CA
A Cancer Journal for Clinicians

ONLINE CONTINUING EDUCATION ACTIVITY

Take free quizzes online at **acsjournals.com/ce**

ARTICLE TITLE: Cardiotoxicity of Anticancer Treatments: Epidemiology, Detection, and Management

CME CNE

CONTINUING MEDICAL EDUCATION ACCREDITATION AND DESIGNATION STATEMENT:

Blackwell Futura Media Services is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

Blackwell Futura Media Services designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CONTINUING NURSING EDUCATION ACCREDITATION AND DESIGNATION STATEMENT:

The American Cancer Society (ACS) is accredited as a provider of continuing nursing education (CNE) by the American Nurses Credentialing Center's Commission on Accreditation.

Accredited status does not imply endorsement by the ACS or the American Nurses Credentialing Center of any commercial products displayed or discussed in conjunction with an educational activity. The ACS gratefully acknowledges the sponsorship provided by Wiley for hosting these CNE activities.

EDUCATIONAL OBJECTIVES:

After reading the article "Cardiotoxicity of Anticancer Treatments: Epidemiology, Detection and Management," the learner should be able to:

1. Review the most common and most serious types of cardiotoxicity associated with treatment of cancer.
2. Describe options for prevention, diagnosis, and treatment of cardiovascular disease associated with anticancer systemic therapies and radiotherapy.

ACTIVITY DISCLOSURES:

No commercial support has been accepted related to the development or publication of this activity.

ACS CONTINUING PROFESSIONAL EDUCATION COMMITTEE DISCLOSURES:

Editor, Director of Continuing Professional Education, and ACS Director of Medical Content:
Ted Gansler, MD, MBA, MPH, has no financial relationships or interests to disclose.
Deputy Editor and ACS Director of Cancer Control Intervention:
Durado Brooks, MD, MPH, has no financial relationships or interests to disclose.
Lead Nurse Planner and Associate Editor:
Marcia Grant, RN, PhD, FAAN, has no financial relationships or interests to disclose.
Associate Editor and ACS Chief Cancer Control Officer:
Richard C. Wender, MD, has no financial relationships or interests to disclose.

NURSING ADVISORY BOARD DISCLOSURES:

Maureen Berg, RN, has no financial relationships or interests to disclose.
Susan Jackson, RN, MPH, has no financial relationships or interests to disclose.
Barbara Lesser, BSN, MSN, has no financial relationships or interests to disclose.

AUTHOR DISCLOSURES:

Susan Dent, MD, reports consulting fees from Hoffman-La Roche, Novartis, and Amgen outside the submitted work. Daniel Lenihan, MD, reports grants from Takeda and Acorda; personal fees from Roche (Data Safety and Monitoring Board), and consultant fees from Bristol Myers Squibb and Onyx. Giuseppe Curigliano, MD, PhD; Daniela Cardinale, MD, PhD; Carmen Criscitiello, MD, PhD; Olexiy Aseyev, MD, PhD; and Carlo Maria Cipolla, MD, have no financial relationships or interests to disclose.

SCORING:

A score of 70% or better is needed to pass a quiz containing 10 questions (7 correct answers), or 80% or better for 5 questions (4 correct answers).

CME INSTRUCTIONS ON RECEIVING CME CREDIT:

This activity is intended for physicians. For information concerning the applicability and acceptance of CME credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within 1.5 hours; physicians should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

CNE INSTRUCTIONS ON RECEIVING CNE CREDIT:

This activity is intended for nurses. For information concerning the applicability and acceptance of CNE credit for this activity, please consult your professional licensing board.

This activity is designed to be completed within 1.5 hours; nurses should claim only those credits that reflect the time actually spent in the activity. To successfully earn credit, participants must complete the activity during the valid credit period, which is up to 2 years from the time of initial publication.

FOLLOW THESE STEPS TO EARN CREDIT:

- Log on to acsjournals.com/ce.
- Read the target audience, educational objectives, and activity disclosures.
- Read the activity contents in print or online format.
- Reflect on the activity contents.
- Access the examination, and choose the best answer to each question.
- Complete the required evaluation component of the activity.
- Claim your certificate.

This activity will be available for CME/CNE credit for 1 year following its launch date. At that time, it will be reviewed and potentially updated and extended for an additional 12 months.

All CME/CNE quizzes are offered online **FREE OF CHARGE.** Please log in at acsjournals.com/ce. New users can register for a FREE account. Registration will allow you to track your past and ongoing activities. After successfully completing each quiz, you may instantly print a certificate, and your online record of completed courses will be updated automatically.

Cardiotoxicity of Anticancer Treatments: Epidemiology, Detection, and Management

Giuseppe Curigliano, MD, PhD[1]; Daniela Cardinale, MD, PhD[2]; Susan Dent, MD[3]; Carmen Criscitiello, MD, PhD[1]; Olexiy Aseyev, MD, PhD[3]; Daniel Lenihan, MD[4]; Carlo Maria Cipolla, MD[2]

Cancer and heart disease are the leading causes of morbidity and mortality in the industrialized world. Modern treatment strategies have led to an improvement in the chances of surviving a diagnosis of cancer; however, these gains can come at a cost. Patients may experience adverse cardiovascular events related to their cancer treatment or as a result of an exacerbation of underlying cardiovascular disease. With longer periods of survival, late effects of cancer treatment may become clinically evident years or decades after completion of therapy. Current cancer therapy incorporates multiple agents whose deleterious cardiac effects may be additive or synergistic. Cardiac dysfunction may result from agents that can result in myocyte destruction, such as with anthracycline use, or from agents that appear to transiently affect left ventricular contractility. In addition, cancer treatment may be associated with other cardiac events, such as severe treatment-induced hypertension and vasospastic and thromboembolic ischemia, as well as rhythm disturbances, including QTc prolongation, that may be rarely life-threatening. Early and late effects of chest radiation can lead to radiation-induced heart disease, including pericardial disease, myocardial fibrosis, cardiomyopathy, coronary artery disease, valvular disease, and arrhythmias, in the setting of myocardial fibrosis. The discipline of cardio-oncology has developed in response to the combined decision making necessary to optimize the care of cancer patients, whether they are receiving active treatment or are long-term survivors. Strategies to prevent or mitigate cardiovascular damage from cancer treatment are needed to provide the best cancer care. This review will focus on the common cardiovascular issues that may arise during or after cancer therapy, the detection and monitoring of cardiovascular injury, and the best management principles to protect against or minimize cardiotoxicity during the spectrum of cancer treatment strategies. **CA Cancer J Clin 2016;66:309-325.**

Keywords: cancer treatment, cardiac dysfunction, cardio-oncology, cardiotoxicity, hypertension, rhythm disturbances, vascular events

To earn free CME credit or nursing contact hours for successfully completing the online quiz based on this article, go to **acsjournals.com/ce.**

Introduction

Mortality rates from cancer have declined over the past 30 years largely because of early detection strategies, improved surgical approaches, as well as advances in cancer therapeutics.[1-3] Improvement in survivorship, however, can be associated with other organ injuries, including impact on cardiovascular health.[4] Cardiovascular (CV) disease (CVD) is now the second leading cause of long-term morbidity and mortality among cancer survivors.[1-3,5,6] Conventional chemotherapy and targeted therapies are associated with an increased risk of cardiac damage, including left ventricular (LV) dysfunction (LVD) and heart failure (HF),[7,8] treatment-induced hypertension, vasospastic and thromboembolic ischemia, as well as rhythm disturbances, including conduction system damage and potentially QTc prolongation, that may be rarely life-threatening. Although some of these cardiac adverse effects are irreversible and cause progressive CVD, others induce only temporary dysfunction with no apparent long-term sequelae.[9] Early and late effects of chest radiation can lead to radiation-induced heart disease (RIHD), which may involve a spectrum of cardiac conditions, such as pericardial disease, myocardial fibrosis,

[1]Director, Division of Experimental Therapeutics, Division of Medical Oncology, European Institute of Oncology, Milan, Italy; [2]Director, Division of Cardiology, Cardio-Oncology Program, International Cardio-Oncology Society (ICOS), European Institute of Oncology, Milan, Italy; [3]Associate Professor and Postdoctoral fellow, The Ottawa Hospital Cancer Center, Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada; [4]Director, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN

Corresponding author: Giuseppe Curigliano, MD, PhD, Istituto Europeo di Oncologia, Division of Experimental Therapeutics, Via Ripamonti 435, 20133 Milano, Italy; giuseppe.curigliano@ieo.it

DISCLOSURES: Susan Dent reports consulting fees from Hoffman-La Roche, Novartis, and Amgen outside the submitted work. Daniel Lenihan reports grants from Takeda and Acorda; personal fees from Roche (Data Safety and Monitoring Board), and consultant fees from Bristol Myers Squibb and Onyx. The remaining authors report no conflicts of interest.

We thank Dr. Lucia Gelao for the editorial support.

doi: 10.3322/caac.21341. Available online at cacancerjournal.com

cardiomyopathy, coronary artery disease (CAD), valvular disease, and arrhythmias in the setting of myocardial fibrosis.[10] Oncologists face the challenge of treating patients with the best cancer therapies available without adversely impacting CV health. The discipline of cardio-oncology has developed in response to the combined decision making necessary to optimize the care of patients with cancer, whether they are receiving active treatment or are long-term survivors after successful treatment. This review will focus on the common CV issues that may arise during or after cancer therapy, the detection and monitoring of CV injury, and the best management principles to protect or minimize the impact of CV issues during the spectrum of cancer therapies.

Epidemiology of Cancer Therapy-Induced Cardiotoxicity

Cancer and heart disease are the leading causes of morbidity and mortality in the industrialized world. However, there is cause for optimism. Modern treatment strategies have led to an improvement in the chances of surviving a diagnosis of cancer; the 5-year survival for early stage breast cancer increased from 79% in 1990 to 88% in 2012,[2,3,6,11] and similar improvements have been seen with some other solid and hematological cancers, including non-Hodgkin lymphoma and testicular cancer.[1] Long-term cancer survivors are expected to increase by approximately 30% in the next decade to an estimated 18 million by 2022 in the United States alone.[12] These improvements in survivorship can come at a cost.[4] Current anticancer therapies are associated with unique and various degrees of direct (eg, myocardial toxicity, ischemia, hypertension, arrhythmias)[13-17] as well as indirect CV insults (eg, unfavorable lifestyle changes). The incidence of cancer treatment-induced CV injury varies widely, depending on the specific cancer therapy used, duration of therapy, and underlying patient comorbidities. In a recent comprehensive review of breast cancer survivors in the United States, women were noted to be at significantly increased risk of death caused by CVD, exceeding their risk of death from the initial cancer itself or from recurrent disease.[5,6,11] CVD is the predominant cause of mortality in breast cancer patients over 50 years of age[18] and is a more common contributor than cancer to mortality among older cancer survivors.[5,6,11,18] CVD is not always caused by toxicity from cancer therapy exposures, and it can be a normal disease process in older adults. However, the impact of cancer therapies on CVD in the general adult cancer survivor population is largely unknown. We can gain some insight from longitudinal studies in the pediatric population. The Childhood Cancer Survivor Study showed that, 15 to 25 years after diagnosis, survivors of childhood cancer have an 8.2-fold higher rate of cardiac death compared with the age-matched and sex-matched national average.[18,19] Compared with controls, long-term childhood cancer survivors had 15-fold increased rates of congestive HF, 10-fold higher rates of CVD, and 9-fold higher rates of stroke.[20] These results have significant implications for adult cancer survivors who face the CV effects of aging compounded by the potential detrimental impact of cancer therapy. Recognition of the importance of CV health in adult cancer patients is paramount if we are to sustain the survival gains achieved with modern cancer therapies.

Common CV Adverse Events

LVD and HF

Cardiac dysfunction and HF are among the most serious CV consequences of systemic cancer treatment.[9] Conventional chemotherapeutics, such as anthracyclines, antimetabolites, and cyclophosphamide, can induce permanent myocardial cell injury, leading to acute or chronic LVD.[21,22] Anthracyclines, commonly used in the treatment of solid tumors (ie, breast cancer, osteosarcoma, etc) and hematologic malignancies (Hodgkin/non-Hodgkin lymphoma, acute lymphoblastic leukemia, etc), can trigger significant LVD. Anthracycline-related LVD has historically been considered to be dose-dependent, cumulative, and progressive,[22,23] which manifest as decreased LV ejection fraction (LVEF) and, ultimately, symptomatic HF in up to 5% of patients.[24] The mechanism of anthracycline-induced cardiac injury has been studied extensively and is still not clearly understood.[15] Structural cardiomyocyte alterations and cell death induced by anthracyclines are mediated in part by reactive oxygen species (ROS) generated in iron-dependent chemical reactions. ROS lead to the peroxidation of myocyte membranes and, after calcium influx, into the intracellular space, which can ultimately lead to permanent myocyte damage. In addition, mechanisms have been identified, including disturbances in DNA topoisomerase 2-β (Top2b) metabolism.[25] The risk of doxorubicin-induced HF (which can occur within hours, weeks, or years after exposure) increases with cumulative dose of anthracycline: 3% to 5% with 400 mg/m^2, 7% to 26% at 550 mg/m^2, and 18% to 48% at 700 mg/m^2.[24,26,27] High-risk patients include those at the extremes of age (<5 or >65 years), those who received prior or concurrent chest radiation, and those with preexisting cardiac disease or established CV risk factors.[22]

In a Surveillance, Epidemiology, and End Results (SEER) database review of elderly breast cancer patients, the adjusted hazard ratio (HR) for HF was 1.26 (95% confidence interval [CI], 1.12-1.42) for those who received adjuvant anthracyclines compared with those who received nonanthracycline adjuvant regimens.[18] The cumulative incidence of HF at 10 years was 38% after anthracyclines, 32.5% with nonanthracycline chemotherapy regimens, and 29% with no chemotherapy.[18,28] The likelihood of anthracycline-induced HF almost doubles with each 10-year increase in age.

TABLE 1. Potential Cardiac Toxicity Induced by Anticancer Chemotherapeutic Agents

DRUG	STUDY	TOXIC DOSE RANGE	CARDIAC TOXICITY	FREQUENCY OF OCCURRENCE[a]
Doxorubicin	Chlebowski 1979[30]	> 450 mg/m^2	Left ventricular dysfunction	Common
Epirubicin	Tjuljandin 1990[31]	> 900 mg/m^2		Common
Idarubicin	Anderlini 1995[32]	150-290 mg/m^2		Intermediate
Paclitaxel	Perez 1998[33]	Conventional dose	Left ventricular dysfunction	Intermediate
Docetaxel	Kenmotsu & Tanigawara 2015[34]			Intermediate
Cyclophosphamide	Gottdiener 1981,[35] Goldberg 1986[36]	>100-120 mg/kg	Left ventricular dysfunction	Intermediate
Ifosfamide	Kandylis 1989,[37] Tascilar 2007,[38] Cancer Care Ontario[39]	>10 mg/m^2		Uncommon
Capecitabine	Sentürk 2009[40]	Conventional dose	Cardiac ischemia	Intermediate
Fluorouracil	Sentürk 2009,[40] Schimmel 2004,[41] Chanan-Khan 2004[42]			Intermediate
Paclitaxel	Perez 1998[33]	Conventional dose	Cardiac ischemia	Uncommon
Docetaxel	Kenmotsu & Tanigawara 2015[34]			Intermediate
Trabectedin	Lebedinsky 2011[43]	Conventional dose	Cardiac ischemia	Intermediate
Arsenic trioxide	Brana & Taberno 2010[44]	Conventional dose	QTc prolongation	Common
Paclitaxel	Perez 1998[33]	Conventional dose	QTc prolongation	Uncommon

[a]Common indicates that more than 5% reported incidence; intermediate, between 1% and 5% reported incidence; uncommon, less than 1% reported incidence.

Peripheral and coronary artery disease (CAD) (HR, 1.31 and 1.58, respectively), diabetes (HR, 1.74), hypertension (HR, 1.45), as well as emphysema and chronic bronchitis (HR, 1.68), represent additional predictors of increased risk for cardiac dysfunction.[29] The risk of HF remains higher for patients who receive anthracyclines compared with those who receive other agents, even after excluding elderly patients and those with relevant comorbidities.[18,29] Cancer treatment-induced HF occurs with several other traditional chemotherapeutic agents, including cyclophosphamide (7%-28%)[21]and docetaxel (2.3%-8%)[26] (Table 1).[30-44] The potential for permanent cardiac damage with exposure to anthracyclines has led to the adoption, in some clinical settings (ie, early stage breast cancer), of chemotherapy regimens with lower cumulative anthracycline exposure.

Many targeted therapies, particularly monoclonal antibodies and tyrosine kinase inhibitors (TKIs), targeting human epidermal growth factor receptor 2 (HER-2) (ie, trastuzumab, pertuzumab, etc), vascular endothelial growth factor (VEGF), and VEGF receptors (ie, bevacizumab, sunitinib, sorafenib, etc), and Abl kinase activity (ie, imatinib, nilotinib, dasatinib, etc), have been demonstrated to interfere with molecular pathways crucial to CV health.[12,13]

LVD associated with targeted therapies has been most extensively evaluated in the breast cancer population treated with trastuzumab. Trastuzumab binds to the extracellular domain of the erb-b2 receptor tyrosine kinase 2 (ErbB2)/HER2 and leads to reduced ErbB2 signaling via several mechanisms. It has been speculated that the cardiac dysfunction associated with trastuzumab is a direct consequence of ErbB2 inhibition in cardiomyocytes.[15] Mice with cardiac-specific deletion of ErbB2 develop dilated cardiomyopathy and demonstrate exaggerated systolic dysfunction in response to pressure overload compared with normal mice.[15] Therefore, it would appear that ErbB2 receptor signaling is important in the maintenance of myocardial function.[15] In contrast to anthracycline-induced cardiotoxicity, trastuzumab exposure can result in LVD and HF that appears mostly reversible.[45] At highest risk for cardiotoxicity from trastuzumab exposure are those aged >50 years, patients with underlying heart disease or hypertension, those with baseline LVEF between 50% and 55% or lower, and those who have also received anthracycline therapy. The introduction of adjuvant trastuzumab for patients with HER2-positive, early stage breast cancer has reduced the risk of breast cancer recurrence by 50% and mortality by 33%.[46] However, in the 5 major adjuvant trastuzumab trials (summarized in Table 2),[47-50] symptomatic, severe HF/cardiac events, ranging from 0% to 3.9%, were observed with the addition of trastuzumab to traditional chemotherapy.[51-53] Long-term follow-up of the pivotal adjuvant trials have demonstrated the cardiac safety of trastuzumab with no substantial increase in CV events over 8 to 10 years, even with longer term trastuzumab therapy.[49,54] However, it is difficult to generally define cardiac toxicity across studies, as criteria vary by trial. Current clinical trials in early breast cancer are taking advantage of the role of dual HER2 blockade, including the synergistic activity of pertuzumab and trastuzumab. To date, there has not been any additional cardiac safety concern when those agents were combined[55,56]; however, we await the results of a large, prospective, randomized trial (Aphinity trial) exploring this combination in the adjuvant setting.[57] Two neoadjuvant studies (Neosphere, Tryphaena) demonstrated higher pathological complete response rates in women with breast cancer treated with chemotherapy and dual HER2 blockade (pertuzumab, trastuzumab) compared with chemotherapy

TABLE 2. Cardiotoxicity in the Major Adjuvant Trastuzumab Trials for HER2-Positive Patients

TRIAL	DESIGN	ASYMPTOMATIC DROP IN LVEF, %	SYMPTOMATIC DROP IN LVEF, %	SEVERE CHF/CARDIAC EVENTS (CHF OR DEATH), %	DISCONTINUED H FOR CARDIAC REASONS, %
NSABP B31 (Perez 2011[47]), n = 2043	AC × 4 + T vs AC × 4 + TH + H	34 vs 17		3.9 vs 1.3	18[a]
NCCTG N9831 (Perez 2011[47]), n = 2766	AC × 4 + T vs AC + T + H vs AC × 4 + TH + H			3.3 vs 2.8 vs 0.3	5[b]
BCIRG 006 (Samon 2011[48]), n = 3222; update with SABCS 2009	AC × 4 + T vs AC × 4 + TH + H vs TCaH[c]	18 vs 10 vs 8.6		1.87 vs 0.38 vs 0.38	
HERA (Goldhirsch 2013,[49] Baselga 2006[50]), n = 5102	Adj CT → H vs Adj chemo alone[d]	3.04 vs 0.53 OR 7.03 vs 2.05	1.7 vs 0.06	0.6 vs 0	4.3
FinHer (Baselga 2006[50]), n = 232	V or T ± H → FEC × 3[e]	3.5 vs 6.0		0	

±, with or without; A, anthracycline; AC, anthracycline plus cyclophosphamide; Adj, adjuvant; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; Ca, carboplatin; chemo, chemotherapy; CHF, cardiac heart failure; E, epirubicin; F, 5-flouroacil; FEC, 5-fluorouracil, epidoxorubicin, plus cyclophosphamide; FinHer, Finland Herceptin trial; H, trastuzumab; HERA, Herceptin Adjuvant trial; LVEF, left ventricular ejection fraction; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; SABCS, San Antonio Breast Cancer Symposium; T, taxane; TCaH, taxane, carboplatin, plus trastuzumab; V, vinorelbine. [a]Because of unacceptable drops in LVEF, 3.23% did not receive H after A. [b]Because of unacceptable drops in LVEF, 5.0% did not receive H after A. [c]The study included an A-free arm. [d]Ninety-six percent of chemotherapy was A-containing. [e]There were no patients who had prior A exposure before H exposure; H exposure was limited to 9 weeks.

and trastuzumab therapy alone. In the Tryphanea study, the primary endpoint of cardiac safety was met, with a low incidence of symptomatic and asymptomatic LV systolic dysfunction across all arms.[58]

Cardiac dysfunction has also been reported with angiogenesis inhibitors, including bevacizumab (1.7%-3%) and sunitinib (4%-11%).[59] Inhibitors of VEGF receptors, such as sunitinib and sorafenib, block several tyrosine kinase receptors,[52] thus making it difficult to identify which targets mediate cardiotoxicity.[59] Preclinical studies have associated sunitinib therapy with LV systolic dysfunction related to the inhibition of 5′ adenosine monophosphate-activated protein kinase (AMPK), a regulator of cardiomyocyte response to stress.[60] This inhibition leads to a condition of energy depletion and consequent cardiomyocyte dysfunction. Mitochondrial dysfunction may explain the transient episodes of LV systolic dysfunction observed in clinical practice. A marked increase in systemic vasoconstriction, increasing the afterload on a susceptible LV, provides another plausible explanation for LV systolic dysfunction.[61]

The hypothesis of reversibility for cardiac damage is not unique to toxic exposure from chemotherapy or targeted agents, because the features of stunning or hibernation of the myocardium are well established in cardiac physiology.[62] Myocyte injury may also be reversible if the extent of damage has not met a threshold of irreversibility; if cell death exceeds this threshold, then it will result in potential permanent LV contractile dysfunction. The distinction between reversible and irreversible cardiac dysfunction, however, is somewhat arbitrary. In fact, if LVD is detected early and appropriate HF-based treatment is instituted, even anthracycline cardiac damage may be reversible.[63]

Hypertension

The TKIs, which include certain VEGF signaling pathway (VSP) inhibitors, such as sorafenib and sunitinib, commonly cause hypertension.[64] Although these are effective anticancer agents, their clinical use may be limited by their potential negative impact on CV health. Hypertension is the most frequent cardiotoxicity observed with VSP inhibitors, with a reported incidence of 19% to 47% (see Table 3).[60,65-76] The mechanisms of hypertension induced by VSP inhibitors have recently been reviewed[15] and include: reduced nitric oxide production in the wall of arterioles, increased endothelin-1 production, and capillary rarefaction that results in the reduction of effective capillary beds.[12,77] In addition, VSP inhibitor-induced hypertension is perhaps related to VEGF-mediated suppression of nephrin, a transmembrane protein that is important for the maintenance of the glomerular slit diaphragm, which may contribute to proteinuria seen with this class of drugs. Strategies to attenuate or prevent VSP inhibitor-induced hypertension are necessary to prevent cardiac dysfunction and early termination of effective anticancer therapy.

Vascular Thrombosis and Ischemia

Several of the newer TKIs (dasatinib, nilotinib, and ponatinib) that have revolutionized the treatment of some hematologic cancers appear to be associated with important vascular events.[78,79] There is also an increased rate of thrombotic adverse events in patients treated with combination therapy for multiple myeloma that includes dexamethasone, revlimid, and proteasome inhibitors like carfilzomib.[80,81] The nature

TABLE 3. Rates of Hypertension With Selected Angiogenesis Inhibitors

DISEASE	DRUG	STUDY	GRADE 3/4 HYPERTENSION RATES, %	
			ANTIANGIOGENIC	CONTROL
Colon cancer	Bevacizumab	Dewdney 2012,[65] Mir 2011[66]	11	2.3
Renal cell cancer	Bevacizumab	Fraeman 2013[67]	36	NA
Lung cancer	Bevacizumab	Mir 2011,[66] Chen 2015[68]	7	0.7
Breast cancer	Bevacizumab	Fraeman 2013,[67] Gampenrieder 2014[69]	14.8	14.6
Ovarian cancer	Bevacizumab	Fraeman 2013[67]	26.4	16.7
Renal cell cancer	Sunitinib	Larochelle 2012[71]	8	1
GIST	Sunitinib	George 2012[72]	3	0
Breast cancer	Sunitinib	Sungyub & Chamberlain 2015[73]	6	NA
Breast cancer	Sorafenib	Funakoshi 2013[74]	17	12
Lung cancer	Cediranib	Langenberg 2009[75]	35	NA
Breast cancer	Cediranib	Langenberg 2009[75]	42	NA
Phase 1	Sorafenib and bevacizumab	Castellano 2013,[76] Azad 2008[70]	33	NA

GIST, gastrointestinal stromal tumor; NA, not available.

of these events varies, depending on the exact agent used and the severity of the hematologic malignancy being treated. The range of vascular problems is related to the vascular beds affected. For instance, dasatinib rarely induces pleural effusions or pulmonary hypertension,[82] although the vascular issues noted with nilotinib are completely different and likely represent progressive atherosclerosis.[83,84] In addition, combination therapies used in myeloma may increase the risk of venous and arterial thrombotic events.[85] Overall, it is fair to say that these myriad vascular complications are important and ultimately require specific strategies to manage them effectively.

Rhythm Disturbances and QTc Prolongation

Cancer therapies may be associated with a variety of rhythm disturbances but most notably can prolong the QT interval, potentially leading to ventricular arrhythmias. The use of some medications used in supportive care during cancer therapy (eg, antiemetics, antidepressants) in combination with cancer treatments can lead to QT prolongation. A careful review of drug interactions should be considered the standard of care for all patients receiving cancer treatment.[86] There are specific therapies that have been associated with certain rhythm disturbances, but the mechanism for this association is frequently related to electrolyte abnormalities or concomitant medications that occur in a particular population. Potential QT interval changes may be related to the pharmacologic targets, but this association is difficult to prove.[86-88] In general, electrolyte abnormalities should be carefully managed, and concomitant medications should be chosen that have minimal impact on rhythm disturbances.

Radiotherapy-Induced CV Damage

The association of radiotherapy (RT) and cardiac dysfunction is well recognized. Radiation-associated cardiac injuries are especially important in young patients with curable malignancies, in whom the risk of developing clinically significant late cardiotoxicity is high. The development of CV damage after RT may be progressive and can include coronary artery disease, valvular disease, myocardium damage, defects in the conduction system, and diastolic dysfunction.[89] The relative risk of fatal CV events after mediastinal irradiation for Hodgkin disease and for left-sided breast cancer, which are the two most common reasons for RT in young patients, is between 2.0 and 7.0 and between 1.0 and 2.2, respectively.[89-91] In addition, it is worth highlighting that these data may not reflect contemporary radiation treatment protocols, because RT methods have significantly changed over time. Damage to the arterial endothelium can induce premature atherosclerosis in the coronary circulation, particularly in the left anterior descending and right coronary arteries.[90] This usually occurs 10 to 15 years after RT. Acute pericarditis and either symptomatic or asymptomatic chronic pericardial effusion may appear 6 to 12 months after RT. Stenosis and regurgitation of mitral and aortic valves have been reported. Fibrosis of the conduction system with disturbed heart rate and heart block (either complete or incomplete) may also occur. These late radiation-induced cardiac effects have been seen with doses from 30 to 40 grays.[91] Newer RT techniques, including 3-dimensional (3D) treatment planning with dose-volume histograms to precisely calculate both heart volume and dose, should decrease the risk of direct cardiac damage.[89-91] The prone position and deep inspiration breath hold are also commonly used as techniques. Models to predict the risk of radiation damage include the normal tissue

complication probability (NTCP) method, which takes into account the dose and the volume of normal tissues that are subject to radiation exposure.[92] The NTCP model predicts the correlation between the given dose and the risk of cardiac mortality within 15 years after RT.[93]

Detection of Cardiac Dysfunction and Evidence for Cardiotoxicity

Echocardiographic Imaging

Echocardiography, particularly 2-dimensional imaging (2D-Echo), is the most commonly used imaging technique to monitor cardiac function during and after chemotherapy. It is a widely available, reproducible, noninvasive modality that permits safe, serial assessment of cardiac function. There are many technical limitations to any technique, and 2D-Echo is no exception. Recent reviews have detailed these considerations.[94] Common parameters that are followed include LVEF and myocardial strain.

LVEF

LVEF is the most commonly accepted parameter of cardiac function that independently predicts short-term and long-term mortality from CV events, including myocardial infarction, ischemic and idiopathic cardiomyopathy, as well as anthracycline-induced cardiomyopathy.[95-99] However, the measurement of LVEF presents several challenges related to image quality, assumption of LV geometry, load dependency, and expertise. Moreover, LVEF measurement remains a relatively insensitive tool for detecting cardiotoxicity at an early stage.[100] This is largely because a decrease in LVEF does not occur until a critical amount of myocardial damage has taken place and cardiac compensatory mechanisms are exhausted. Interestingly, in a recent study involving a large, predominantly breast cancer population treated with anthracyclines, prospective and close monitoring of LVEF with standard 2D-Echo during the first 12 months after the completion of chemotherapy allowed early detection of almost all cases of cardiotoxicity (98%), and prompt treatment led to normalization of cardiac function in most cases (82%). In this study, candidate variables were age, sex, CV risk factors, cumulative anthracycline dose, mediastinal RT, left chest RT, body mass index, and year of recruitment; and baseline and final (at the end of chemotherapy) LVEF measurements were collected. LVEF at the end of chemotherapy was an independent predictor of further development of cardiotoxicity.[101]

However, only 11% of patients had a full recovery—ie, showed an LVEF value equal to or better than the baseline value (before chemotherapy initiation); in the remaining 89% of patients, cardiac function was below the baseline value. This evidence suggests that strategies aimed at preventing the development of LVD appear strategically more effective than therapy interventions aimed at counteracting existing damage, which can be progressive and irreversible in many cases.

Diastolic dysfunction may precede LVEF reduction in patients with chemotherapy-induced cardiotoxicity.[101] Accordingly, abnormal diastolic filling without evidence of LVEF decrease has been demonstrated in chemotherapy-treated patients.[102] However, no diastolic parameters have been proven to definitively predict cardiotoxicity, and the role of diastolic dysfunction in screening for the detection of early subclinical cardiotoxicity currently remains controversial.

Myocardial strain

Newer technology has emerged that allows for an improvement in the accuracy of calculating LVEF. One of the most promising is strain-echocardiography. Strain is a measurement of myocardial deformation. As the ventricle contracts, muscle shortens in the longitudinal and circumferential dimensions and thickens and lengthens in the radial direction. Strain imaging can provide an assessment of global and regional cardiac function and can be measured using either tissue Doppler or 2D-based methods.[103] Several small studies evaluating tissue Doppler and LV strain rate imaging have detected early subclinical changes in cardiac function that preceded a decrease in LVEF.[104-106] By using tissue Doppler-based strain imaging, a common measurement known as the peak systolic longitudinal strain rate can be used to reliably recognize most early myocardial deformation variations during anticancer therapy; whereas, with speckle tracking echocardiography, an advancement of strain imaging, peak systolic global longitudinal strain (GLS) would appear to be the most accurate measure. A 10% to 15% early decrease in GLS by speckle tracking echocardiography during therapy seems to be the most useful parameter for the early detection of cardiotoxicity, defined as a drop in LVEF or HF.[103] However, currently, long-term data on large populations confirming the clinical significance of such changes are not available. Moreover, there are currently important limitations of these techniques: data analysis is currently offline, time-consuming, and still depends on the quality of the acoustic windows. In addition, different echo machines and software packages may yield different strain results, making them difficult to compare. Consequently, these new echo imaging techniques are not typically included in a routine assessment of cardiac function during chemotherapy.[94]

The role of other imaging techniques

Multiple-gated acquisition (MUGA) scans can limit interobserver variability in assessing LVEF, but it has the disadvantages of exposing the patient to radiation and provides limited information on cardiac structure and diastolic function. Magnetic resonance imaging is considered to be the

TABLE 4. Studies Demonstrating Troponins as Predictor of Antitumor Drug-Induced Left Ventricular Dysfunction

STUDY	NO. OF PATIENTS	CANCER TYPE	DRUGS	TROPONIN TYPE	CUTOFF, ng/mL	TIMING OF ASSESSMENT
Lipshultz 1997[113]	15[a]	ALL	AC	T	0.03	Before CT; 1–3 d after each dose
Cardinale 2000[114]	201	Various	HD CT	I	0.04	0, 12, 24, 36, and 72 h after CT
Cardinale 2002[115]	232	Breast cancer	HD CT	I	0.04	0, 12, 24, 36, and 72 h after CT
Auner 2002[116]	30	Hematological	HD CTX	T	0.03	Before CT; 1-14 d after CT
Sandri 2003[117]	179	Various	HD CT	I	0.04	0, 12, 24, 36, and 72 h after CT
Cardinale 2004[110]	703	Various	HD CT	I	0.04	0, 12, 24, 36, and 72 h after CT
Specchia 2005[118]	79	Hematological	AC	I	0.15	Before CT; weekly × 4
Kilickap 2005[119]	41	Various	AC	T	0.10	Before CT; 3-5 d after first and last dose
Lee 2008[120]	86	Hematological	AC	I	0.20	Before each dose
Schmidinger 2008[121]	74	Renal carcinoma	Sunitinib/sorafenib	I	0.03	Before CT; bimonthly during CT
Cardinale 2010[122]	251	Breast cancer	TRZ	I	0.04	Before and after each cycle
Morris 2011[123]	95	Breast cancer	AC + taxanes + TRZ/LAP	I	0.30	Every 2 wk during CT
Sawaya 2011[124]	43	Breast cancer	AC + taxanes + TRZ	HS-I	0.015	Before CT; after 3 and 6 mo during CT
Lipshultz 2012[125]	205[a]	ALL	AC/AC + dexrazoxane	I/T	Any detectable amount	Before CT; 1-7 d after each dose; end CT
Sawaya 2012[126]	81	Breast cancer	AC + taxane+ TRZ	HS-I	30 pg/mL	Before CT; after 3 and 6 mo during CT
Geiger 2012[127]	50	Various	AC	T	NA	Before CT; after 6 h,7 d, 3 mo
Drafts 2013[104]	53	Various	AC	I	0.06	Before CT; after 1, 3, and 6 mo
Mornos & Petrescu 2013[128]	74	Various	AC	HS-T	NA	Before CT; after 6, 12, 24, and 52 wk
Mavinkurve-Groothuis 2013[129]	60[a]	ALL	AC	HS-T	0.01	Before CT; after 3 and 12 mo
Ky 2014[108]	78	Breast cancer	AC + taxanes + TRZ	HS-I	NA	Before CT; after 3 and 6 mo during CT
Mornos 2014[130]	92	Various	AC	HS-T	NA	Before CT; after 12 and 36 wk

Abbreviations: AC indicates anthracycline-containing chemotherapy; ALL, acute lymphoblastic leukemia; CT, chemotherapy; CTX, cyclophosphamide; HD, high-dose; HS-I, high-sensitivity troponin 1; HS-T, high-sensitivity troponin; I, troponin I; LAP, lapatinib; NA, not available; T, troponin T; TRZ, trastuzumab. [a]This was a pediatric population.

gold standard for the evaluation of cardiac volumes, mass, and both systolic and diastolic function. However, because of high cost and lack of availability, this imaging modality is not routinely used.[103,105]

Cardiac Biomarkers

A strategy based on the use of biochemical markers, in particular cardiac troponins, has developed in the last 15 years for early real-time identification, assessment, and monitoring of antitumor drug-induced cardiotoxicity. This approach negates the interobserver variability reported with strategies using imaging; but, unfortunately, the exact timing of biomarker measurement and the variability in techniques have not been adequately determined.[103,107,108]

Troponins

Cardiac troponins are regulatory proteins within the myocardium that are released into the circulation when damage to the myocyte has occurred.[109] Troponins are the first blood biomarkers identified to detect cardiac damage. They are medium-sized proteins regulating the contractile elements actin and myosin. Although they are normally undetectable, troponins may increase within 2 or 3 hours after cardiac damage occurs.[110-112] Studies have shown that troponins may detect cardiotoxicity at a preclinical phase, long before any reduction in LVEF has occurred, in patients treated with antitumor drugs (Table 4).[104,108,110,113-130] Measurement of troponins may provide additional information, including:

1. Prediction of the severity of future LVD, because the peak value of troponin after chemotherapy is closely correlated to the extent of LVEF reduction;
2. Stratification of cardiac risk after chemotherapy, which allows for the personalization of the intensity of post-chemotherapy monitoring of cardiac function;
3. Selection of patients more prone to develop cardiotoxicity, in whom a cardioprotective therapy can be considered; and
4. Exclusion of most patients from prolonged cardiologic monitoring.

In a study of 703 predominantly breast cancer patients, troponin I (TnI) was assessed before chemotherapy, during the 3 days after the end of chemotherapy (early evaluation), and after 1 month (late evaluation).[110] Three different troponin release patterns were identified. TnI was regularly within the normal range in 70% of patients, increased only at early evaluation in 21%, and increased at both early and late evaluations in 9%. Patients without a TnI increase after chemotherapy showed no significant reduction in LVEF and had a low incidence of cardiac events (1%) during the

>3-year follow-up. In contrast, TnI-positive patients had a greater incidence of major adverse cardiac events. In particular, among TnI-positive patients, the persistence of the TnI rise 1 month after chemotherapy was associated with a greater LVEF reduction and a higher incidence of cardiac events compared with patients who had only a transient increase in the marker (84% vs 37%; $P < .001$). An additional study in leukemia patients suggested that a troponin elevation may identify those at risk for LVD.[131]

High-sensitivity troponins

Recent improvements in assay technology have led to more sensitive and precise troponin assays. These new high-sensitivity (HS) assays can now reliably measure small increases that are undetectable by using other troponin assays.[132] The most recent study in which HS troponin was assessed was that by Ky et al,[108] who investigated the association between multiple biomarker increases and successive development of cardiotoxicity in breast cancer patients being treated with anthracyclines, taxanes, and trastuzumab.[108] In that study, however, the most important risk of cardiotoxicity was associated with HS TnI change in absolute values at the end of anthracycline treatments as well an increase in myeloperoxidase, a marker of oxidative stress.

Natriuretic peptides

Increased natriuretic peptide (NP) levels can detect chemotherapy-induced LVD in both adult and pediatric populations.[133,134] Unfortunately, many studies failed to find a correlation between the increase in NP and the development of cardiac dysfunction, probably because significant volume changes can occur in patients who are receiving chemotherapy without any significant change in LVEF. It is noteworthy that, when considering only the two most used NPs—B-type NP (BNP) and N-terminal pro-BNP (NT-proBNP)—the significant differences in analytical characteristics and measured values among the most widely used commercial methods underline that clinicians must be careful and cautious when comparing results obtained by laboratories that use different methods. Understanding the utility of NP as an adjunct to clinical care in patients being treated with potential cardiotoxic therapy is necessary.[135] New prospective and multicenter studies that include large populations, using well standardized methods for dosage, and with well defined timing of sampling and cardiac endpoints are paramount to clarify the appropriate use of NP and to interpret the results in the clinical context.

An Integrated Approach of Markers and Cardiac Imaging

An integrated approach combining biomarkers as well as imaging data may yield progressive utility in predicting subsequent cardiotoxicity. In a recent multicenter study, HS troponins, NT-pro-BNP, ST2 (interleukin 1 receptor-like 1), LVEF, and echocardiographic parameters of myocardial deformation were used to detect LVD in patients receiving anthracyclines, taxanes, and trastuzumab. Decreases in peak longitudinal strain and increases in HS TnI concentrations at the completion of the anthracycline treatment were predictive of subsequent LVD. The combined assessment of the two endpoints showed an improved specificity (93%) compared with either parameter alone (both 73%).[124] However, this result was associated with a reduction in sensitivity to 35%.[126]

Other Proposed Biomarkers

Other potential markers of cardiotoxicity have been investigated in small studies. These include markers of endothelial dysfunction (tissue-type plasminogen activator, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule-1, and circulating endothelial cells), markers of myocardial ischemia (fatty acid binding protein), as well as markers of oxidative stress and inflammation (glutathione peroxidase, high-sensitivity C-reactive protein, interleukins).[132,133] Although many of these proposed biomarkers have shown significant changes during chemotherapy, the impact of these changes on cardiac function are unknown; thus, further research is needed.[136]

In summary, a novel approach based on the use of cardiac biomarkers has emerged in the last decade, resulting in a promising, cost-effective diagnostic tool for early, real-time identification, assessment, and monitoring of cardiotoxicity. Further trials are necessary to confirm their use in clinical practice. Standardization of the use of routine biomarkers in this clinical setting is a current unmet need, and future larger, prospective, multicenter studies should provide clear indications of the appropriate use of these biomarkers in clinical practice.

Management of Anticancer Drug-Related Cardiotoxicity

The Role of Cardioprotective Therapy for Prevention

The cardioprotective effects of many pharmacologic agents have been demonstrated during cancer therapy in a laboratory setting; however, most of these agents have not been proven to be cardioprotective for cancer treatment-related cardiotoxicity. Several agents—dexrazozane, beta-blockers, angiotensin antagonists, statins, and aldosterone antagonists—have been shown to be potentially cardioprotective in patients exposed to anthracyclines or trastuzumab (Table 5).[137-146]

Dexrazoxane

Dexrazoxane significantly reduces anthracycline-related cardiotoxicity in adults with different solid tumors and in children with acute lymphoblastic leukemia and Ewing sarcoma.[147-149] There is a large amount of evidence that

TABLE 5. Cardiovascular Drugs Showing a Prophylactic Effect Against Anthracycline/Trastuzumab-Induced Cardiotoxicity in Adult Cancer Populations

STUDY	STUDY DESIGN/ FOLLOW-UP	NO. OF PATIENTS	CANCER TYPE	DRUGS	INTERVENTION	RESULTS
ACEI						
Cardinale 2006[137]	RCT/12 mo	114	Various	HD CT	Enalapril	No LVEF↓; MACE incidence↓
ARB						
Nakamae 2005[138]	RCT/7 d	40	NHL	AC	Valsartan	No LVEDD↑; no BNP and ANP↑; no QT↑
Cadeddu 2010[139]	RCT/18 mo	49	Various	AC	Telmisartan	No peak strain rate↓; no interleukin 6↑
Aldosterone antagonists						
Akpek 2015[140]	RCT/6 mo	83	Breast cancer	AC	Spironolactone	No LVEF↓; no TNI and BNP↑
Beta-blockers						
Kalay 2006[141]	RCT/6 mo	50	Various	AC	Carvedilol	No LVEF↓
Kaya 2013[142]	RCT/6 mo	45	Breast cancer	AC	Nebivolol	No LVEF and NT-proBNP↑
Seicean 2013[143]	Retrospective/5 y	318	Breast cancer	AC, TRZ	Beta-blockers	HF↓
ACEI + beta-blockers						
Bosch 2013[144]	RCT/6 mo	90	Hematological	AC	Enalapril + carvedilol	No LVEF↓; death↓; HF↓
Statin						
Acar 2011[145]	RCT/6 mo	40	Hematological	AC	Atorvastatin	No LVEF↓
Seicean 2012[146]	Retrospective/5 y	67	Breast cancer	AC	Statins	HF↓

↓, decrease; ↑, increase; ACEI, angiotensin-converting enzyme inhibitor; ANP, atrial natriuretic peptide; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; HD CT, high-dose chemotherapy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; HF, heart failure; MACE, major adverse cardiac events; NHL, non-Hodgkin lymphoma; NT-proBNP, N-terminal-probrain natriuretic peptide; QT, QT interval; RCT, randomized controlled trial; TNI, troponin I; TRZ, trastuzumab.

patients who received dexrazoxane had a decreased incidence of HF compared with those who did not receive the drug. Despite these consistent positive findings, the use of dexrazoxane has not been widely adopted, and it is recommended as a cardioprotectant by the American Society of Clinical Oncology (ASCO) only in patients with metastatic breast cancer who have already received more than 300 mg/m^2 of doxorubicin.[150] This might be explained by the suspicion—never confirmed—of interference with the efficacy of anthracyclines, by the occurrence of secondary malignancies, or by its possible additive effects of myelosuppression.

Beta-blockers

Carvedilol, a nonselective beta-blocker with antioxidant activity that is considered crucial in the treatment of patients with HF and LVD, is an effective cardioprotective agent during doxorubicin treatment.[151] This effect was confirmed in a randomized study in which prophylactic use of the drug protected both systolic and diastolic LV function in a small population of anthracycline-treated patients.[141] The protective effect of nebivolol, a beta-selective beta-blocker with a nitric oxide donor capacity, has also been demonstrated to be beneficial in a recent randomized study of 47 breast cancer patients receiving anthracycline-therapy[142]; notably, LVEF and NT-proBNP remained unchanged after 6 months in patients who received nebivolol. Conversely, in the placebo group, a significant decrease in LVEF and an increase in NT-proBNP were observed.[142]

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

The possible role of telmisartan, an angiotensin receptor blocker, in preventing myocardial injury induced by epirubicin was evaluated by Cadeddu et al[139] in a randomized trial that included 49 patients with a variety of solid cancers.[139] Twenty-five patients who started telmisartan 1 week before chemotherapy showed no significant reductions in myocardial deformation parameters (peak strain rate), as evaluated using a tissue Doppler echo technique, and no significant rise in ROS or interleukin-6, as found in 24 control patients.[139] These results suggest that telmisartan might protect against epirubicin-induced ROS production and inhibit the generation of inflammation, thus preventing the development of early myocardial impairment.[139] The cardioprotective effects of enalapril, an angiotensin-converting enzyme inhibitor (ACE-I), were studied in a randomized, controlled trial that included 473 patients (53% had breast cancer) treated with high-dose anthracyclines.[137] One-hundred fourteen patients (24%) showed an early troponin increase and were randomized to receive enalapril or no treatment. Enalapril was started 1 month after the end of chemotherapy and continued for 1 year. In the enalapril-treated group, LVEF did not change during the follow-up period. Conversely, in patients who did not receive enalapril, a progressive decrease in LVEF and an increase in end-diastolic and end-systolic volumes were observed. Moreover, enalapril-treated patients had a significantly lower incidence of adverse cardiac events compared with controls at 1-year follow-up (2% vs 52%; $P < .001$).[137]

The preventive effects of combined enalapril and carvedilol recently were tested in a randomized trial of 90 patients with hematologic malignancies who were treated with anthracyclines.[144] After 6 months, LVEF did not change in the intervention group; conversely, LVEF significantly decreased in controls ($P = .035$). Importantly, compared with controls,

patients in the intervention group had a lower incidence of the combined event of death or HF (6.7% vs 22%; $P = .036$) or of death, HF, and a final LVEF below 45% (7% vs 24%; $P = .02$).[144]

Statins

Statins exert antioxidative, anti-inflammatory, and other pleiotropic effects in addition to reducing low-density lipoprotein (LDL) cholesterol. In an animal model, it was demonstrated that pretreatment with fluvastatin blunted anthracycline-induced toxicity, reducing oxidative stress, enhancing the expression of antioxidative enzyme mitochondrial superoxide-dismutase-2, and limiting cardiac inflammation.[153] In a retrospective case-control study, 67 women with breast cancer treated with anthracyclines who also were receiving a statin drug were compared with 134 matched controls.[146] Women treated with statins showed a lower incidence of HF at a mean of 2.5 years of follow-up.[146] Finally, in a small clinical trial of 40 patients who had normal LVEF before undergoing chemotherapy (which included anthracyclines), the 6-month LVEF value was unchanged among patients treated with atorvastatin compared with an 8% absolute decrease in controls.[145]

Aldosterone antagonists

Aldosterone antagonism has been evaluated in a very recent trial that included 83 patients with breast cancer who were randomized to spironolactone or placebo and a concomitant anthracycline-containing chemotherapy control groups.[140] During at least 24 weeks of treatment, including 3 weeks after completing anthracycline-containing chemotherapy, spironolactone prevented a decrease in LVEF, blunted the increase in TnI and NT-proBNP, and preserved diastolic function.[140]

Ongoing Studies

Currently, several studies are ongoing to evaluate CV drugs as cardioprotectant agents. The MANTICORE-101 (Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research) trial is evaluating the use of perindopril versus bisoprolol in patients with HER2-positive breast cancer who are undergoing treatment with trastuzumab in the prevention of LVD as assessed by cardiac magnetic resonance imaging.[154] At the end of trastuzumab therapy, neither drug had an impact on LV end-diastolic volume (the primary outcome of change from baseline in the study). In univariate analysis, only bisoprolol was associated with preservation of baseline function (from 62% to 61%; secondary outcome). However, in multivariate analysis, the use of both cardiac drugs significantly predicted preserved LV function (for perindopril, $P = .013$; for bisoprolol, $P < .001$). These data were presented during the 2015 San Antonio Breast Cancer Symposium.

The PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) trial is assessing whether the use of candesartan, metoprolol, or their combination can prevent the development of LVD in patients on adjuvant epirubicin-containing chemotherapy with or without trastuzumab.[155] The results demonstrated that candesartan—but not metoprolol—concomitantly administrated with adjuvant chemotherapy, including epirubicin with or without trastuzumab, can protect against early decline in LVEF, assessed with cardiac magnetic resonance.

The International Cardioncology Society (ICOS)-ONE trial is the only randomized study that is designed to compare the use of enalapril administration concomitantly with anthracycline-containing chemotherapy (primary prevention) versus enalapril administration after preclinical cardiotoxicity detection, as revealed by the increase in troponins (secondary prevention; national clinical trial NCT01968200; clinicaltrials.gov).

In the NCT01708798 study (clinicaltrials.gov), the potential ability of the aldosterone antagonist eplerenone to prevent doxorubicin-induced cardiotoxicity will be explored in a randomized controlled trial of breast cancer patients.

Finally, at Memorial Sloan Kettering Cancer Center, an ongoing randomized trial (NCT02177175; clinicaltrials.gov) is assessing the use of carvedilol for the prevention of anthracycline/trastuzumab therapy-associated cardiotoxicity among women with HER2-positive breast cancer using myocardial strain for early risk stratification. In this trial, carvedilol is started in women who show an absolute decrease in GLS below 19% or in those who have a decrease $\geq$11% from baseline. It is hoped that the findings from these trials will provide important insights into the best strategy for managing cardiotoxicity induced by anticancer drugs.

Treatment

The Role of ACE-I and Beta-Blockers

Limited data exist regarding the treatment of patients with antitumor drug-associated cardiomyopathy. Typically, these patients have been excluded from large randomized trials evaluating the effectiveness of HF therapies. The use of ACE-I and beta-blocking agents in this particular clinical setting were first evaluated in a very few retrospective studies, which involved small populations (Table 6).[45,63,99,101,156-163] More recently, the effectiveness of ACE-I and beta-blockers were prospectively assessed in this setting. In 201 consecutive patients with anthracycline-induced LVD, enalapril (combined with carvedilol when possible) was initiated at the time of LVEF impairment detection and was up-titrated to the maximal tolerated dose.[63] The investigators found that the time elapsed from the end of chemotherapy to the start of HF therapy was a crucial variable for the recovery of cardiac function. Indeed, among patients who were treated within

TABLE 6. Clinical Studies Evaluating Angiotensin-Converting Enzyme Inhibitors and Beta-Blockers in Anticancer Drug-Induced Cardiomyopathy

TREATMENT	AUTHOR (YEAR)	NO. OF PATIENTS	MEAN AGE, Y	STUDY	DRUGS	FOLLOW-UP, MO	B-LVEF, %	F-LVEF, %	REPORTED EVENT
Dig + Diur + ACEI	Saini 1987[156]	3	49	CR	AC	12-16	20	48	Relief of symptoms, LVEF↑
Dig + Diur; Dig + Diur + ACEI	Jensen 1996[157]	9	58	P	AC	26	27	47	CD, HF
Dig + Diur + ACEI; BB	Fazio 1998[158]	1	35	CR	AC	12	14	45	Relief of symptoms
BB; BB + ACEI	Noori 2000[159]	2; 6	51	R	AC	32	28	41	LVEF↑
Dig + Diur; Dig + Diur + ACEI	Jensen 2002[99]	10	54	P	AC	30	27	41	HF
BB; BB + ACEI	Mukai 2004[160]	3; 2	53	CR	AC	27	37	53	LVEF↑, NYHA↓
ACEI; ACEI + BB	Tallaj 2005[161]	10; 15	47	R	AC	70	25	34	CD, TXS
ACEI; ACEI + BB	Ewer 2005[45]	38	52	R	AC, TRZ	10	43	56	LVEF↑
ACEI + BB	Tabet 2006[162]	1	52	CR	AC	8	NA	30	HF
ACEI + BB	Cardinale 2010[63]	201	53	P	AC	12-96	38	46	LVEF↑ up to ≥50%
ACEI; ACEI + BB	Thakur & Witteles 2014[134]	79	52	R	AC, TRZ, TKI	NA	41	53	LVEF ↑
ACEI + BB	Cardinale 2015[101]	226	50	P	AC	4-228	40	52	LVEF↑ of 5 points + ≥50%

↓, decrease; ↑, increase; AC, anthracycline-containing chemotherapy; ACEI, angiotensin-converting enzyme inhibitor; BB, beta-blockers; B-LVEF, baseline left ventricular ejection fraction; CD, cardiac death; CS, case report; Dig, digoxin; Diur, diuretics; F-LVEF, final left ventricular ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction; NA, not available; NYHA, New York Heart Association; P, prospective; R, retrospective; TKI, tyrosine kinase inhibitor; TRZ, trastuzumab; TXS, cardiac transplantation.

2 months after the end of chemotherapy, 64% had a complete recovery of LVEF. Conversely, after 2 months, the percentage of patients who recovered progressively decreased, with no complete recovery seen after 6 months.[63] Consistent with these findings, a greater improvement in cardiac function was observed in a large population of patients with anthracycline-induced LVD who were receiving a combination of enalapril and carvedilol or bisoprolol. Initiation of HF medications promptly after the detection of symptomatic and asymptomatic anthracycline-induced cardiomyopathy was associated with recovery in 82% of patients over a mean period of 8 ± 5 months. Long-term studies are needed to determine if therapy with ACE-I and beta-blockers should be prolonged lifelong, or discontinued after achievement of complete recovery of LVEF.

QTc Prolongation Management

Prolongation of the QT interval can lead to life-threatening cardiac arrhythmias, including "torsade de pointes." Although prolongation of the QT interval is not the best predictor of proarrhythmic risk, it represents the principal clinical surrogate marker by which to evaluate the arrhythmic risk of a drug and has led to withdrawal of several anticancer drugs from the market. Although drugs leading to prolonged QT may possess significant risks of serious adverse events, the clinical benefit of therapy in the oncologic setting, including the possibility of cure for a cancer patient, may outweigh the potential risks of QTc prolongation, even when the prolongation is significant. Patients with a history of QT interval prolongation; patients who are taking antiarrhythmics; or patients with relevant CVD, bradycardia, thyroid dysfunction, or electrolyte disturbances should be screened and monitored. Periodic monitoring with on-treatment electrocardiograms and electrolytes should be considered.[163,164]

Hypertension Treatment and Management

A collaboration between oncologists, a primary care health care provider, and cardiologists is essential to properly monitor and manage hypertension, which is an unwanted adverse effect of many antiangiogenic agents associated with VSP inhibition. Aggressive management of hypertension beginning from the initiation of therapy is important to avoid cardiac dysfunction; and, again, an understanding of the potential cardiac toxicities of the chemotherapeutic regimen used is essential, giving further support to the concept of a multidisciplinary strategy for management. Patients who are candidates for treatment with VEGF/TKI inhibitors should be considered at higher risk for CV complications if they have systolic blood pressure (BP) ≥160 mm Hg or diastolic BP ≥100 mm Hg; diabetes mellitus; established CV disease, including any history of ischemic stroke, cerebral hemorrhage, or transient ischemic attack; myocardial infarction, angina, coronary revascularization, or HF; peripheral artery disease; subclinical organ damage previously documented by electrocardiogram or 2D-Echo revealing LV hypertrophy; cigarette smoking; and dyslipidemia. Repeated BP measurements and aggressive management of BP elevations are recommended to prevent clinically limiting complications.[79,164,165]

Anticoagulation in Cancer Patients

Venous thromboembolism (VTE) is an important cause of morbidity and mortality in cancer patients. Patients receiving chemotherapy or antiangiogenic agents have a 7-fold higher risk of developing VTE compared with patients

TABLE 7. Predictive Model for Chemotherapy-Associated Venous Thromboembolism

VARIABLE	RISK SCORE[a]
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count $\geq 350 \times 10^9$/L	1
Hemoglobin level <10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count $>11 \times 10^9$/L	1
Body mass index ≥ 35 kg/m^2	1

[a]Risk categories included low risk (score 0), intermediate risk (score 1–2), and high risk (score ≥3). Modified from Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood*. 2008;111:4902–4907.[167]

without cancer. Several randomized trials have demonstrated a significant thromboprophylactic effect of low-molecular-weight heparins (LMWH) in ambulatory cancer patients who are receiving chemotherapy.[166,167] However, routine thromboprophylaxis is currently not recommended for ambulatory cancer patients by ASCO because of the limited absolute risk reduction demonstrated with LMWH and the concern with bleeding complications. The prophylactic use of LMWH may be considered for highly selected, high-risk patients only, according to the risk-assessment model validated by Khorana et al[167] (Table 7), ie, in patients with scores ≥3 and a low bleeding risk.[167,168] Data about the new oral anticoagulants (dabigatran, apixaban, rivaroxaban) for either prophylaxis or treatment of VTE in patients with cancer are still limited, and their use is currently not recommended (ASCO).[168]

Conclusions

Modern cancer treatment strategies have led to a significant improvement in the chances of surviving a diagnosis of cancer for many years. These gains in overall outcome may be offset by the potential negative impact of cancer therapy on CV health. Cancer therapies may have short-term and long-term side effects involving the heart and circulation, as well as exacerbating and/or unmasking existing heart disease. The development of CV disease during the course of cancer treatment can adversely impact the management of the underlying malignancy by interfering with the optimal doses and timing of lifesaving cancer therapy. In addition, the development of a potentially important cancer therapy

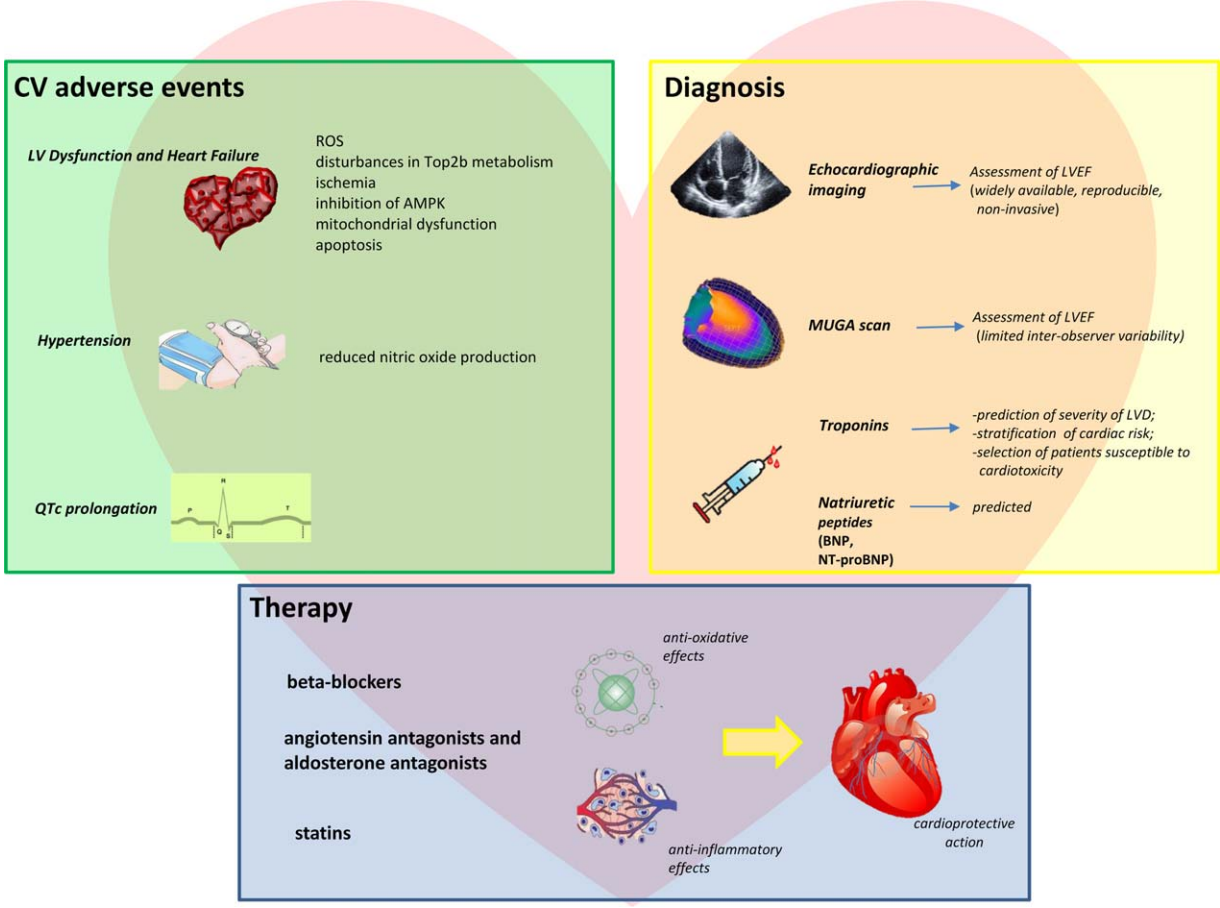

FIGURE 1. Cardiotoxicity Diagnosis and Management. AMPK, 5′ adenosine monophosphate-activated protein kinase; CV, cardiovascular; BNP, B-type natriuretic peptide; LV, left ventricle; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ROS, reactive oxygen species.

may be halted or abandoned because of a perceived increased CV risk. The discipline of cardio-oncology has developed in response to the combined decision making necessary to optimize the care of patients with cancer, whether they are receiving active treatment or are long-term survivors after successful treatment (Fig. 1). Cardiology and oncology organizations around the world (ie, European Society for Medical Oncology, American College of Cardiology, ASCO, European Society of Cardiology, Canadian Cardiovascular Society) are now recognizing the importance of this collaboration, resulting in the ongoing development of several clinical practice guidelines and position statements.[94,164,165] Although these initiatives will provide important guidance for clinicians on best practices for patients today, many questions remain unanswered: How can we predict who will develop cardiotoxicity, what is the best prevention strategy, how should we monitor those at risk of cardiotoxicity, and what are the best management strategies? There is an urgent need for collaborative research to address these questions. Vibrant collaborative partnerships between oncologists, cardiologists, and other allied health care professionals will play an important role in the development and promotion of clinical care models, educational programs (for patients and health care providers), and evidence-based research to improve the care of patients being treated for cancer. ■

References

1. Jemal A, Ward E, Thun M. Declining death rates reflect progress against cancer [serial online]. *PLoS One.* 2010;5:e9584.
2. Howlader N, Ries LAG, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved estimates of cancer-specific survival rates from population-based data. *J Natl Cancer Inst.* 2010;102:1584-1598.
3. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970–2002. *JAMA.* 2005; 294:1255-1259.
4. Dent S, Liu P, Brezden-Masley C, Lenihan D. Cancer and cardiovascular disease: the complex labyrinth [serial online]. *J Oncol.* 2015;2015:516450.
5. Bodai BI, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. *Perm J.* 2015;19:48-79.
6. Siegel R, DeSantis C, Virgo K, et al. Cancer treatment and survivorship statistics, 2012. *CA Cancer J Clin.* 2012;62:220-241.
7. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. *J Am Coll Cardiol.* 2012;60:2504-2512.
8. Bowles EJ, Wellman R, Feigelson HS, et al. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. *J Natl Cancer Inst.* 2012;104:1293-1305.
9. Aleman BM, Moser EC, Nuver J, et al. Cardiovascular disease after cancer therapy. *EJC Suppl.* 2014;12:18-28.
10. Taunk NK, Haffty BG, Kostis JB, Goyal S. Radiation-induced heart disease: pathologic abnormalities and putative mechanisms [serial online]. *Front Oncol.* 2015;5:39.
11. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin.* 2015;65: 5-29.
12. Force T, Kolaja KL. Cardiotoxicity of kinase inhibitors: the prediction and translation of preclinical models to clinical outcomes. *Nat Rev Drug Discov.* 2011;10:111-126.
13. Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments [serial online]. *Nat Rev Cardiol.* 2015;12:620.
14. Ali MK, Ewer MS, Gibbs HR, Swafford J, Graff KL. Late doxorubicin-associated cardiotoxicity in children. The possible role of intercurrent viral infection. *Cancer.* 1994;74:182-188.
15. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies [serial online]. *J Am Heart Assoc.* 2014;3:e000665.
16. Suter TM, Ewer MS. Cancer drugs and the heart: importance and management. *Eur Heart J.* 2013;34:1102-1111.
17. Procter M, Suter TM, de Azambuja E, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. *J Clin Oncol.* 2010;28:3422-3428.
18. Pinder MC, Duan Z, Goodwin JS, Hortobagyi GN, Giordano SH. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol.* 2007;25:3808-3815.
19. Yeh ET, Tong AT, Lenihan DJ, et al. Cardiovascular complications of cancer therapy: diagnosis, pathogenesis, and management. *Circulation.* 2004;109:3122-3131.
20. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the Childhood Cancer Survivor Study. *J Clin Oncol.* 2014;32:1218-1227.
21. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol.* 2009;53:2231-2247.
22. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. *Cancer.* 2003;97:2869-2879.
23. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* 1979;91:710-717.
24. Wouters KA, Kremer LCM, Miller TL, Herman EH, Lipshultz SE. Protecting against anthracycline-induced myocardial damage: a review of the most promising strategies. *Br J Haematol.* 2005;131:561-578.
25. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. *Nat Med.* 2012;18:1639-1642.
26. Martin M, Pienkowski T, Mackey J, et al. Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med.* 2005;352: 2302-2313.
27. Barrett-Lee PJ, Dixon JM, Farrell C, et al. Expert opinion on the use of anthracyclines in patients with advanced breast cancer at cardiac risk. *Ann Oncol.* 2009; 20:816-827.
28. Crozier JA, Swaika A, Moreno-Aspitia A. Adjuvant chemotherapy in breast cancer: to use or not to use, the anthracyclines. *World J Clin Oncol.* 2014;5:529-538.
29. Harbeck N, Ewer MS, De Laurentiis M, Suter TM, Ewer SM. Cardiovascular complications of conventional and targeted adjuvant breast cancer therapy. *Ann Oncol.* 2011;22:1250-1258.
30. Chlebowski RT. Adriamycin (doxorubicin) cardiotoxicity: a review. *West J Med.* 1979;131:364-368.
31. Tjuljandin SA, Doig RG, Sobol MM, et al. Pharmacokinetics and toxicity of two schedules of high dose epirubicin. *Cancer Res.* 1990;50:5095-5101.
32. Anderlini P, Benjamin RS, Wong FC, et al. Idarubicin cardiotoxicity: a retrospective study in acute myeloid leukemia and myelodysplasia. *J Clin Oncol.* 1995;13:2827-2834.
33. Perez E. Paclitaxel in breast cancer. *Oncologist.* 1998;3:373-389.
34. Kenmotsu H, Tanigawara Y. Pharmacokinetics, dynamics and toxicity of docetaxel: why the Japanese dose differs from the Western dose. *Cancer Sci.* 2015;106:497-504.
35. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. *Arch Intern Med.* 1981;141: 758-763.
36. Goldberg MA, Antin JH, Guinan EC, Rappeport JM. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood.* 1986;68:1114-1118.
37. Kandylis K, Vassilomanolakis M, Tsoussis S, Efremidis AP. Ifosfamide cardiotoxicity in humans. *Cancer Chemother Pharmacol.* 1989;24:395-396.
38. Tascilar M, Loos WJ, Seynaeve C, Verweij J, Sleijfer S. The pharmacologic basis of

ifosfamide use in adult patients with advanced soft tissue sarcomas. *Oncologist.* 2007;12:1351-1360.

39. Cancer Care Ontario. Ifosfamide: Drug Monograph. Cancer Care Ontario Drug Formulary-April 2014. Toronto, ON: Cancer Care Ontario; 2014.
40. Senturk T, Kanat O, Evrensel T, Aydinlar A. Capecitabine-induced cardiotoxicity mimicking myocardial infarction. *Neth Heart J.* 2009;17(7–8):277-280.
41. Schimmel KG, Richel DJ, van den Brink RB, Guchelaar HJ. Cardiotoxicity of cytotoxic drugs. *Cancer Treat Rev.* 2004;30: 181-191.
42. Chanan-Khan A, Srinivasan S, Czuczman MS. Prevention and management of cardiotoxicity from antineoplastic therapy. *J Support Oncol.* 2004;2:251-256; discussion 259–261, 264–266.
43. Lebedinsky C, Gomez J, Park YC, et al. Trabectedin has a low cardiac risk profile: a comprehensive cardiac safety analysis. *Cancer Chemother Pharmacol.* 2011;68: 1223-1231.
44. Brana I, Tabernero J. Cardiotoxicity. *Ann Oncol.* 2010;21(suppl 7):vii173-vii179.
45. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol.* 2005;23:7820-7826.
46. Smith I, Procter M, Gelber RD, et al. Two-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. *Lancet.* 2007;369:29-36.
47. Perez EA, Romond EH, Suman VJ, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol.* 2011;29:3366-3373.
48. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med.* 2011;365: 1273-1283.
49. Goldhirsch A, Gelber RD, Piccart-Gebhart MJ, et al. Two years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial. *Lancet.* 2013;382: 1021-1028.
50. Baselga J, Perez EA, Pienkowski T, Bell R. Adjuvant trastuzumab: a milestone in the treatment of HER-2-positive early breast cancer. *Oncologist.* 2006;11(suppl 1):4-12.
51. Mackey JR, Clemons M, Cote MA, et al. Cardiac management during adjuvant trastuzumab therapy: recommendations of the Canadian Trastuzumab Working Group. *Curr Oncol.* 2008;15:24-35.
52. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med.* 2005;353:1673-1684.
53. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.* 2005;353:1659-1672.
54. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol.* 2012;30:3792-3799.
55. Lenihan D, Suter T, Brammer M, Neate C, Ross G, Baselga J. Pooled analysis of cardiac safety in patients with cancer treated with pertuzumab. *Ann Oncol.* 2012;23: 791-800.
56. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13:25-32.
57. Reynolds K, Sarangi S, Bardia A, Dizon DS. Precision medicine and personalized breast cancer: combination pertuzumab therapy. *Pharmgenomics Pers Med.* 2014; 7:95-105.
58. Sevcikova K, Vertakova-Krakovska B, Spanik S. Neoadjuvant treatment in patients with HER2-positive breast cancer [serial online]. *ISRN Oncol.* 2013;2013:362467.
59. Chu TF, Rupnick MA, Kerkela R, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. *Lancet.* 2007; 370:2011-2019.
60. Cheng H, Force T. Molecular mechanisms of cardiovascular toxicity of targeted cancer therapeutics. *Circ Res.* 2010;106:21-34.
61. Chintalgattu V, Ai D, Langley RR, et al. Cardiomyocyte PDGFR-β signaling is an essential component of the mouse cardiac response to load-induced stress. *J Clin Invest.* 2010;120:472-484.
62. Kloner RA, Jennings RB. Consequences of brief ischemia: stunning, preconditioning, and their clinical implications: part 2. *Circulation.* 2001;104:3158-3167.
63. Cardinale D, Colombo A, Lamantia G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol.* 2010;55:213-220.
64. Aslam S, Eisen T. Vascular endothelial growth factor receptor tyrosine kinase inhibitors in metastatic renal cell cancer: latest results and clinical implications. *Ther Adv Med Oncol.* 2013;5:324-333.
65. Dewdney A, Cunningham D, Barbachano Y, Chau I. Correlation of bevacizumab-induced hypertension and outcome in the BOXER study, a phase II study of capecitabine, oxaliplatin (CAPOX) plus bevacizumab as peri-operative treatment in 45 patients with poor-risk colorectal liver-only metastases unsuitable for upfront resection. *Br J Cancer.* 2012;106:1718-1721.
66. Mir O, Coriat R, Cabanes L, et al. An observational study of bevacizumab-induced hypertension as a clinical biomarker of antitumor activity. *Oncologist.* 2011;16:1325-1332.
67. Fraeman KH, Nordstrom BL, Luo W, Landis SH, Shantakumar S. Incidence of new-onset hypertension in cancer patients: a retrospective cohort study [serial online]. *Int J Hypertens.* 2013;2013:379252.
68. Chen J, Lu Y, Zheng Y. Incidence and risk of hypertension with bevacizumab in non-small-cell lung cancer patients: a meta-analysis of randomized controlled trials. *Drug Des Dev Ther.* 2015;9:4751-4760.
69. Gampenrieder SP, Romeder F, Muß C, et al. Hypertension as a predictive marker for bevacizumab in metastatic breast cancer: results from a retrospective matched-pair analysis. *Anticancer Res.* 2014;34: 227-233.
70. Azad NS, Posadas EM, Kwitkowski VE, et al. Combination targeted therapy with sorafenib and bevacizumab results in enhanced toxicity and antitumor activity. *J Clin Oncol.* 2008;26:3709-3714.
71. Larochelle P, Kollmannsberger C, Feldman RD, et al. Hypertension management in patients with renal cell cancer treated with anti-angiogenic agents. *Curr Oncol.* 2012;19:202-208.
72. George S, Reichardt P, Lechner T, Li S, Cohen DP, Demetri GD. Hypertension as a potential biomarker of efficacy in patients with gastrointestinal stromal tumor treated with sunitinib. *Ann Oncol.* 2012; 23:3180-3187.
73. Sungyub L, Chamberlain RS. Hypertension risk among cancer patients treated with sunitinib: a meta-analysis and systematic review [serial online]. *Targeted Oncol.* targetedonc.com/publications/targeted-therapies-cancer/2015/June-2015/Hypertension-Risk-Among-Cancer-Patients-Treated-With-Sunitinib-A-Meta-analysis-and-Systematic-Review. Accessed September 18, 2015.
74. Funakoshi T, Latif A, Galsky MD. Risk of hypertension in cancer patients treated with sorafenib: an updated systematic review and meta-analysis. *J Hum Hypertens.* 2013;27:601-611.
75. Langenberg MH, Van Herpen CM, De Bono J, et al. Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: results from a phase II randomized, factorial, double-blind study of cediranib in patients with advanced solid tumors. *J Clin Oncol.* 2009;27:6152-6159.
76. Castellano D, Capdevila J, Sastre J, et al. Sorafenib and bevacizumab combination targeted therapy in advanced neuroendocrine tumour: a phase II study of Spanish Neuroendocrine Tumour Group (GETNE0801). *Eur J Cancer.* 2013;49:3780-3787.
77. Kamba T, McDonald DM. Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer.* 2007;96:1788-1795.
78. Li W, Croce K, Steensma DP, McDermott DF, Ben-Yehuda O, Moslehi J. Vascular and metabolic implications of novel targeted cancer therapies. *J Am Coll Cardiol.* 2015;66:1160-1178.
79. Moslehi JJ, Deininger M. Tyrosine kinase inhibitor-associated cardiovascular toxicity in chronic myeloid leukemia. *J Clin Oncol.* 2015;33:4210-4218.
80. Grandin EW, Ky B, Cornell RF, Carver J, Lenihan DJ. Patterns of cardiac toxicity associated with irreversible proteasome inhibition in the treatment of multiple myeloma. *J Card Fail.* 2015;21:138-144.
81. Atrash S, Tullos A, Panozzo S, et al. Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib [serial online]. *Blood Cancer J.* 2015;5:e272.

82. Montani D, Bergot E, Gunther S, et al. Pulmonary arterial hypertension in patients treated by dasatinib. *Circulation.* 2012; 125:2128-2137.

83. Giles FJ, Mauro MJ, Hong F, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: a retrospective cohort analysis. *Leukemia.* 2013;27:1310-1315.

84. Kim TD, Rea D, Schwarz M, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. *Leukemia.* 2013;27:1316-1321.

85. Cesarman-Maus G, Braggio E, Fonseca R. Thrombosis in multiple myeloma (MM). *Hematology.* 2012;17(suppl 1):S177-S180.

86. Brell JM. Prolonged QTc interval in cancer therapeutic drug development: defining arrhythmic risk in malignancy. *Prog Cardiovasc Dis.* 2010;53:164-172.

87. Guglin M, Aljayeh M, Saiyad S, Ali R, Curtis AB. Introducing a new entity: chemotherapy-induced arrhythmia. *Europace.* 2009;11:1579-1586.

88. Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol.* 2014; 63:945-953.

89. Heidenreich PA, Hancock SL, Lee BK, Mariscal CS, Schnittger I. Asymptomatic cardiac disease following mediastinal irradiation. *J Am Coll Cardiol.* 2003;42:743-749.

90. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med.* 2013;368:987-998.

91. Heidenreich PA, Hancock SL, Vagelos RH, Lee BK, Schnittger I. Diastolic dysfunction after mediastinal irradiation. *Am Heart J.* 2005;150:977-982.

92. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2012;23(suppl 7):vii155-vii166.

93. Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol.* 2010;76:S77-S85.

94. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2014;27:911-939.

95. Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popovíc ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. *J Am Coll Cardiol.* 2013; 61:77-84.

96. Betriu A, Castaner A, Sanz GA, et al. Angiographic findings 1 month after myocardial infarction: a prospective study of 259 survivors. *Circulation.* 1982;65:1099-1105.

97. Daneault B, Genereux P, Kirtane AJ, et al. Comparison of 3-year outcomes after primary percutaneous coronary intervention in patients with left ventricular ejection fraction <40% versus ≥40% (from the HORIZONS-AMI trial). *Am J Cardiol.* 2013;111:12-20.

98. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials [serial online]. *BMC Cancer.* 2010;10:337.

99. Jensen BV, Skovsgaard T, Nielsen SL. Functional monitoring of anthracycline cardiotoxicity: a prospective, blinded, long-term observational study of outcome in 120 patients. *Ann Oncol.* 2002;13:699-709.

100. Ewer MS, Lenihan DJ. Left ventricular ejection fraction and cardiotoxicity: is our ear really to the ground? *J Clin Oncol.* 2008;26:1201-1203.

101. Cardinale D, Colombo A., Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. *Circulation.* 2015;131: 1981-1989.

102. Nagueh SF, Appleton CP, Gillebert TC, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *Eur J Echocardiogr.* 2009;10:165-193.

103. Thavendiranathan P, Poulin F, Lim K-D, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol.* 2014;63(25 pt A):2751-2768.

104. Drafts BC, Twomley KM, D'Agostino R, et al. Low to moderate dose anthracycline-based chemotherapy is associated with early noninvasive imaging evidence of subclinical cardiovascular disease. *JACC Cardiovasc Imaging.* 2013;6:877-885.

105. Fallah-Rad N, Walker JR, Wassef A, et al. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant trastuzumab therapy. *J Am Coll Cardiol.* 2011;57:2263-2270.

106. Negishi K, Negishi T, Haluska BA, Hare JL, Plana JC, Marwick TH. Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. *Eur Heart J Cardiovasc Imaging.* 2014;15:324-331.

107. Ky B, Carver JR. Biomarker approach to the detection and cardioprotective strategies during anthracycline chemotherapy. *Heart Fail Clin.* 2011;7:323-331.

108. Ky B, Putt M, Sawaya H, et al. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. *J Am Coll Cardiol.* 2014;63:809-816.

109. Daubert MA, Jeremias A. The utility of troponin measurement to detect myocardial infarction: review of the current findings. *Vasc Health Risk Manag.* 2010;6:691-699.

110. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation.* 2004;109:2749-2754.

111. Hequet O, Le QH, Moullet I, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. *J Clin Oncol.* 2004;22:1864-1871.

112. Colombo A, Sandri MT, Salvatici M, Cipolla CM, Cardinale D. Cardiac complications of chemotherapy: role of biomarkers. *Curr Treat Options Cardiovasc Med.* 2014;16:313-313.

113. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. *Circulation.* 1997;96:2641-2648.

114. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol.* 2000;36:517-522.

115. Cardinale D, Sandri MT, Martinoni A, et al. Myocardial injury revealed by plasma troponin I in breast cancer treatment with high dose chemotherapy. *Ann Oncol.* 2002;13:710-715.

116. Auner HW, Tinchon C, Linkesch W, Tiran A, Quehenberger F, Link H. Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. *Ann Hematol.* 2003;82:218-222.

117. Sandri MT, Cardinale D, Zorzino L, et al. Minor increases in plasma troponin I predict decreased left ventricular ejection fraction after high-dose chemotherapy. *Clin Chem.* 2003;49:248-252.

118. Specchia G, Buquicchio C, Pansini N, Di Serio F, Liso V, Pastore D. Monitoring of cardiac function on the basis of serum troponin I levels in patients with acute leukemia treated with anthracyclines. *J Lab Clin Med.* 2005;145:212-220.

119. Kilickap S, Barista I, Akgul E, Aytemir K, Aksoyek S, Aksoy S. cTnT can be a useful marker for early detection of anthracycline cardiotoxicity. *Ann Oncol.* 2005;16:798-804.

120. Lee HS, Son CB, Shin SH, Kim YS. Clinical correlation between brain natriutetic peptide and anthracyclin-induced cardiac toxicity. *Cancer Res Treat.* 2008;40:121-126.

121. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol.* 2008;26:5204-5212.

122. Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol.* 2010;28: 3910-3916.

123. Morris PG, Chen C, Steingart RM, Fleisher M, et al. Troponin I and C-reactive protein are commonly detected in patients with breast cancer treated with dose-dense chemotherapy incorporating trastuzumab and lapatinib. *Clin Cancer Res.* 2011;17:3490-3499.

124. Sawaya H, Sebag IA, Plana JC, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. *Am J Cardiol.* 2011;107:1375-1380.

125. Lipshultz SE, Miller TL, Scully RE, et al. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients With high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. *J Clin Oncol.* 2012;30:1042-1049.

126. Sawaya H, Sebag IA, Plana JC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging.* 2012;5:596-603.

127. Geiger S, Stemmler HJ, Suhl P, et al. Anthracycline-induced cardiotoxicity: cardiac monitoring by continuous wave-Doppler ultrasound cardiac output monitoring and correlation to echocardiography. *Onkologie.* 2012;35:241-246.

128. Mornos C, Petrescu L. Early detection of anthracycline-mediated cardiotoxicity: the value of considering both global longitudinal left ventricular strain and twist. *Can J Physiol Pharmacol.* 2013;91:601-607.

129. Mavinkurve-Groothuis AM, Marcus KA, Pourier M, et al. Myocardial 2D strain echocardiography and cardiac biomarkers in children during and shortly after anthracycline therapy for acute lymphoblastic leukaemia: a prospective study. *Eur Heart J Cardiovasc Imaging.* 2013;14:562-569.

130. Mornos C, Manolis AJ, Cozma D, Kouremenos N, Zacharopoulou I, Ionac A. The value of left ventricular global longitudinal strain assessed by three-dimensional strain imaging in the early detection of anthracycline-mediated cardiotoxicity. *Hellenic J Cardiol.* 2014;55:235-244.

131. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol.* 2005;23:2900-2902.

132. Cardinale D, Salvatici M, Sandri MT. Role of biomarkers in cardioncology. *Clin Chem Lab Med.* 2011;49:1937-1948.

133. Christenson ES, James T, Agrawal V, Park BH. Use of biomarkers for the assessment of chemotherapy-induced cardiac toxicity. *Clin Biochem.* 2015;48(4-5):223-235.

134. Thakur A, Witteles RM. Cancer therapy-induced left ventricular dysfunction: interventions and prognosis. *J Card Fail.* 2014; 20:155-158.

135. Stevens PL, Lenihan DJ. Cardiotoxicity due to chemotherapy: the role of biomarkers [serial online]. *Curr Cardiol Rep.* 2015;17:603.

136. Carver JR, Shapiro CL, Ng A, et al. American Society of Clinical Oncology clinical evidence review on the ongoing care of adult cancer survivors: cardiac and pulmonary late effects. *J Clin Oncol.* 2007;25:3991-4008.

137. Cardinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation.* 2006;114:2474-2481.

138. Nakamae H, Tsumura K, Terada Y, et al. Notable effects of angiotensin II receptor blocker, valsartan, on acute cardiotoxic changes after standard chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone. *Cancer.* 2005; 104:2492-2498.

139. Cadeddu C, Piras A, Mantovani G, et al. Protective effects of the angiotensin II receptor blocker telmisartan on epirubicin-induced inflammation, oxidative stress, and early ventricular impairment. *Am Heart J.* 2010;160:487.e1–487.e7.

140. Akpek M, Ozdogru I, Sahin O, et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. *Eur J Heart Fail.* 2015;17:81-89.

141. Kalay N, Basar E, Ozdogru I, et al. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. *J Am Coll Cardiol.* 2006;48:2258-2262.

142. Kaya MG, Ozkan M, Gunebakmaz O, et al. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. *Int J Cardiol.* 2013;167:2306-2310.

143. Seicean S, Seicean A, Alan N, Plana JC, Budd GT, Marwick TH. Cardioprotective effect of β-adrenoceptor blockade in patients with breast cancer undergoing chemotherapy: follow-up study of heart failure *Circ Heart Fail.* 2013;6:420-426.

144. Bosch X, Rovira M, Sitges M, et al. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies). *J Am Coll Cardiol.* 2013;61:2355-2362.

145. Acar Z, Kale A, Turgut M, et al. Efficiency of atorvastatin in the protection of anthracycline-induced cardiomyopathy. *J Am Coll Cardiol.* 2011;58:988-989.

146. Seicean S, Seicean A, Plana JC, Budd GT, Marwick TH. Effect of statin therapy on the risk for incident heart failure in patients with breast cancer receiving anthracycline chemotherapy: an observational clinical cohort study. *J Am Coll Cardiol.* 2012;60:2384-2390.

147. Lipshultz SE, Rifai N, Dalton VM, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. *N Engl J Med.* 2004;351:145-153.

148. Lipschultz SE, Scully RE, Lipsitz SR, et al. Assessment of dexrazoxane as a cardioprotectant in doxorubicin-treated children with high-risk acute lymphoblastic leukaemia: long-term follow-up of a prospective, randomized, multicentre trial. *Lancet Oncol.* 2010;11:950-961.

149. Sieswerda E, van Dalen EC, Postma A, Cheuk DK, Caron HN, Kremer LC. Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer [serial online]. *Cochrane Database Syst Rev.* 2011;9:CD008011.

150. Hensley ML, Hagerty KL, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol.* 2009;27:127-145.

151. Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. *Eur J Cancer.* 2013;49:2900-2909.

152. Cardinale D, Civelli M, Cipolla CM. Troponins in prediction of cardiotoxic effects [letter]. *Ann Oncol* 17:173, 2006; author reply 173–174.

153. Riad A, Bien S, Westermann D, et al. Pretreatment with statin attenuates the cardiotoxicity of doxorubicin in mice. *Cancer Res.* 2009;69:695-699.

154. Pituskin E, Haykowsky M, Mackey JR, et al. Rationale and design of the Multidisciplinary Approach to Novel Therapies in Cardiology Oncology Research Trial (MANTICORE 101-Breast): a randomized, placebo-controlled trial to determine whether conventional heart failure pharmacotherapy can prevent trastuzumab-mediated left ventricular remodeling among patients with HER2+ early breast cancer using cardiac MRI [serial online]. *BMC Cancer.* 2011;11:318.

155. Heck SL, Gulati G, Ree AH, et al. Rationale and design of the prevention of cardiac dysfunction during an Adjuvant Breast Cancer Therapy (PRADA) Trial. *Cardiology.* 2012;123:240-247.

156. Saini J, Rich MW, Lyss AP. Reversibility of severe left ventricular dysfunction due to doxorubicin cardiotoxicity. Report of three cases. *Ann Intern Med.* 1987;106:814-816.

157. Jensen BV, Nielsen SL, Skovsgaard T. Treatment with angiotensin-converting-enzyme inhibitor for epirubicin-induced dilated cardiomyopathy. *Lancet.* 1996;347:297-299.

158. Fazio S, Calmieri EA, Ferravate B, Bone F, Biondi B, Sacca L. Doxorubicin-induced cardiomyopathy treated with carvedilol. *Clin Cardiol.* 1998;21:777-779.

159. Noori A, Lindenfeld J, Wolfel E, Ferguson D, Bristow MR, Lowes BD. Beta-blockade in Adriamycin-induced cardiomyopathy. *J Card Fail.* 2000;6:115-119.

160. Mukai Y, Yoshida T, Nakaike R, et al. Five cases of anthracycline-induced cardiomyopathy effectively treated with carvedilol. *Intern Med.* 2004;43:1087-1088.

161. Tallaj JA, Franco V, Rayburn BK, et al. Response of doxorubicin-induced cardiomyopathy to the current management strategy of heart failure. *J Heart Lung Transplant.* 2005;24:2196-2201.

162. Tabet JY, Meurin P, Ben Driss A, et al. Beta-blockade intolerance in anthracycline-induced cardiomyopathy. *Int J Cardiol.* 2006;106:132-134.

163. OncologyPRO, European Society for Medical Oncology. QT Prolongation-All Kinase Inhibitors. oncologypro.esmo.org/Guidelines-Practice/Drug-Drug-Interactions-with-Kinase-Inhibitors/Types-of-Drug-Drug-Interactions/QT-Prolongation. Accessed November 14, 2015.

164. Curigliano G, Cardinale D, Suter T, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2012;23(suppl 7):vii155-vii166.

165. McDonagh TA, Blue L, Clark AL, et al. European Society of Cardiology Heart Failure Association standards for delivering heart failure care. *Eur J Heart Fail.* 2011; 13:235-241.

166. Munoz Martin AJ, Font Puig C, Navarro Martin LM, Borrega Garcia P, Martin Jimenez M; Spanish Society for Medical Oncology. Clinical guide SEOM on venous thromboembolism in cancer patients. *Clin Transl Oncol.* 2014;16:1079-1090.

167. Khorana AA, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood.* 2008;111:4902-4907.

168. Mandala M, Falanga A, Roila F. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2011;22(suppl 6): vi85-vi92.