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Oncocardiology—Past, Present, and Future:

A Review

Edward T. H. Yeh, MD and **Hui-Ming Chang, MD, MPH**

Department of Internal Medicine, University of Missouri, Columbia (Yeh, Chang); Department of Cardiology, The University of Texas MD Anderson Cancer Center, Houston (Yeh)

Abstract

IMPORTANCE—Oncocardiology is a medical discipline that focuses on the identification, prevention, and treatment of cardiovascular complications related to cancer therapy. This discipline has gained interest from the cardiology community in recent years because of a remarkable increase in the number of cancer survivors and the proliferation of new cancer therapies causing cardiovascular complications, such as hypertension, heart failure, vascular complications, and cardiac arrhythmia. In this review, we provide historical perspectives, highlight new discoveries, and speculate on the opportunity created by merging the research interests and clinical practices of cardiology and oncology.

OBSERVATIONS—The old paradigm of anthracycline cardiotoxic effects is replaced by new insights that anthracycline targets topoisomerase II β to cause DNA double-strand breaks and a profound change in the transcriptome leading to the generation of reactive oxygen species and the development of mitochondriopathy. Prevention of anthracycline cardiotoxic effects should be based on inhibiting or degrading topoisomerase II β. New challenges were posed by the introduction of trastuzumab and tyrosine kinase inhibitors that revolutionized cancer therapy. The on-target cardiotoxic effects of trastuzumab were owing to a prosurvival benefit of Her2 that binds to neuregulin, whereas the off-target effect of multitargeted tyrosine kinase inhibitors may be mediated by disruption of the vascular endothelial growth factor signaling pathway or the stress-induced angiogenesis. Sensitive imaging techniques, such as global strain, and biomarkers have allowed for early detection of cardiotoxic effects. Early treatment with heart failure medications may be beneficial in preventing the development of late cardiotoxic effects.

Corresponding Author: Edward T. H. Yeh, MD, Department of Internal Medicine, University of Missouri, Columbia, MO 65212 (yehet@health.missouri.edu).

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CONCLUSIONS AND RELEVANCE—Close collaboration between cardiologists and oncologists is required to meet the demand of an increasing number of cancer survivors. New insights based on mechanistic studies or genetic discoveries will pave the way for better prevention, diagnosis, and treatment of cancer therapy-induced cardiovascular complications.

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

New Insights in Anthracycline Induced Cardiotoxic Effects

Daunorubicin, the first anthracycline isolated from cultures of *Streptomycespeucetius*, was reported in 1963 by French and Italian researchers (Table 1).[1,2] An early clinical study[3] showed that pediatric patients with leukemia could achieve partial or complete hematologic remission from a single dose of daunorubicin; moreover, prolonged remission could be obtained by maintenance therapy. However, patients of-ten developed heart failure with maintenance daunorubicin therapy (Table 2). In a retrospective analysis,[4] the cumulative probability of congestive heart failure (CHF) was shown to be dependent on the cumulative dose of doxorubicin. Long-term follow-up data[5] from adult survivors of childhood cancer showed that upto 30% of patients treated with doxorubicin had signs of cardiac dysfunction when more sensitive detection techniques were used.

Doxorubicin targets topoisomerase II to block DNA replication.[6] Because cardiomyocytes were considered to be terminally differentiated, researchers believed that doxorubicin could not cause cardiotoxic effects by inhibiting DNA replication. Therefore, the reactive oxygen species (ROS)/iron hypothesis was proposed because doxorubicin is capable of causing redox changes in an iron-dependent manner to produce highly toxic hydroxyl radicals.[7,8] Thus, inhibition of ROS formation and iron chelation were tested as strategies to prevent doxorubicin-induced cardiotoxic effects. Although *N*-acetylcysteine was effective in quenching ROS in tissue cultures, it was not effective inpreventing doxorubicin-induced cardiotoxic effects.[9] Furthermore, iron chelation failed to prevent doxorubicin-induced cardiotoxic effects in an animal model.[10] Remarkably, dexrazoxane, the only effective protect antagainst doxorubicin cardiotoxic effects, was shown to be acatalytic inhibitor of topoisomerase II.[11]

There are 2 topoisomerase II isozymes. Topoisomerase II a, highly expressed in cancer cells and required for cell division, is the target for anthracycline's antitumor effect.[12,13] However, adult cardiomyocytes express only topoisomerase II β, which is not required for cell division.[14] Since dexrazoxane binds to topoisomerase II β and inhibits doxorubicin-induced DNA double-strand break, it is likely that doxorubicin causes cardiotoxic effects by targeting topoisomerase II β. We generated a mouse model in which topoisomerase II β could be genetically deleted in adult cardiomyocytes and showed that both doxorubicin-induced DNA double-strand breaks and apoptosis were blunted.[15]

Doxorubicin also causes a profound change in the transcriptome of cardiomyocytes because topoisomerase II β/doxorubicin binds to selective promoters to regulate gene transcription. Key antioxidative enzymes are reduced following doxorubicin treatment only in

cardiomyocytes with intact topoisomerase II β. This explains why doxorubicin-induced ROS production is dependent on topoisomerase II β. Interestingly, peroxisome proliferator-activated receptor- coactivator1a (PGC1a) and PGC1β, 2 key transcription factors important to mitochondrial biogenesis, are also decreased in the doxorubicin-treated cardiomyocytes. As a result, mitochondrial electron transport proteins are decreased. Electron microscopy of heart samples showed classic histological changes in the mitochondria of cardiomyocytes treated with doxorubicin, but not in topoisomerase II β-depleted cardiomyocytes. Together, these findings show that topoisomerase II β is the molecular basis of anthracycline-induced cardiotoxic effects. This new paradigm retains the old observation of doxorubicin-induced ROS generation and mitochondriopathy but explains them in terms of topoisomerase II β (Figure).[15,16]

The identification of topoisomerase II β as the molecular basis of anthracycline-induced cardiotoxic effects leads to 3 useful predictions. First, a new anthracycline specific for topoisomerase II a, but not for topoisomerase II β, should have antitumor activity but no cardiotoxic effects. Second, determining a patient's topoisomerase II β expression level may be useful in predicting the patient's susceptibility to anthracycline-induced cardiotoxic effects before chemotherapy is initiated. Finally, inhibition of topoisomerase II β should be the most effective strategy to prevent anthracycline-induced cardiotoxic effects.[17] However, an early clinical trial showed that patients who received dexrazoxane and doxorubicin had reduced objective response rate, but time to progression and survival were not different compared with placebo and doxorubicin.[18] Thus, the US Food and Drug Administration limited the use of dexrazoxane to metastatic breast cancer patients who have already received 300mg/m^2 of doxorubicin. Since doxorubicin causes subclinical cardiac damage even at low doses, the use of dexrazoxane in patients who have received more than 300 mg/m^2 of doxorubicin is clearly too late. With the new understanding of the pathogenesis of anthracycline-induced cardiotoxic effects, further clinical trials of dexrazoxane in cardioprotection is warranted.

Harnessing the Cardiotoxic Effects of Anti-HER2 Therapy

Cancer treatment underwent a remarkable revolution in 1998 with the approval of trastuzumab (herceptin) for the treatment of meta-static ERBB2 (HER2)-positive breast cancer.[19] ERBB2 belongs to the family of human epidermal growth factor receptors (EGFRs). In cancer cells, amplified ERBB2 binds to ERBB3 to form an oncogenic ERBB2/ERBB3 complex.[20] Trastuzumab inhibits ERBB2/ERBB3 dimerization by binding to domain 4 of ERBB2 to block phosphatidylinositol-3-kinase signaling. However, ERBB2 is also expressed on cardiomyocytes and deletion of *ERBB2* gene in the cardiomyocytes led to development of dilated cardiomyopathy in the mouse model.[21,22] In cell cultures, adult rat ventricular myocytes (ARVMs) treated with doxorubicin showed a concentration-dependent increase in myofilament disarray. Concomitant treatment of myocytes with anti-ERBB2 and doxorubicin caused a significant increase in myofibrillar disarray compared with doxorubicin treatment alone.[23] Furthermore, *HER2*/*ERBB2*-deleted cardiomyocytes were more sensitive to doxorubicin.[22] Thus, trastuzumab has the potential to cause cardiotoxic effects with or without doxorubicin.

In the pivotal trastuzumab trial,[19] New York Heart Association class 3 or 4 heart failure was observed in 27% of patients receiving anthracycline, cyclophosphamide, and trastuzumab; in 8% of patients given an anthracycline or cyclophosphamide alone; in 13% of patients given combined paclitaxel and trastuzumab; and in 1% of patients given paclitaxel alone. Thus, trastuzumab can induce cardiotoxic effects by itself, and the severity of these effects is compounded by concomitant use of anthracycline.[19] The alarming incidence of cardiotoxic effects prompted a call to more cautious use of trastuzumab.[24]

The high incidence of heart failure in the metastatic breast cancer trial[19] prompted institution of intensive cardiac monitoring in the subsequent adjuvant trials. Newer clinical trials[25] avoiding concomitant use of anthracycline and trastuzumab had much lower incidences of heart failure. The manifestation of cardiotoxic effects is different between anthracyclines and trastuzumab. Cardiac biopsy of trastuzumab-treated patients did not reveal the classic changes of myofibril disarray and mitochondriopathy associated with anthracycline cardiotoxic effects. Clinically, trastuzumab-induced cardiotoxic effects also differ from anthracycline-induced cardiotoxic effects. In contrast to cardiotoxic effects induced by anthracycline, trastuzumab-induced cardiotoxic effects is not dose-related; it is often reversible with cessation of therapy and initiation of conventional heart failure therapy.[26] Furthermore, rechallenge with trastuzumab is generally well tolerated.

Other anti-HER2 therapies have been developed that showed less cardiotoxic effects. T-DM1 is trastuzumab linked to an antimicrotubule drug, emtansine.[27] No significant cardiotoxic effects were observed with T-DM1 in patients previously treated with trastuzumab and a taxane.[28] Pertuzumab is a monoclonal antibody binding to domain 2 of ERBB2 to inhibit ligand-dependent ERBB2 dimerization.[29] Pertuzumab prolongs the survival of patients diagnosed with metastatic breast cancer when added to trastuzumab and anthracyclines.[30] In clinical trials, pertuzumab has emerged as a safe drug, with little or no cardiac toxic effects.[31] Thus, we have learned to harness the toxicity of anti-HER2 therapy, by intensive monitoring, by avoiding concomitant use of anthracyclines, and by introducing antibody targeting a different domain of *ERBB2*.

Targeted Therapy With Off-Target Effects

Another major advance in cancer treatment was the approval of imatinib (Gleevec) in 2001 for the treatment of chronic myelogenous leukemia.[32] Imatinib, an inhibitor of BCR-Abl, was touted as a magic bullet in cancer therapy and heralded the development of a large number of tyrosine kinase inhibitors (TKIs) in clinical use today.[33] Some of these TKIs have specific targets, whereas others can target multiple kinases. Thus, off-target effects can result in off-target toxic effects. For example, Force et al[33] reported 10 patients who developed severe CHF while receiving imatinib therapy and showed that imatinib-treated mice developed left ventricular contractile dysfunction.[34] A more extensive review[35] of patients treated with imatinib showed that, of 1276 patients, only 22 (1.7%) developed systolic heart failure; of these 22 patients, 11 continued to receive imatinib therapy with dose adjustments and were monitored for CHF symptoms without further complications. Thus, the initial report of potential cardiotoxic effects of TKIs needs to be validated by larger clinical trials,

and early identification of toxicity or dose-reduction may allow a lifesaving drug to remain on the market.[36]

Sunitinib, approved for treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors, caused hypertension in 47% of treated patients and CHF in 8% in a small study[37] of 75 patients. In a larger meta-analysis[38] of 6935 patients, the incidence of all-grade and high-grade CHF in patients treated with sunitinib was 4.1% and 1.5%, respectively. Congestive heart failure was reversible by withholding sunitinib therapy and/or initiation of heart failure therapy in 56% of patients in a retrospective adjudication of comprehensive cardiovascular adverse events from 2 phase 3 trials.[39] Sunitinib is a multikinase inhibitor that inhibits vascular endothelial growth factor receptors (VEGFRs), fibroblast growth factor receptors, and platelet-derived growth factor receptors (PDGFRs). Thus, it is not surprising that hypertension can result from inhibition of multiple receptors involved in the homeostasis of the vasculature.[40] In an animal model, PDGFR-β is required for cardiomyocytes to respond to stress-induced cardiac angiogenesis.[41] Mice that underwent cardiomyocyte-specific deletion of PDGFR-β developed heart failure when exposed to load-induced stress, such as hypertension. Thus, hypertension and heart failure caused by sunitinib and other TKIs that target the VEGF signaling pathway can be explained mechanistically and prevented by aggressive treatment of hypertension.[42]

Recently, ponatinib (iclusig), a TKI approved for imatinib-resistant chronic myelogenous leukemia, was pulled from the market temporarily owing to a 27% incidence of arterial and venous thrombosis or occlusion.[43] However, ponatinib was shown to inhibit platelet aggregate formation in whole blood under shear stress.[44] Similar to ponatinib, nilotinib has also been associated with increased incidence of arterial and venous thrombosis. Further studies are needed to clarify the mechanism of action contributing to accelerated atherosclerosis and thromboembolism in patients treated with ponatinib and nilotinib. Regardless of the mechanism of vascular toxic effects, careful modification of cardiac risk factors and close follow-up are required in patients treated with selected TKIs, especially TKIs targeting the VEGF signaling pathway.[40] It is clear that the off-target effects of TKIs provide an opportunity for both basic and translational research in our field.

An Emerging Field: Cardiologist Collaborating With Oncologist

The use of targeted therapy in the past 15 years has converted several cancers from a terminal illnesses to a chronic diseases, vastly increasing the number of cancer survivors. In 2012, there were 12 million cancer survivors in the United States. This number is estimated to double by the end of the next decade.[45] Among cancer survivors, half will die of cancer recurrence, but a third will die of cardiovascular disease. Thus, the need for optimal cardiac care in the cancer population has become evident. Chemotherapy can cause myriad cardiovascular complications, including hypertension, CHF, thromboembolic diseases, ischemic heart disease, QT prolongation, and bradycardia.[46] Radiation therapy can cause acute complications, such as pericarditis and long-term complications, such as accelerated coronary artery disease, valvular disease, and restrictive or constrictive pericarditis.[47] Thus, cardiologists could play a pivotal role in the care of cancer patients undergoing chemotherapy and/or radiation therapy.

Early detection of cardiotoxic effects requires timely imaging studies and monitoring with biomarkers. Determining left ventricular ejection fraction (LVEF) with the use of noninvasive techniques, such as echocardiography or multiplegated acquisition (MUGA) scanning, during chemotherapy is recommended by all guidelines.[48,49] Because of radiation exposure, echocardiography is generally preferred in cardiac monitoring over MUGA scanning. In a large population-based study[50] of patients diagnosed with breast cancer aged 66 years or older, adequate cardiac monitoring was obtained in only 36% of patients. In a retrospective study,[51] early detection of LVEF reduction followed by intervention was shown to improve long-term outcome. A recent consensus from the American Society of Echocardiography (ASE) went beyond LVEF to recommend monitoring of global longitudinal strain (GLS).[48,52] Although GLS is more sensitive than LVEF, technical limitations and general availability may not allow for this measurement to be used for all cancer patients undergoing chemotherapy. Both the ASE and the European Society for Medical Oncology recommended troponin for detection of early signs of cardiotoxic effects during chemotherapy.[49] A combination of troponin and GLS could be a more powerful predictor of early cardiotoxic effects.[52] Further studies are required to determine the best frequency of monitoring during chemotherapy.

In the past decade, cardiologists have carried out multiple small clinical studies with drugs used in heart failure therapy, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers, or β-blockers (BB), to provide either primary or secondary prevention for anthracycline-induced cardiotoxic effects.[53–56] Many of these studies showed benefit; however, the short-term benefits may have been owing to changes in hemodynamics, not a result of true cardioprotection. Larger and more long-term clinical studies are required to demonstrate true efficacy. This is important because in a pediatric study, the short-term benefit of ACEIs disappeared with long-term follow-up.[57] However, ACEIs in this study may not show efficacy because the drug was started a median of 8 years after chemotherapy. Taken together, the best evidence for primary prevention of anthracycline-induced cardiotoxic effects is dexrazoxane based on its mechanism of action.[11,15] At present, ACEIs, BB, aldosterone antagonists, or statin cannot be recommended in primary prevention owing to insufficient evidence.

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

In a study[59] of childhood cancer survivors, the overall mortality ratio was 8.3-fold higher and the cardiovascular mortality ratio was 5-fold higher in cancer survivors than in the general population. In another large study[60] that compared childhood cancer survivors with their siblings, the cumulative incidence of coronary artery disease, CHF, valvular disease, and arrhythmia in survivors by age 45 years was much higher than those found in their siblings. Cancer therapy greatly accelerates the development of cardiovascular diseases, which can be reduced by lowering the intensity of radiation therapy and anthracycline exposure.[61] Further improvement in quality of life in cancer survivors can be achieved through exercise, weight control, dietary discretion, and complementary medicine.[62]

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

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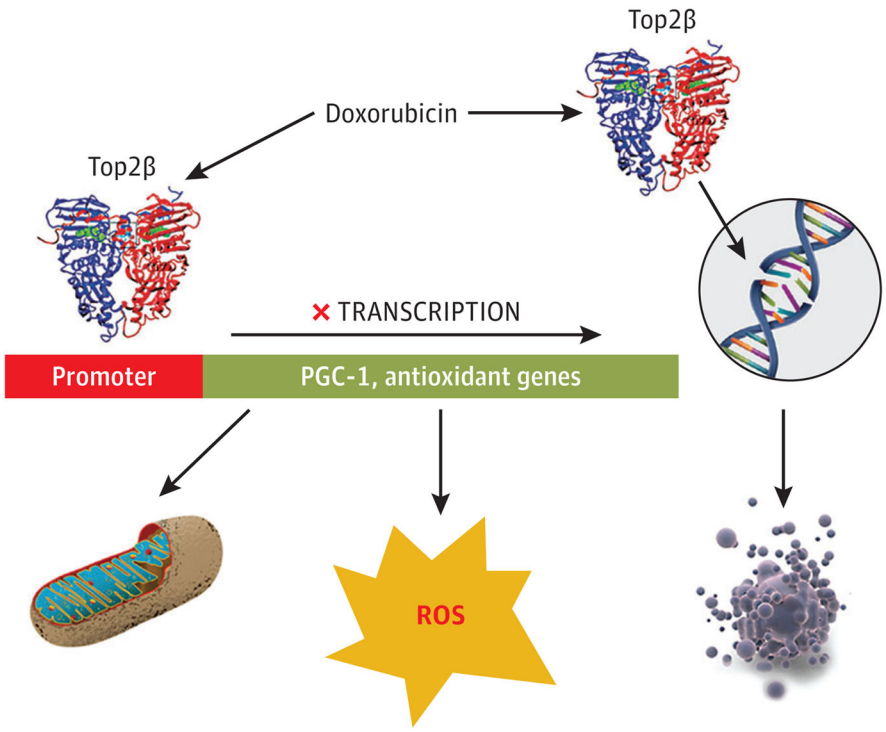

Figure. Doxorubicin Induces DNA Double-Strand Breaks Though Inhibition of Topoisomerase 2β, Activating the Apoptotic Program

Doxorubicin-bound topoisomerase II β also binds to promoters of genes encoding PGC-1 and antioxidative enzymes, causing mitochondriopathy and an increase in reactive oxygen species (ROS).

Table 1

Milestones in Oncocardiology

Year	Milestones
1963	Discovery of daunorubicin (1st anthracycline)[1,2]
1966	Early report of anthracycline-induced cardiotoxic effects[3]
1977	Anthracycline cardiotoxic effects is dependent on the cumulative dose[4,63]
1980	Efforts to reduce anthracycline-induced cardiotoxic effects through dose limitation, chemical protection, change in formulation, or change in delivery schedule[64]
1998	Early report of trastuzumab (herceptin)-induced cardiotoxic effects[24]
2007	Reports of multikinase inhibitors causing hypertension, heart failure, vascular occlusion[40]
2012	Discovery of Topoisomerase IIβ as the molecular basis of anthracycline-induced cardiotoxic effects[15]

Table 2

Commonly Used Anticancer Agents Associated With Cardiovascular Complications

Chemotherapy Agents[a]	Incidence, %	Prevention/Treatment[46]
Heart failure/left ventricular dysfunction		
Anthracyclines		Monitor EF, GLS, troponin
Doxorubicin (adriamycin)	3.0–26.0[b]	Dexrazoxane, continuous infusion, liposomal preparation, ACEI/β-blockers
Epirubicin (ellence)	0.9–3.3[b]	
Idarubicin (idamycin PFS)	5.0–18.0[b]	
Monoclonal antibody-based tyrosine kinase inhibitor		
Trastuzumab (herceptin)	2.0–28.0[c]	Avoid concomitant use with anthracyclines
Small molecule tyrosine kinase inhibitors		
Pazopanib (votrient)	0.6–11.0[b]	
Ponatinib (iclusig)	3.0–15.0[c]	Treat hypertension
Sorafenib (nexavar)	1.9–11.0	
Sunitinib (sutent)	1.0–27.0[b]	
Proteasome inhibitor		
Carfilzomib (kyprolis)	7.0	
Myocardial infarction/ischemia		
Antimetabolites		Ischemia workup and treatment
Capecitabine (xeloda)	3.0–9.0[b]	
Fluorouracil (adrucil)	1.0–68.0	
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (avastin)	0.6–8.5[b]	
Small molecule tyrosine kinase inhibitors		
Nilotinib (tasigna)	5.0–9.4[b]	
Ponatinib (iclusig)	12.0[c]	
Hypertension		
Monoclonal antibody-based tyrosine kinase inhibitor		Blood pressure monitoring and intensive blood pressure therapy
Bevacizumab (avastin)	23.0–34.0[b]	
mTor inhibitors		
Everolimus (afinitor)	4.0–13.0	
Temsirolimus (Torisel)	7.0	
Small molecule tyrosine kinase inhibitors		
Pazopanib (votrient)	42.0[b]	
Ponatinib (iclusig)	68.0[b]	

Chemotherapy Agents[a]	Incidence, %	Prevention/Treatment[46]
Sorafenib (nexavar)	9.4–41.0[b]	
Sunitinib (sutent)	15.0–34.0[b]	
Proteasome inhibitors		
Bortezomib (velcade)	6.0	
Carfilzomib(kyprolis)	14.3	
Thromboembolism		
Angiogenesis inhibitors		Modification of cardiac risk factors Anticoagulation
Lenalidomide (revlimid)	3–75[c]	
Thalidomide (thalomid)	1.0–58.0[c]	
Monoclonal antibody-based tyrosine kinase inhibitor		
Bevacizumab (avastin)	6.0–15.1[b]	
Small molecule tyrosine kinase inhibitor		
Ponatinib (iclusig)	5.0[c]	
Bradycardia		
Angiogenesis inhibitor		Stop β-blockers or calcium channel blockers Rule out hypothyroidism Reduction of drug doses Pacemaker may be required
Thalidomide (thalomid)	0.12–55.0[b]	
Antimicrotubule agent		
Paclitaxel (taxol)	<0.1–31.0	
Small molecule tyrosine kinase inhibitors		
Ceritinib (zykadia)	3.0[b]	
Crizotinib (xalkori)	11.0[b]	
Pazopanib (votrient)	2.0–19.0	
QT Prolongation		
Miscellaneous		EKG monitoring Replace potassium and magnesium Follow FDA guidelines
Arsenic trioxide (trisenox)	26.0–93.0[b]	
Histone deacetylase inhibitors		
Belinostat (beleodaq)	4.0–11.0	
Small molecule tyrosine kinase inhibitors		
Dabrafenib (tafinlar)	2.0–13.0	
Dasatinib (sprycel)	<1.0–3.0[b]	
Nilotinib (tasigna)	<1.0–4.1[c]	
Vandetanib (caprelsa)	8.0–14.0[c]	

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

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

[b] Listed as a warning/precaution in package insert.

[c] Black box warning in package insert.