Getting to the Heart of the Matter: An Overview of Cardiac Toxicity Related to Cancer Therapy

Carine E. Hamo[1] and Michelle Weisfelner Bloom[2]

[1]Department of Medicine, Stony Brook University Hospital, Stony Brook, NY, USA. [2]Department of Medicine, Division of Cardiology, Stony Brook University Hospital, Stony Brook, NY, USA.

Supplementary Issue: Heart Failure: An Exploration of Recent Advances in Research and Treatment (A)

ABSTRACT: With the improvement in cancer survival, long-term cardiotoxicity has become an area of increased interest. Various cancer therapies, including chemotherapy and radiation therapy can lead to cardiac toxicities with both acute and chronic manifestations. Awareness and early recognition can lead to improvement in cardiac survival and patient outcomes. The focus of this review is to summarize the cancer therapy agents most often associated with cardiovascular side effects, highlighting their mechanism of action and strategies for surveillance and prevention.

KEYWORDS: heart failure, cardiotoxicity, chemotherapy, radiation, cardio-oncology

SUPPLEMENT: Heart Failure: An Exploration of Recent Advances in Research and Treatment (A)

CITATION: Hamo and Bloom. Getting to the Heart of the Matter: An Overview of Cardiac Toxicity Related to Cancer Therapy. *Clinical Medicine Insights: Cardiology* 2015:9(S2) 47–51 doi: 10.4137/CMC.S19704.

TYPE: Review

RECEIVED: March 10, 2015. **RESUBMITTED:** July 01, 2015. **ACCEPTED FOR PUBLICATION:** July 08, 2015.

ACADEMIC EDITOR: Thomas E. Vanhecke, Editor in Chief

PEER REVIEW: Eight peer reviewers contributed to the peer review report. Reviewers' reports totaled 941 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: michelle.bloom@stonybrookmedicine.edu

Background

Heart disease and cancer are currently the two leading causes of death in the United States, creating an intriguing scenario when these two diseases intersect. An anticipated 1.6 million new cancer cases will be diagnosed in 2015, with almost 600,000 deaths from cancer this year and nearly equivalent numbers of cardiovascular deaths.[1,2] Overall improvements in cancer survival are likely due to advancements in early recognition and novel treatment modalities. Unfortunately, with the improvement in the morbidity and mortality of cancer comes the increase in long-term cardiac toxicity associated with cancer treatments. Cardiovascular side effects negatively impact quality of life and survival. More so, the development of toxicity may warrant adjustments or discontinuation of the chemotherapy regimen, worsening outcomes. As such, early recognition of cardiac dysfunction becomes imperative. The field of cardio-oncology is evolving in an effort to provide an integrative approach to this complicated patient population.

Types of Cardiotoxicity

Cancer therapy has been shown to cause a wide variety of cardiac toxicities, including arrhythmias, myocardial ischemia, coronary artery disease, hypertension, and myocardial dysfunction. With respect to ventricular dysfunction, two categories have been previously proposed and conventionally accepted thus far.

Type I cardiotoxicity, seen classically with anthracyclines, is thought to be irreversible, dose related, and caused by free radical formation, oxidant stress, and myofibrillar disarray.[3] Type II cardiotoxicity, seen traditionally with the use of trastuzumab, has been described as reversible and not dose related, with no accompanied ultrastructural abnormalities.[3]

The distinction between type I and type II may be more complicated than once perceived. Studies have shown improvement in anthracycline-induced cardiac dysfunction with heart failure (HF) therapy,[4] while other studies have shown irreversible scar formation on magnetic resonance imaging in patients treated with trastuzumab.[5] The cardiotoxicity occurring with anthracyclines can be acute, occurring in less than 1% of patients and characterized by a transient decline in myocardial contractility or chronic, occurring in 1.6% to 5% of patients, occurring at least 1 year after the completion of therapy.[6]

Cancer Therapies with Potential Cardiac Toxicities

Anthracyclines. Anthracyclines such as doxorubicin, daunorubicin, and idarubicin are used in the treatment of sarcomas, lymphomas, and leukemias as well as for adjuvant therapy in breast cancer.[6] They are important antitumor agents with a proposed mechanism that includes intercalation into nuclear DNA to impair protein synthesis, in addition to production of reactive oxygen species and inhibition of

Table 1. Cancer agents associated with cardiotoxicity.

CANCER THERAPY	DRUG	CARDIOTOXICITY	MECHANISM OF CARDIOTOXICITY	SCREENING
Anthracycline	Doxorubicin Daunorubicin Idarubicin	LVD, HF	Impaired protein synthesis, formation of reactive oxygen species, inhibition of DNA repair	2D-Echo, Strain*, Biomarkers (troponin, BNP)
Monoclonal antibodies	Trastuzumab Bevacizumab	LVD, HF HTN, LVD, HF	Inhibition or ErbB2 pathway Inhibits VEGF	2D-Echo, Strain*, Biomarkers (troponin, BNP)
Antimetabolites	5-Fluorouracil	Arrhythmia, Ischemia	Coronary vasospasm	EKG
Microtubule-targeting agents	Paclitaxel Docetaxel	Arrhythmia, LVD, HF	Impaired microtubule function, impaired cell division	EKG, 2D-Echo
Proteosome inhibitors	Bortezomib	LVD, HF	Interference with cell cycle degradation proteins	2D-Echo
Alkylating agents	Cyclophosphamide	Pericarditis, LVD, HF	ROS production	2D-Echo
Small Tyrosine kinase Inhibitors	Sunitinib Imatinib Sorafenib Lapatinib	HTN, QT prolongation, LVD, HF LVD, HF Ischemia, HTN QT prolongation, LVD, HF	Impaired cell signal transduction, cell cycle regulation, metabolism and transcription	2D-Echo, EKG
Radiation		Accelerated atherosclerosis, pericarditis, HF, valvular dysfunction	Microvascular injury, macrovascular injury, valve endothelial injury and dysfunction	2D-Echo, EKG, long-term surveillance

Note: *Obtain when available.
Abbreviations: BNP, brain natriuretic peptide; HTN, hypertension; LVD, left ventricular dysfunction; VEGF, vascular endothelial growth factor; HF, heart failure; ROS, reactive oxygen species.

topoisomerase II to inhibit DNA repair (Table 1).[7] The mechanism of cardiotoxicity is thought to relate to the interaction between doxorubicin and topoisomerase II, present on cardiac myocytes, resulting in cell death.[8] Anthracyclines directly damage cardiac myocytes with a 1%–5% incidence of left ventricular dysfunction (LVD).[4] Diastolic dysfunction can occur at cumulative doses of 200 mg/m^2 preceding left ventricular (LV) systolic dysfunction, which can occur at doses beyond 400–600 mg/m^2.[7] Risk factors for cardiac toxicity include higher single dose, intravenous bolus administration, history or prior chest radiation, and concurrent use of other agents with potential cardiotoxic effects. Patients with underlying traditional cardiac risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking history, and known coronary artery disease or LVD are also at increased risk.[6] Monitoring of cardiac dysfunction can be achieved with the use of Multiple-Gated Acquisition[9] or echocardiography.[10] More recently, strain imaging, a measure of deformation of myocardium, has been shown to be a more sensitive means of detecting abnormalities that precede reductions in left ventricular ejection fraction (LVEF).[11] The incorporation of biomarkers such as troponin[12] and brain natriuretic peptide[13] in surveillance can serve as another means of monitoring; however, the optimal biomarker approach requires further study. Antioxidants such as dexrazoxane, given along with anthracyclines, have been shown to reduce cardiac events and the incidence of HF.[14] Carvedilol, which also has antioxidant properties, as well as the angiotensin-converting enzyme inhibitor enalapril, have both been studied in the prevention of cardiotoxicity in patients treated with antracyclines.[15,16]

Monoclonal antibodies. Trastuzumab, a monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2)/ErbB2 protein, is used in the treatment of HER2-positive breast and gastric cancer.[7] In normal cardiac myocytes, the HER2/ErbB2 signaling pathway is responsible for adaptation and response to stress. The interference in this pathway may explain the mechanism of cardiotoxicity.[17] The use of trastuzumab can result in the development of LVD,[18] with an incidence of 2%–28%,[4] and toxicity can be further potentiated when used in combination with anthracyclines.[19] Other risk factors for cardiotoxicity include previous cardiac disease, extremes of age, and previous radiation therapy.[6,20] Discontinuation of the agent is usually associated with subsequent recovery within 1–3 months.[19] The separation in timing of anthracycline and trastuzumab administration can minimize toxicity.[3,21] More recently, the landscape of treatment for HER2-positive tumors has grown to include the combination of trastuzumab with other agents such as lapatinib and pertuzumab with the hopes of increasing efficacy in the setting of treatment failure. With this comes the potential for added cardiotoxicity.[22] A recent meta-analysis has shown limited cardiac toxicity, with dual therapy, though long-term data are not yet available and only select patient populations have been studied thus far.[23]

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF) used in the treatment of breast, lung, renal, and colorectal cancers.[6] The mechanism of cardiotoxicity lies mostly in the interference in endothelial function.[17] Bevacizumab is associated with the development of hypertension[24]; however, there is a low incidence (1%–3%) of clinical HF.[4,25]

Antimetabolites. 5-Fluorouracil is a thymidylate synthase inhibitor used in the treatment of gastrointestinal malignancies such as pancreatic, stomach, colorectal cancers and in breast cancer through the inhibition of DNA replication.[26] There is a reported 1.6%–7.6% incidence of cardiac toxicity[7] with coronary vasospasm causing ischemia, endothelial dysfunction and thrombus formation, accumulation of toxic metabolites, and direct myocardial injury.[19] Clinical presentation is characterized by chest pain, ST-T wave electrocardiogram (ECG) changes, supraventricular/ventricular arrhythmias, and angina.[26] A baseline ECG should be obtained and patients should be carefully monitored during infusions for the development of arrhythmias. The need for further ischemic evaluation should be individualized.[27]

Microtubule-targeting agents. Taxanes such as paclitaxel and docetaxel are used in the treatment of advanced breast and ovarian cancers as well as various other malignancies, impairing microtubule function needed for cell division.[7] Paclitaxel causes massive histamine release that may lead to conduction disturbances and arrhythmias.[19] Taxanes have also been associated with early LVD and HF,[28] with a 5%–15% incidence with paclitaxel and a 2.3%–8% reported incidence with docetaxel.[6] Interestingly, these agents have been shown to potentiate the cardiotoxicity of doxorubicin through an increase in plasma levels and conversion to a more toxic metabolite.[29] Though the incidence of taxane cardiac toxicity is low, periodic monitoring has been suggested.[27]

Proteosome inhibitors. Bortezomib is a proteasome inhibitor approved for the treatment of multiple myeloma and non-Hodgkin's lymphoma,[30] while carfilzomib is used in the treatment of refractory or relapsing multiple myeloma.[31] Proteasome inhibitors interfere with the degradation of cell cycle proteins and ultimately cause cell death. In doing so, these agents can lead to increased apoptosis of smooth muscle cells, endothelial progenitor cells, and impaired endothelial nitric oxide synthase activity, leading to coronary vasospasm. The incidence of clinical HF, reported between 2% and 5% is limited to several case reports.[17,31]

Alkylating agents. Cyclophosphamide is an alkylating agent used in the treatment of bladder and lung cancer as well as sarcoma and chronic myelogenous leukemia.[17] Cyclophosphamide kills rapidly dividing cells as well as resting lymphoid cells, resulting in a decrease in circulating lymphocytes.[32] This agent has been shown to cause an acute myopericarditis as well as LVD in 7%–22% of patients that is thought to be dose related.[4,33–35]

Small tyrosine kinase inhibitors. Tyrosine kinase inhibitors such as sunitinib, imatinib, and lapatinib affect cellular signal transduction, disrupting regulation of the cell cycle, metabolism, transcription, and apoptosis.[36] Sunitinib and sorafenib are nonselective agents that inhibit the VEGF pathway with numerous downstream targets, causing unintended cardiac and vascular side effects.[37] Sunitinib malate is a tyrosine kinase inhibitor, approved for the treatment of renal cell carcinoma, colorectal cancer, chronic myeloid leukemia, and neuroendocrine tumors.[38] Cardiovascular effects of sunitinib include hypertension, QT prolongation, and a 2%–11% incidence of clinical HF.[4,6] In a study of sunitinib, patients were found to develop HF early after initiation of therapy. There was no relation to dose or duration of treatment, and LV dysfunction was not reversible after the termination of therapy.[39] Patients with previous LVD or coronary artery disease or those who have already received treatment with anthracyclines are at increased risk of cardiotoxicity with these agents.[39,40]

Imatinib is used in the treatment of chronic myelogenous leukemia as well as acute lymphoblastic leukemia.[41] Imatinib has been shown to cause reduction in LVEF as well as HF in 0.5%–1.7% of patients.[4,42] Sorafenib, used in the treatment of hepatocellular and renal cell carcinoma,[38] has been shown to cause myocardial ischemia as well as hypertension.[41] Another tyrosine kinase inhibitor lapatinib, which inhibits both ErbB1 and ErbB2, has been shown to cause QT prolongation in addition to reduced LVEF in 1.6% of patients.[7] In contrast to trastuzumab, another inhibitor or ErbB2, lapatinib is less cardiotoxic.[38] Because hypertension is a common effect observed with agents that interfere with the VEGF pathway, frequent monitoring and early initiation of antihypertensive therapy can facilitate safe continuation of treatment.[43]

Radiation therapy. With the use of high-energy particles, radiation results in the interruption of cell growth and viability and is an effective treatment against cancer cells, although cardiac myocytes are particularly vulnerable.[17] Mediastinal radiation therapy, particularly in higher doses, can result in pericarditis, accelerated atherosclerosis, valvular dysfunction, clinical HF, as well as fatal cardiovascular events.[44,45] Risk factors include higher radiation dose (>30 Gy), young age at exposure, large volume of irradiated heart, longer time since exposure, and use of concomitant cytotoxic therapy.[27] Cardiovascular effects of radiation are typically observed several years after exposure, making long-term surveillance critical. Screening echocardiogram and noninvasive stress testing between 5 and 10 years after exposure, depending on risk factors, should be obtained.[46]

Conclusion

Cancer therapies work through a variety of mechanisms to destroy cancer cells. Although there have been improvements in the development of targeted therapy, these treatments often lead to unintended downstream side effects and organ damage. While some toxicities manifest at the onset of therapy, others have a more indolent course. Treatment with chemotherapy serves as an independent risk for the development of cardiovascular disease, and thus, these patients should be monitored accordingly. In fact, patients who receive chemotherapy are considered Stage A Heart Failure according to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[47] Currently, the ACC/AHA Guidelines for HF management have no specific monitoring recommendations for chemotherapy-related cardiotoxicity.[48,49] The American Society

of Clinical Oncology report the potential for cardiac toxicity with anthracyclines, platinum-based chemotherapy, and trastuzumab however they do not provide specific guidelines for the monitoring and treatment of cardiac dysfunction.[50]

Prior to initiation of therapy, patients at risk should undergo a baseline evaluation by an oncologist and cardiologist for risk stratification. Monitoring patients during their treatment can facilitate early intervention with cardioprotective medications or adjustments to the chemotherapy regimen. Several proposed algorithms suggest a measurement of biomarkers and imaging at baseline and at regular intervals throughout therapy.[17,27,51] A rise in biomarkers or any abnormal imaging should prompt a cardio-oncology consultation with consideration for initiation of therapy or adjustments to chemotherapy regimen. Specific recommendations for withholding and resuming therapy with anthracyclines and trastuzumab are outlined by the Food and Drug Administration agency.[52,53] Following treatment, in the absence of guidelines, the frequency of monitoring should be individualized based on the patient's risk factor profile.[54] Treatment of patients who develop HF during therapy is not well described and left to the discretion of the treating physician. Overall, early identification of individuals at risk is essential to limit future complications. A collaborative partnership between the oncologist and cardiologist can facilitate the best care for cancer patients.

Author Contributions

Conceived and designed the experiments: CEH, MWB. Analyzed the data: CEH, MWB. Wrote the first draft of the manuscript: CEH. Contributed to the writing of the manuscript: CEH, MWB. Agree with manuscript results and conclusions: CEH, MWB. Jointly developed the structure and arguments for the paper: CEH, MWB. Made critical revisions and approved final version: CEH, MWB. Both authors reviewed and approved of the final manuscript.

REFERENCES

1. American Cancer Society. *Cancer Facts and Figures* 2015. Atlanta: American Cancer Society; 2015.
2. Gaetano S. Epidemiology of cardiovascular disease in the 21st century: updated numbers and updated facts. *J Cardiovasc Dis*. 2013;1:1–2.
3. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol*. 2005;23:2900–2.
4. Wells QS, Lenihan DJ. Reversibility of left ventricular dysfunction resulting from chemotherapy: can this be reversed? *Prog Cardiovasc Dis*. 2010;53:140–8.
5. Villarraga HR, Herrmann J, Nkomo VT. Cardio-oncology: role of echocardiography. *Prog Cardiovasc Dis*. 2014;57:10–8.
6. Curigliano G, Mayer EL, Burstein HJ, Winer EP, Goldhirsch A. Cardiac toxicity from systemic cancer therapy: a comprehensive review. *Prog Cardiovasc Dis*. 2010;53:94–104.
7. Monsuez JJ, Charniot JC, Vignat N, Artigou JY. Cardiac side-effects of cancer chemotherapy. *Int J Cardiol*. 2010;144:3–15.
8. Lyu YL, Kerrigan JE, Lin CP, et al. Topoisomerase IIbeta mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. *Cancer Res*. 2007;67:8839–46.
9. Gottdiener JS, Mathisen DJ, Borer JS, et al. Doxorubicin cardiotoxicity: assessment of late left ventricular dysfunction by radionucleotide cineangiography. *Ann Intern Med*. 1981;94:430–5.
10. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.
11. Stoodley PW, Richards DA, Boyd A, et al. Left ventricular systolic function in HER2/neu negative breast cancer patients treated with anthracycline chemotherapy: a comparative analysis of left ventricular ejection fraction and myocardial strain imaging over 12 months. *Eur J Cancer*. 2013;49(16):3396–403.
12. 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.
13. Skovgaard D, Hasbak P, Kjaer A. BNP predicts chemotherapy-related cardiotoxicity and death: comparison with gated equilibrium radionucleotide ventriculography. *PLoS One*. 2014;9:1–10.
14. Marty M, Espié M, Llombart A, Monnier A, Rapoport BL, Stahalova V. Multicenter randomized phase III study of the cardioprotective effect of dexrazoxane (Cardioxane) in advanced/metastatic breast cancer patients treated with anthracycline-based chemotherapy. *Ann Oncol*. 2006;17:614–22.
15. Oliveira PJ, Bjork JA, Santos MS, et al. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. *Toxicol Appl Pharmacol*. 2004;200:159–68.
16. 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;61:2355–62.
17. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. *Mayo Clin Proc*. 2014;89:1287–306.
18. Seidman A, Hudis C, Pierri MK, et al. Cardiac dysfunction in the trastuzumab clinical trials experience. *J Clin Oncol*. 2002;20:1215–21.
19. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst*. 2010;102:14–25.
20. Prezioso L, Tanzi S, Galaverna F, et al. Cancer treatment-induced cardiotoxicity: a cardiac stem cell disease. *Cardiovasc Hematol Agents Med Chem*. 2010;8:55–75.
21. 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;23:7820–6.
22. Kumler I, Tuxen MK, Nielsen DL. A systematic review of dual targeting in HER2-positive breast cancer. *Cancer Treat Rev*. 2014;40:259–70.
23. Valachis A, Nearchou A, Polyzos NP, Lind P. Cardiac toxicity in breast cancer patients treated with dual HER2 blockade. *Int J Cancer*. 2013;133:2245–52.
24. Sica DA. Angiogenesis inhibitors and hypertension: an emerging issue. *J Clin Oncol*. 2006;24:1329–31.
25. Choueiri TK, Mayer EL, Je Y, et al. Congestive heart failure risk in patients with breast cancer treated with bevacizumab. *J Clin Oncol*. 2011;29:632–8.
26. Sorrentino MF, Kim J, Eoderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. *Cardiol J*. 2012;19:453–8.
27. 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:vii155–66.
28. Bonita R, Pradhan R. Cardiovascular toxicities of cancer chemotherapy. *Semin Oncol*. 2013;40:156–67.
29. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev*. 2004;56:185–229.
30. Bockorny M, Chakravarty S, Schulman P, Bockorny B, Bona R. Severe heart failure after bortezomib treatment in a patient with multiple myeloma: a case report and review of the literature. *Acta Hematol*. 2012;128:244–7.
31. Grandin EW, Ky B, Cornell RK, Carver J, Leniham DJ. Patterns of cardiac toxicity associated with irreversible proteasome inhibition in the treatment of multiple myeloma. *J Card Fail*. 2015;21:138–44.
32. Gershwin ME, Goetzl EJ, Steinberg AD. Cyclophosphamide: use in practice. *Ann Intern Med*. 1974;80:531–40.
33. Braverman AC, Antin JH, Plappert MT, Cook EF, Lee RT. Cyclophosphamide cardiotoxicity in bone marrow transplantation: a prospective evaluation of new dosing regimens. *J Clin Oncol*. 1991;9:1215–23.
34. Goldberg MA, Antin JH, Guinan EC, Rappeport JM. Cyclophosphamide cardiotoxicity: an analysis of dosing as a risk factor. *Blood*. 1986;68:1114–8.
35. Gottdiener JS, Appelbaum FR, Ferrans VJ, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high-dose cyclophosphamide therapy. *Arch Intern Med*. 1981;141:758–63.
36. Yang B, Papoian T. Tyrosine kinase inhibitor (TKI)-induced cardiotoxicity: approaches to narrow the gaps between preclinical safety evaluation and clinical outcome. *J Appl Toxicol*. 2012;32:945–51.

37. Lal H, Kolaja KL, Force T. Cancer genetics and the cardiotoxicity of the therapeutics. *J Am Coll Cardiol*. 2013;61:267–74.
38. Mellor HR, Bell AR, Valentin JP, Roberts RR. Cardiotoxicity associated with targeting kinase pathways in cancer. *Toxicol Sci*. 2010;120:14–32.
39. Khakoo AY, Kassiotis CM, Tannir N, et al. Heart failure associated with sunitinib malate. *Cancer*. 2008;112:2500–8.
40. Schmidinger M, Zielinski CC, Vogl UM, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2008;26:5204–12.
41. Orphanos GS, Ioannidis GN, Ardavanis AG. Cardiotoxicity induced by tyrosine kinase inhibitors. *Acta Oncol*. 2009;48:964–70.
42. Kerkelä R, Grazette L, Yacobi R, et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nat Med*. 2006;12:908–16.
43. 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;27:6152–9.
44. Heidenreich PA, John RK. Radiation induced heart disease. *Heart*. 2009;95:252–8.
45. Gaya AM, Ashford RF. Cardiac complications of radiation therapy. *Clin Oncol*. 2005;17:153–9.
46. Lancellotti P, Nkomo VT, Badano LP, et al. Expert consensus for multi-modality imaging evaluation of cardiovascular complications of radiotherapy in adults: a report from the European association of cardiovascular imaging and the American society of echocardiography. *J Am Soc Echocardiogr*. 2013;26:1013–32.
47. Bonow RO, Bennett S, Casey DE Jr, et al. ACC/AHA clinical performance measures for adults with chronic heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to develop heart failure clinical performance measures): endorsed by the heart failure society of America. *Circulation*. 2005;112:1853–87.
48. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guidelines for the management of heart failure. *J Am Coll Cardiol*. 2013;62:e147–239.
49. Cheitlin MD, Armstrong WF, Aurigemma GP, et al. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography: summary article. *Circulation*. 2003;108:1146–62.
50. 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;27:127–45.
51. 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. *Eur Heart J*. 2014;15:1063–93.
52. FDA Drug Label for DOXIL- doxorubicin hydrochloride injection, suspension, liposomal. Available at: http://dailymed.nlm.nih.gov.ezproxy.hsclib.sunysb.edu/dailymed/drugInfo.cfm?setid=21d9c619-7e94-49e2-ac41-31e9ea96554a%3E.
53. FDA Drug Label for HERCEPTIN- trastuzumab. Available at: <http://dailymed.nlm.nih.gov.ezproxy.hsclib.sunysb.edu/dailymed/drugInfo.cfm?setid=492dbdb2-077e-4064-bff3-372d6af0a7a2%3E.
54. Carver JR, Szalda D, Ky B. Asymptomatic cardiac toxicity in long-term cancer survivors: defining the population and recommendations for surveillance. *Semin Oncol*. 2013;40:229–38.