtoharnessthetoxicityofanti-
HER2therapy,byintensivemonitoring,byavoidingconcomitant
useofanthracyclines,andbyintroducingantibodytargetingadif-
ferentdomainof

Table 2. Commonly Used Anticancer Agents Associated
With Cardiovascular Complications (continued)

<table>
<thead>
<tr>
<th>Chemotherapy Agentsa</th>
<th>Incidence, %</th>
<th>Prevention/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thromboembolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiogenesis inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide (revlimid)</td>
<td>3-75b</td>
<td>Modification of cardiac risk factors</td>
</tr>
<tr>
<td>Thalidomide (thalomid)</td>
<td>1.0-58.0</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td><strong>Antimicrotubule agent</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (taxol)</td>
<td>&lt;0.1-31.0</td>
<td></td>
</tr>
<tr>
<td><strong>Small molecule tyrosine kinase inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceritinib (zykadia)</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Crizotinib (xalkori)</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>Pazopanib (votrient)</td>
<td>2.0-19.0</td>
<td></td>
</tr>
<tr>
<td>QT Prolongation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic trioxide (trisenox)</td>
<td>26.0-93.0b</td>
<td>EKG monitoring</td>
</tr>
<tr>
<td>Histone deacetylase inhibitors</td>
<td></td>
<td>Replace potassium and magnesium</td>
</tr>
<tr>
<td>Belinostat (beleodaq)</td>
<td>4.0-11.0</td>
<td>Follow FDA guidelines</td>
</tr>
<tr>
<td>Small molecule tyrosine kinase inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabrafenib (tafinlar)</td>
<td>2.0-11.0</td>
<td></td>
</tr>
<tr>
<td>Dasatinib (sprycel)</td>
<td>&lt;1.0-3.0b</td>
<td></td>
</tr>
<tr>
<td><strong>Histone deacetylase inhibitors</strong></td>
<td></td>
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</tr>
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<td></td>
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<tr>
<td>Dasatinib (sprycel)</td>
<td>&lt;1.0-3.0b</td>
<td></td>
</tr>
<tr>
<td><strong>Proteasome inhibitors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vandetanib (caprexa)</td>
<td>8.0-14.0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; EF, ejection fraction; EKG, electrocardiogram; FDA, US Food and Drug Administration; GLS, global longitudinal strain.

For a complete list see chapter 12, MD Anderson Practices in Onco-Cardiology (http://www.cancerandtheheart.org).

b Listed as a warning/precaution in package insert.

b Black box warning in package insert.
Targeted Therapy With Off-Target Effects

Another major advance in cancer treatment was the approval of imatinib (Gleevec) in 2001 for the treatment of chronic myelogenous leukemia. Imatinib, an inhibitor of BCR-Ab1, was touted as a magic bullet in cancer therapy and heralded the development of a large number of tyrosine kinase inhibitors (TKIs) in clinical use today. Some of these TKIs have specific targets, whereas others can target multiple kinases. Thus, off-target effects can result in off-target toxic effects. For example, Force et al reported 10 patients who developed severe CHF while receiving imatinib therapy and showed that imatinib-treated mice developed left ventricular contractile dysfunction. A more extensive review of patients treated with imatinib showed that, of 1276 patients, only 22 (1.7%) developed systolic heart failure; of these 22 patients, 11 continued to receive imatinib therapy with dose adjustments and were monitored for CHF symptoms without further complications. Thus, the initial report of potential cardiotoxic effects of TKIs needs to be validated by larger clinical trials, and early identification of toxicity or dose-reduction may allow a lifesaving drug to remain on the market.

Sunitinib, approved for treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors, caused hypertension in 47% of treated patients and CHF in 8% in a small study of 75 patients. In a larger meta-analysis of 6935 patients, the incidence of all-grade and high-grade CHF in patients treated with sunitinib was 4.1% and 1.5%, respectively. Congestive heart failure was reversible by withholding sunitinib therapy and/or initiation of heart failure therapy in 56% of patients in a retrospective adjudication of comprehensive cardiovascular adverse events from 2 phase 3 trials. Sunitinib is a multikinase inhibitor that inhibits vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors, and platelet-derived growth factor receptors (PDGFRs). Thus, it is not surprising that hypertension can result from inhibition of multiple receptors involved in the homeostasis of the vasculature. In an animal model, PDGFR-β is required for cardiomyocytes to respond to stress-induced cardiac angiogenesis. Mice that underwent cardiomyocyte-specific deletion of PDGFR-β developed heart failure when exposed to load-induced stress, such as hypertension. Thus, hypertension and heart failure caused by sunitinib and other TKIs that target the VEGF signaling pathway can be explained mechanistically and prevented by aggressive treatment of hypertension.

Recently, ponatinib (iclusig), a TKI approved for imatinib-resistant chronic myelogenous leukemia, was pulled from the market temporarily owing to a 27% incidence of arterial and venous thrombosis or occlusion. However, ponatinib was shown to inhibit platelet aggregate formation in whole blood under shear stress. Similar to ponatinib, nilotinib has also been associated with increased incidence of arterial and venous thrombosis. Further studies are needed to clarify the mechanism of action contributing to accelerated atherosclerosis and thromboembolism in patients treated with ponatinib and nilotinib. Regardless of the mechanism of vascular toxic effects, careful modification of cardiac risk factors and close follow-up are required in patients treated with selected TKIs, especially TKIs targeting the VEGF signaling pathway. It is clear that the off-target effects of TKIs provide an opportunity for both basic and translational research in our field.

An Emerging Field: Cardiologist Collaborating With Oncologist

The use of targeted therapy in the past 15 years has converted several cancers from a terminal illnesses to a chronic diseases, vastly increasing the number of cancer survivors. In 2012, there were 12 million cancer survivors in the United States. This number is estimated to double by the end of the next decade. Among cancer survivors, half will die of cancer recurrence, but a third will die of cardiovascular disease. Thus, the need for optimal cardiac care in the cancer population has become evident. Chemotherapy can cause myriad cardiovascular complications, including hypertension, CHF, thromboembolic diseases, ischemic heart disease, QT prolongation, and bradycardia. Radiation therapy can cause acute complications, such as pericarditis and long-term complications, such as accelerated coronary artery disease, valvular disease, and restrictive or constrictive pericarditis. Thus, cardiologists could play a pivotal role in the care of cancer patients undergoing chemotherapy and/or radiation therapy.

Early detection of cardiotoxic effects requires timely imaging studies and monitoring with biomarkers. Determining left ventricular ejection fraction (LVEF) with the use of noninvasive techniques, such as echocardiography or multiple gated acquisition (MUGA) scanning, during chemotherapy is recommended by all guidelines. Because of radiation exposure, echocardiography is generally preferred in cardiac monitoring over MUGA scanning. In a large population-based study of patients diagnosed with breast cancer aged 66 years or older, adequate cardiac monitoring was obtained in only 36% of patients. In a retrospective study, early detection of LVEF
reduction followed by intervention was shown to improve long-term outcome. A recent consensus from the American Society of Echocardiography (ASE) went beyond LVEF to recommend monitoring of global longitudinal strain (GLS).48,52 Although GLS is more sensitive than LVEF, technical limitations and general availability may not allow for this measurement to be used for all cancer patients undergoing chemotherapy. Both the ASE and the European Society for Medical Oncology recommended troponin for detection of early signs of cardiotoxic effects during chemotherapy.49 A combination of troponin and GLS could be a more powerful predictor of early cardiotoxic effects.53 Further studies are required to determine the best frequency of monitoring during chemotherapy.

In the past decade, cardiologists have carried out multiple small clinical studies with drugs used in heart failure therapy, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, or β-blockers (BB), to provide either primary or secondary prevention for anthracycline-induced cardiotoxic effects.53-56 Many of these studies showed benefit; however, the short-term benefits may have been owing to changes in hemodynamics, not a result of true cardioprotection. Larger and more long-term clinical studies are required to demonstrate true efficacy. This is important because in a pediatric study, the short-term benefit of ACEIs disappeared with long-term follow-up.57 However, ACEIs in this study may not show efficacy because the drug was started a median of 8 years after chemotherapy. Taken together, the best evidence for primary prevention of anthracycline-induced cardiotoxic effects is dexrazoxane based on its mechanism of action.13,55 At present, ACEIs, BB, aldosterone antagonists, or statin cannot be recommended in primary prevention owing to insufficient evidence.

Because cancer is usually a criterion for exclusion in cardiovascular trials, there is a paucity of evidence-based recommendations for diagnosing, preventing, and treating cancer therapy-induced cardiovascular complications. A number of guidelines have been published, based primarily on a consensus of committee members.48,49 However, these guidelines are not routinely followed by clinicians. We must carry out clinical studies and establish registries to address specific issues that are pertinent to our unique practice rather than relying on consensus or inadequate clinical studies. Furthermore, oncocardiology is not limited to clinical studies; basic research exemplified by the discovery of the molecular target for anthracycline-induced cardiotoxic effects provides a new playing field for physicians and scientists.15 The National Institutes of Health has conducted a workshop, published a white paper, and established a funding mechanism (PA-16-035, PA-16-036) for the study of basic and clinical research relevant to oncocardiology.58

In a study59 of childhood cancer survivors, the overall mortality ratio was 8.3-fold higher and the cardiovascular mortality ratio was 5-fold higher in cancer survivors than in the general population. In another large study60 that compared childhood cancer survivors with their siblings, the cumulative incidence of coronary artery disease, CHF, valvular disease, and arrhythmia in survivors by age 45 years was much higher than those found in their siblings. Cancer therapy greatly accelerates the development of cardiovascular diseases, which can be reduced by lowering the intensity of radiation therapy and anthracycline exposure.61 Further improvement in quality of life in cancer survivors can be achieved through exercise, weight control, dietary discretion, and complementary medicine.62

Recent advances in oncology are rapidly developing personalized cancer therapies based on the identification of driver mutations and the application of targeted therapy. We may be able to identify the driver mutations that cause cardiotoxic effects in susceptible individuals to make decisions on anticancer drug choices. For example, patients with high topoisomerase 2β levels in peripheral blood may be more susceptible to anthracycline-induced cardiotoxic effects. In these high-risk patients, we can consider nonanthracycline alternatives or provide early cardioprotection with dexrazoxane. With better understanding of the genetics of dilated cardiomyopathies, we may consider patients with positive family history or with susceptible genes to be at high risk for developing cancer therapy-induced cardiotoxic effects. These patients should be monitored closely and treated with less aggressive radiation or chemotherapy. These are exciting challenges and opportunities that will test the ingenuity and persistence of the next generation of oncocardiologists.

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