Curr. Treat. Options in Oncol. (2020) 21: 79
DOI 10.1007/s11864-020-00777-1

Cardio-oncology (MG Fradley, Section Editor)

The Role of Biomarkers to Evaluate Cardiotoxicity

Jenica N. Upshaw, MD, MS

Address
Division of Cardiology, Tufts Medical Center, 800 Washington St, Box 5931, Boston, MA, 02111, USA
Email: jupshaw@tuftsmedicalcenter.org

Published online: 7 August 2020

This article is part of the Topical Collection on *Cardio-oncology*

Keywords Cardio-oncology · Biomarkers · Heart failure · Chemotherapy · Anthracyclines · Radiation · Cardiovascular disease

Opinion statement

Moderate-level evidence suggests that cardiac troponin and natriuretic peptides are useful for risk stratification and early identification of anthracycline cardiotoxicity; however, many of these studies used older chemotherapy regimens, and thus, the applicability to current anthracycline treatment regimens is uncertain. Further research is needed to determine optimal timing and thresholds for troponin and natriuretic peptides in anthracycline-treated patients and evaluate these and other promising biomarkers for anti-HER2 therapies, thoracic radiation, anti-VEGF therapy, and fluoropyrimidine therapy–related cardiotoxicity. Risk tools that combine cardiac risk factors, cancer treatment variables, biomarkers, and imaging parameters are most likely to accurately identify individuals at highest risk for cancer therapy cardiotoxicity. Clinical trials focusing cardioprotective strategies on high-risk individuals are more likely to result in clinically significant results compared with primary prevention cardioprotective approaches.

Introduction

Advances in early detection and treatment have reduced cancer-specific mortality for many cancers [1]. In 2016, there were more than 16 million cancer survivors in the USA, and this number is expected to increase to approximately 26 million in 2040 [2]. Compared with age- and gender-matched controls, cancer survivors are at increased risk for common cardiovascular conditions such heart failure (HF), myocardial infarction, stroke, arrhythmias, and valvular disease [3–5]. The cardiovascular toxicity of cancer treatment as well as prevalent comorbid cardiovascular risk factors contributes to excess cardiovascular events in patients with cancer. Biomarkers such as cardiac troponin and natriuretic peptides are used routinely in cardiovascular medicine for diagnosis and risk stratification. Serum biomarkers can assist with early detection and diagnosis of disease and

improve understanding of disease pathophysiology. This review summarizes the current evidence regarding biomarkers for the detection of cardiovascular toxicity during and after cancer therapy.

Anthracycline cardiotoxicity

Anthracycline chemotherapeutic agents can lead to cardiomyopathy and clinical HF. Anthracyclines interact with topoisomerase 2b causing oxidative and nitrosative stress, double-stranded DNA breaks, mitochondrial dysfunction, and apoptosis [6–8]. While the use of anthracyclines is declining to some extent in breast cancer, anthracycline-based regimens remain standard of care for many patients with leukemia, lymphoma, sarcoma, and breast cancer [9, 10]. Studies of primary prevention cardioprotective strategies have shown only modest benefits and thus have not been widely applied in the routine care of anthracycline treated patients. However, early detection of anthracycline cardiotoxicity using biomarkers and imaging followed by prompt initiation of cardioprotective strategies may be more acceptable to patients than primary prevention cardioprotective strategies. The following sections describe the evidence for individual biomarkers of anthracycline cardiotoxicity.

Cardiac troponin

Troponin (Tn) assays are routinely used in cardiovascular medicine to detect myocardial injury and have been applied during and after anthracycline treatment for risk stratification and early detection of cardiotoxicity. In a seminal single center study out of Italy, 703 participants receiving high-dose chemotherapy with autologous stem cell rescue, most with prior anthracycline exposure (mean doxorubicin dose 300 mg/m2), were assessed with serum Tn values 12, 24, 36, and 72 h and 1 month after chemotherapy [11•]. Among the 70% of patients with a TnI <0.08 ng/ml, there was an associated negative predictive value of 99% for a cardiac event, defined as CV death, HF, life-threatening arrhythmia, or asymptomatic LVEF reduction of 25% or more. However, among the 208 individuals with a positive TnI after high-dose chemotherapy, 51% had a cardiac event. Furthermore, among the group with a persistently positive TnI 1 month after chemotherapy, 84% had a cardiac event. Subsequent studies focused on the higher risk individuals with elevated troponin values (TnI >0.07 ng/ml) during chemotherapy demonstrating clinically and statistically significant improvement in cardiac outcomes with randomization to enalapril versus control [12••]While this remains the largest study to date, it is uncertain if these results are applicable to current anthracycline regimens outside of high-dose chemotherapy with autologous stem cell rescue or which thresholds are predictive using newer high-sensitivity Tn assays. Several smaller studies have also shown a correlation between early elevations in serum troponin and LVEF changes or cardiac events in cohorts of

adults treated with current standard-of-care anthracycline regimens for breast cancer and hematologic malignancies, although with variable predictive performance [13•, 14–17]. Tn has also been shown to be predictive of cardiotoxicity in pediatric populations treated with anthracyclines [18–20].

Natriuretic peptides

Brain natriuretic peptide (BNP) and the N-terminal proBNP (NT-proBNP) are widely used as important diagnostic and prognostic markers in established heart failure. In a single-center study of 111 patients treated with anthracyclines, both baseline BNP and posttreatment BNP were significantly higher in patients who developed a cardiac event (defined as significant asymptomatic LVEF declines, symptomatic HF, significant arrhythmia, sudden death, or acute coronary syndrome) [21]. In this study, using a threshold of TnI of >0.4 ng/ml, only 2 individuals developed an elevated Tn, both in the setting of acute coronary syndrome. In another prospective cohort study of 53 individuals with breast cancer treated with epirubicin, baseline BNP was associated with posttreatment cardiac events (defined as clinical HF or significant LVEF declines) with BNP values of 55.5±72.3 pg/ml in those with versus 26.1±21.4 pg/ml in those without a cardiac event [22]. Posttreatment BNP or NT-proBNP at various times after anthracycline treatment in pediatric populations is also associated with echocardiographic measures of ventricular remodeling [20, 23, 24].

Markers of oxidative and nitrosative stress

Anthracycline chemotherapeutic agents can cause heart failure through oxidative and nitrosative stress. Several prospective cohort studies have demonstrated predictive value of myelopyroxidase and arginine-NO metabolites for subsequent cardiac dysfunction [8, 14, 25]. In one multicenter prospective cohort study of HER2-positive breast cancer patients treated with anthracyclines followed by trastuzumab, myelopyroxidase levels in the 90th percentile were associated with an elevated incidence of cardiotoxicity [14]. Plasma levels of asymmetric dimethylarginine, N-monomethylarginine, and arginine were associated with cardiotoxicity [8]. Future research is needed to determine the incremental value of these markers and clarify specific assays and cutpoints should these be used for routine screening.

Plasma microRNAs

Circulating plasma microRNAs are short noncoding RNAs that play a role in cardiovascular disease and are being studied as potential biomarkers of anthracycline cardiotoxicity. Mice exhibit alterations in microRNA expression profiles in myocardium following anthracycline treatment, and circulating miRNA alterations have been found in pediatric and adult cancer patients treated with anthracyclines [26–29]. Further research is needed to determine whether microRNAs can be used as early markers of anthracycline cardiotoxicity.

Multiple biomarkers

Of particular interest is the possibility of combining multiple serum biomarkers or serum biomarkers with imaging markers of early cardiotoxicity to improve the sensitivity for detecting subclinical cardiotoxicity. For example, among 81 patients with HER2-positive breast cancer treated with anthracyclines followed by trastuzumab, high-sensitivity TnI >30 pg/ml or GLS less than −19% measured after completion of anthracyclines were predictive of significant reductions in LVEF or HF, and the absence of either marker had a 91% negative predictive value for reduced ejection fraction or HF [13•]. In another analysis of the same multicenter cohort of HER2-positive breast cancer participants receiving sequential anthracyclines and trastuzumab, the combination of troponin and myeloperoxidase measured 3 months after initiation of anthracycline therapy had improved predictive ability than either marker alone [14]. Larger studies combining multiple biomarkers and imaging variables as well as clinical variables and genetic markers of cardiotoxicity risk and assessing long-term follow-up for clinical events are necessary to develop and validate multimarker screening algorithms for anthracycline cardiotoxicity. Validated models that incorporate clinical, genetic, biomarker, and imaging variables would set the stage for randomized trials of tailored cardioprotective strategies to individuals at elevated risk for cardiac events after cancer therapy.

Trastuzumab cardiotoxicity

In human epidermal growth factor receptor 2 (HER2)–positive breast cancer, the addition of monoclonal antibodies that block HER2 signaling improves survival [30–34]. Anti-HER2 therapy can disrupt cardiac homeostasis and mitochondrial function, resulting in LVEF reductions and HF [35]. In clinical trial populations, asymptomatic reductions in LVEF occurred in 10–15% of participants and HF occurred in 1–4% [36–38]. Prospective cohort studies of unselected women with HER2-positive breast cancer undergoing treatment with sequential doxorubicin and trastuzumab show rates of LVEF reductions to less than normal in upwards of 40% of women with only partial recovery of LVEF after treatment [8, 39]. Individuals older than 65 years of age may be at higher risk for cardiotoxicity with incident clinical HF reported in 29% of trastuzumab users and 19% of trastuzumab nonusers with breast cancer [40].

Biomarkers of trastuzumab cardiotoxicity

The majority of biomarker studies of trastuzumab cardiotoxicity included sequential anthracycline and trastuzumab therapy; thus, it is largely unknown whether biomarkers would be predictive in the setting of trastuzumab with nonanthracycline chemotherapy. Troponin, natriuretic peptides, and myelopyroxidase have been shown to predict significant LVEF reductions at various time points after sequential anthracycline and trastuzumab treatment [13•, 14, 25,41, 42, 43•]. Other studies of trastuzumab cardiotoxicity have included

individuals both with and without prior anthracycline chemotherapy but highly enriched for prior anthracycline therapy finding that high-sensitivity c-reactive protein and troponin were predictive of trastuzumab cardiotoxicity [44, 45•]. Due to a declining use of anthracyclines in HER2-positive breast cancer, further research is needed in nonanthracycline trastuzumab-treated cohorts to define the predictive value of biomarkers in this population.

Radiation cardiovascular toxicity

Radiation therapy (RT) that includes the heart or vascular structures in the treatment field can lead to cardiovascular late effects. RT causes microvascular endothelial damage, capillary loss, inflammation, and fibrosis and the late effects of RT include coronary artery disease, HF, valvular disease, constrictive pericarditis, conduction disease, and stroke [46–52]. Survivors of childhood cancer treated with chest or neck radiation have significantly increased ischemic heart disease, HF, and stroke events. Validated prediction models for childhood cancer survivors incorporate treatment information and allow for personalized risk estimates for HF and stroke risk up to the age of 50; however, these models do not include biomarkers or clinical cardiac risk factor variables [53, 54]. The existing biomarker studies of radiation cardiovascular toxicity are small and do not provide sufficient evidence for the utility of biomarkers in the screening and treatment of radiation-induced cardiovascular toxicity. In breast cancer cohorts with sample sizes ranging from 59 to 75 participants, elevations in BNP, NTproBNP, and troponin I correlated with measures of cardiac radiation dose [55, 56•, 57]. In a prospective cohort study of 87 participants with breast cancer, lymphoma or lung cancer receiving thoracic radiation, placental growth factor, and growth differentiation factor 15 were elevated after radiation in lymphoma and lung cancer and associated with mean heart dose [58]. At this point, there is no evidence that early identification of radiation cardiovascular toxicity and treatment with cardioprotective medications prevent cardiovascular events. Future studies are needed to explore whether statins, other medications, or lifestyle interventions can help prevent radiation heart disease and whether early detection with serum biomarkers or imaging is beneficial for screening and early treatment.

Vascular endothelial growth factor inhibitor cardiovascular toxicity

Vascular endothelial growth factor (VEGF) inhibitor therapy is associated with hypertension in over 50% of patients and cardiomyopathy in up to 10% of treated patients [59–62]. There are numerous anti-VEGF agents used in clinical practice, ranging from monoclonal antibodies to small molecule tyrosine kinase inhibitors, with variable side effect profiles [61]. Hypertension is induced in part by increased endothelin signaling and decreased nitric oxide production in endothelial cells with detectable elevations in circulating endothelin-1 levels [63, 64]. Clinically, acute hypertension contributes to acute ischemic or hemorrhagic events including myocardial infarction, stroke, and flash pulmonary edema and long-term increased risk of arterial occlusive events and HF [65]. In

cohorts of patients treated with VEGF inhibition, up to 25% had elevations in BNP or NT-proBNP and up to 10% developed elevated serum troponin [62, 66, 67]. Randomized trials of blood pressure agents are needed to identify effective, well-tolerated, antihypertensive regimens that do not decrease oncologic efficacy as well as clarify the potential role of biomarkers in the management of VEGF inhibitor treated patients.

Immunotherapy cardiovascular toxicity

Immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T cell therapy have improved outcomes in many cancers but can cause immune-related adverse events. While less frequent than gastrointestinal or endocrine immune adverse events, myocarditis occurs in 0.5–2% of individuals treated with ICIs and is associated with major adverse cardiac events in approximately half of cases of suspected cases [68–70]. The risk appears to be higher with combination checkpoint inhibitor therapy, but further research is needed to determine and validate other risk factors for myocarditis [68]. ICI therapy also appears to increase the risk of pericarditis and vasculitis [71]. Elevations in cardiac troponin, changes on electrocardiogram, and reductions in global longitudinal strain may be sensitive, although not specific, markers of myocarditis [68]. Given the low incidence of myocarditis, routine screening in asymptomatic patients is not currently the standard of care; however, an high index of suspicion for early detection of myocarditis in symptomatic patients and low threshold for treatment with high-dose steroids is recommended.

Fluoropyrimidine cardiotoxicity

The fluoropyrimidines, 5-fluorouracil and the oral pro-drug capecitabine, are fundamental components of many chemotherapy regimens; however, they may cause coronary artery vasospasm, vascular endothelial damage, and direct myocardial toxic effects leading to unstable angina, myocardial infarction, prolonged QTc, arrhythmias, cardiomyopathy, and cardiac arrest [72]. The incidence of acute, symptomatic cardiotoxicity attributed to 5-FU or capecitabine ranges from 0.5 to 19% [72–77]. There are currently no evidence-based screening for fluoropyrimidine cardiotoxicity; however, in patients with symptoms, serial ECG and troponin assessment followed by invasive or noninvasive evaluation of coronary artery disease are indicated.

Conclusions

While moderate-level evidence suggests that cardiac troponin and natriuretic peptides can help with risk stratification and early identification of anthracycline cardiotoxicity, further research is needed to determine optimal timing and thresholds for these biomarkers as well as develop and validate risk tools that combine clinical variables, biomarkers, and imaging parameters. Further research is needed to determine whether biomarker screening is useful to detect cardiotoxicity for nonanthracycline regimens including anti-HER2 therapies, thoracic radiation, anti-VEGF therapy, and fluoropyrimidine therapy.

Compliance with Ethical Standards

Conflict of Interest
Jenica N. Upshaw declares that she has no conflict of interest.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
2. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016;25(7):1029–36.
3. Strongman H, Gadd S, Matthews A, Mansfield KE, Stanway S, Lyon AR, et al. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. Lancet. 2019;394(10203):1041–54.
4. Armstrong GT, Oeffinger KC, Chen Y, Kawashima T, Yasui Y, Leisenring W, et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(29):3673–80.
5. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019;40:3889–97.
6. Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med. 2012;18(11):1639–42.
7. Narayan HK, Finkelman B, French B, Plappert T, Hyman D, Smith AM, et al. Detailed echocardiographic phenotyping in breast cancer patients: associations with ejection fraction decline, recovery, and heart failure symptoms over 3 years of follow-up. Circulation. 2017;135(15):1397–412.
8. Finkelman BS, Putt M, Wang T, Wang L, Narayan H, Domchek S, et al. Arginine-nitric oxide metabolites and cardiac dysfunction in patients with breast Cancer. J Am Coll Cardiol. 2017;70(2):152–62.
9. Giordano SH, Lin YL, Kuo YF, Hortobagyi GN, Goodwin JS. Decline in the use of anthracyclines for breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(18):2232–9.
10. Network NCC. NCCN guidelines. www.nccn.org. Published 2019. Accessed.
11.• 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(22):2749–54.

Large study demonstrating troponin as an early biomarker of cardiotoxicity with high dose chemotherapy.

12.•• 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(23):2474–81. Randomized trial among individuals with elevated troponin during high dose chemotherapy (mostly anthracyclines), demonstrating efficacy of enalapril for prevention of cardiac events in troponin positive individuals.
13.• 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(5):596–603. Prospective cohort study in breast cancer treated with sequential anthracycline and trastuzumab demonstrating improved sensitivity with a combination of a serum biomarker (High sensitivity troponin) and echocardiographic imaging parameter (global longitudinal strain) for cardiotoxicity.
14. Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr, Sebag IA, 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(8):809–16.
15. Garrone O, Crosetto N, Lo Nigro C, Catzeddu T, Vivenza D, Monteverde M, et al. Prediction of anthracycline cardiotoxicity after chemotherapy by biomarkers kinetic analysis. Cardiovasc Toxicol. 2012;12(2):135–42.

16. Katsurada K, Ichida M, Sakuragi M, Takehara M, Hozumi Y, Kario K. High-sensitivity troponin T as a marker to predict cardiotoxicity in breast cancer patients with adjuvant trastuzumab therapy. SpringerPlus. 2014;3:620.
17. Auner HW, Tinchon C, Linkesch W, Tiran A, Quehenberger F, Link H, et al. Prolonged monitoring of troponin T for the detection of anthracycline cardiotoxicity in adults with hematological malignancies. Ann Hematol. 2003;82(4):218–22.
18. Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, et al. Predictive value of cardiac troponin T in pediatric patients at risk for myocardial injury. Circulation. 1997;96(8):2641–8.
19. Lipshultz SE, Rifai N, Dalton VM, Levy DE, Silverman LB, Lipsitz SR, et al. The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia. N Engl J Med. 2004;351(2):145–53.
20. Lipshultz SE, Miller TL, Scully RE, Lipsitz SR, Rifai N, Silverman LB, et al. Changes in cardiac biomarkers during doxorubicin treatment of pediatric patients with high-risk acute lymphoblastic leukemia: associations with long-term echocardiographic outcomes. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(10):1042–9.
21. Lenihan DJ, Stevens PL, Massey M, Plana JC, Araujo DM, Fanale MA, et al. The utility of point-of-care biomarkers to detect Cardiotoxicity during Anthracycline chemotherapy: a feasibility study. J Card Fail. 2016;22(6):433–8.
22. Feola M, Garrone O, Occelli M, Francini A, Biggi A, Visconti G, et al. Cardiotoxicity after anthracycline chemotherapy in breast carcinoma: effects on left ventricular ejection fraction, troponin I and brain natriuretic peptide. Int J Cardiol. 2011;148(2):194–8.
23. Armenian SH, Gelehrter SK, Vase T, Venkatramani R, Landier W, Wilson KD, et al. Screening for cardiac dysfunction in anthracycline-exposed childhood cancer survivors. Clin Cancer Res. 2014;20(24):6314–23.
24. Mavinkurve-Groothuis AM, Groot-Loonen J, Bellersen L, et al. Abnormal NT-pro-BNP levels in asymptomatic long-term survivors of childhood cancer treated with anthracyclines. Pediatr Blood Cancer. 2009;52(5):631–6.
25. Putt M, Hahn VS, Januzzi JL, Sawaya H, Sebag IA, Plana JC, et al. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. Clin Chem. 2015;61(9):1164–72.
26. Desai VG, Kwekel JC, Vijay V, et al. Early biomarkers of doxorubicin-induced heart injury in a mouse model. Toxicol Appl Pharmacol. 2014;281:221–9.
27. Oatmen KE, Toro-Salazar OH, Hauser K, Zellars KN, Mason KC, Hor K, et al. Identification of a novel microRNA profile in pediatric cancer patients treated with anthracycline chemotherapy. Am J Physiol Heart Circ Physiol. 2018;315:H1443–52.
28. Leger KJ, Leonard D, Nielson D, de Lemos JA, Mammen PP, Winick NJ. Circulating microRNAs: potential markers of cardiotoxicity in children and young adults treated with anthracycline chemotherapy. J Am Heart Assoc. 2017;6(4).
29. Freres P, Bouznad N, Servais L, et al. Variations of circulating cardiac biomarkers during and after anthracycline-containing chemotherapy in breast cancer patients. BMC Cancer. 2018;18(1):102.
30. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344(11):783–92.
31. Baselga J, Cortes J, Kim SB, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366(2):109–19.
32. Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. Lancet. 2017;389(10075):1195–205.
33. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673–84.
34. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.
35. Kitani T, Ong SG, Lam CK, Rhee JW, Zhang JZ, Oikonomopoulos A, et al. Human-induced pluripotent stem cell model of trastuzumab-induced cardiac dysfunction in patients with breast cancer. Circulation. 2019;139(21):2451–65.
36. Procter M, Suter TM, de Azambuja E, Dafni U, van Dooren V, Muehlbauer S, et al. Longer-term assessment of trastuzumab-related cardiac adverse events in the Herceptin Adjuvant (HERA) trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(21):3422–8.
37. Tan-Chiu E, Yothers G, Romond E, Geyer CE Jr, Ewer M, Keefe D, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23(31):7811–9.
38. Perez EA, Suman VJ, Davidson NE, Sledge GW, Kaufman PA, Hudis CA, et al. Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(8):1231–8.

39. Narayan HK, French B, Khan AM, Plappert T, Hyman D, Bajulaiye A, et al. Noninvasive measures of ventricular-arterial coupling and circumferential strain predict cancer therapeutics-related cardiac dysfunction. J Am Coll Cardiol Img. 2016;9(10):1131–41.
40. Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, et al. Trastuzumab-related cardiotoxicity among older patients with breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(33):4222–8.
41. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, et al. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol. 2011;107(9):1375–80.
42. De Iuliis F, Salerno G, Taglieri L, et al. Serum biomarkers evaluation to predict chemotherapy-induced cardiotoxicity in breast cancer patients. Tumour Biol. 2016;37(3):3379–87.
43.• Zardavas D, Suter TM, Van Veldhuisen DJ, et al. Role of troponins I and T and N-terminal prohormone of brain natriuretic peptide in monitoring cardiac safety of patients with early-stage human epidermal growth factor receptor 2-positive breast cancer receiving trastuzumab: a herceptin adjuvant study cardiac marker substudy. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(8):878–84. In this substudy (n=452) of the Herceptin Adjuvant (HERA) study, elevated troponin values approximately 3 months after anthracycline treatment but before trastuzumab was associated with increased risk for significant LVEF declines.
44. Onitilo AA, Engel JM, Stankowski RV, Liang H, Berg RL, Doi SA. High-sensitivity C-reactive protein (hs-CRP) as a biomarker for trastuzumab-induced cardiotoxicity in HER2-positive early-stage breast cancer: a pilot study. Breast Cancer Res Treat. 2012;134(1):291–8.
45.• Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(25):3910–6. In this prospective cohort study of 251 women with HER2 positive breast cancer treated with trastuzumab (78% with prior anthracyclines), an elevated troponin value was associated with an increased risk of cardiotoxicity and lower chance of LVEF recovery.
46. Stewart FA, Seemann I, Hoving S, Russell NS. Understanding radiation-induced cardiovascular damage and strategies for intervention. Clin Oncol. 2013;25(10):617–24.
47. Saiki H, Petersen IA, Scott CG, Bailey KR, Dunlay SM, Finley RR, et al. Risk of heart failure with preserved ejection fraction in older women after contemporary radiotherapy for breast cancer. Circulation. 2017;135(15):1388–96.
48. Darby SC, Ewertz M, Hall P. Ischemic heart disease after breast cancer radiotherapy. N Engl J Med. 2013;368(26):2527.
49. Taylor C, McGale P, Bronnum D, et al. Cardiac structure injury after radiotherapy for breast cancer: cross-sectional study with individual patient data. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(22):2288–96.
50. Atkins KM, Rawal B, Chaunzwa TL, Lamba N, Bitterman DS, Williams CL, et al. Cardiac radiation dose, cardiac disease, and mortality in patients with lung cancer. J Am Coll Cardiol. 2019;73(23):2976–87.
51. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med. 2015;175(6):1007–17.
52. Arthurs E, Hanna TP, Zaza K, Peng Y, Hall SF. Stroke after radiation therapy for head and neck cancer: what is the risk? Int J Radiat Oncol Biol Phys. 2016;96(3):589–96.
53. Chow EJ, Chen Y, Hudson MM, Feijen EAM, Kremer LC, Border WL, et al. Prediction of ischemic heart disease and stroke in survivors of childhood cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(1):44–52.
54. Chow EJ, Chen Y, Kremer LC, Breslow NE, Hudson MM, Armstrong GT, et al. Individual prediction of heart failure among childhood cancer survivors. J Clin Oncol. 2015;33(5):394–402.
55. D'Errico MP, Grimaldi L, Petruzzelli MF, et al. N-terminal pro-B-type natriuretic peptide plasma levels as a potential biomarker for cardiac damage after radiotherapy in patients with left-sided breast cancer. Int J Radiat Oncol Biol Phys. 2012;82(2):e239–46.
56.• D'Errico MP, Petruzzelli MF, Gianicolo EA, et al. Kinetics of B-type natriuretic peptide plasma levels in patients with left-sided breast cancer treated with radiation therapy: results after one-year follow-up. Int J Radiat Biol. 2015;91(10):804–9.

BNP values correlated with cardiac dose in a prospective cohort study of 59 individuals with breast cancer treated with left-sided radiation.

57. Erven K, Florian A, Slagmolen P, Sweldens C, Jurcut R, Wildiers H, et al. Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys. 2013;85(5):1172–8.
58. Demissei BG, Freedman G, Feigenberg SJ, Plastaras JP, Maity A, Smith AM, et al. Early changes in cardiovascular biomarkers with contemporary thoracic radiation therapy for breast cancer, lung cancer, and lymphoma. Int J Radiat Oncol Biol Phys. 2019;103(4):851–60.
59. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(6):1061–8.
60. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov. 2016;15(6):385–403.

61. Touyz RM, Lang NN, Herrmann J, van den Meiracker AH, Danser AHJ. Recent advances in hypertension and cardiovascular toxicities with vascular endothelial growth factor inhibition. Hypertension. 2017;70(2):220–6.
62. Narayan V, Keefe S, Haas N, Wang L, Puzanov I, Putt M, et al. Prospective evaluation of sunitinib-induced cardiotoxicity in patients with metastatic renal cell carcinoma. Clin Cancer Res. 2017;23(14):3601–9.
63. Gopal S, Lu Q, Man J, et al. A phosphoproteomic signature in endothelial cells predicts vascular toxicity of tyrosine kinase inhibitors used in CML. Blood Adv. 2018;2(14):1680–4.
64. Kappers MH, van Esch JH, Sluiter W, Sleijfer S, Danser AH, van den Meiracker AH. Hypertension induced by the tyrosine kinase inhibitor sunitinib is associated with increased circulating endothelin-1 levels. Hypertension. 2010;56(4):675–81.
65. Touyz RM, Herrmann SMS, Herrmann J. Vascular toxicities with VEGF inhibitor therapies-focus on hypertension and arterial thrombotic events. J Am Soc Hypertens. 2018;12(6):409–25.
66. Schmidinger M, Zielinski CC, Vogl UM, Bojic A, Bojic M, Schukro C, et al. Cardiac toxicity of sunitinib and sorafenib in patients with metastatic renal cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(32):5204–12.
67. Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. JACC Heart Fail. 2013;1(1):72–8.
68. Mahmood SS, Fradley MG, Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, et al. Myocarditis in patients treated with immune checkpoint inhibitors. J Am Coll Cardiol. 2018;71(16):1755–64.
69. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med. 2016;375(18):1749–55.
70. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. Circulation. 2017;136(21):2085–7.
71. Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol. 2018;19(12):1579–89.
72. Polk A, Vaage-Nilsen M, Vistisen K, Nielsen DL. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. Cancer Treat Rev. 2013;39(8):974–84.
73. Upshaw JN, O'Neill A, Carver JR, et al. Fluoropyrimidine cardiotoxicity: time for a contemporaneous appraisal. Clin Colorectal Cancer. 2019;18(1):44–51.
74. de Forni M, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, et al. Cardiotoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1992;10(11):1795–801.
75. Wacker A, Lersch C, Scherpinski U, Reindl L, Seyfarth M. High incidence of angina pectoris in patients treated with 5-fluorouracil. A planned surveillance study with 102 patients. Oncology. 2003;65(2):108–12.
76. Kosmas C, Kallistratos MS, Kopterides P, et al. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. J Cancer Res Clin Oncol. 2008;134(1):75–82.
77. Clasen SC, Ky B, O'Quinn R, Giantonio B, Teitelbaum U, Carver JR. Fluoropyrimidine-induced cardiac toxicity: challenging the current paradigm. J Gastrointest Oncol. 2017;8(6):970–9.

Publisher's note