REVIEW

Protecting the heart in cancer therapy [version 1; referees: 2 approved]

J. Emanuel Finet¹, W. H. Wilson Tang¹,²

¹Section of Heart Failure and Transplantation Medicine, Robert and Suzanne Tomsich Department of Cardiovascular Medicine, and Sydell and Arnold Miller Family Heart and Vascular Institute, Cleveland Clinic, Cleveland, USA
²Cleveland Clinic Lerner College of Medicine at Case Western Reserve University; Center for Clinical Genomics; Cleveland Clinic, Cleveland, USA

Abstract
Recent advances in cancer prevention and management have led to an exponential increase of cancer survivors worldwide. Regrettably, cardiovascular disease has risen in the aftermath as one of the most devastating consequences of cancer therapies. In this work, we define cancer therapeutics-induced cardiotoxicity as the direct or indirect cardiovascular injury or injurious effect caused by cancer therapies. We describe four progressive stages of this condition and four corresponding levels of prevention, each having a specific goal, focus, and means of action. We subsequently unfold this didactic framework, surveying mechanisms of cardiotoxicity, risk factors, cardioprotectants, biomarkers, and diagnostic imaging modalities. Finally, we outline the most current evidence-based recommendations in this area according to multidisciplinary expert consensus guidelines.

Keywords
Cardiovascular disease, cancer, heart, cardioprotection, cardiotoxicity, prevention, biomarkers
**Introduction**

Recent advances in cancer prevention and management have led to an exponential increase of cancer survivors worldwide\(^1\). Regrettably, cardiovascular disease (CVD) has risen in the aftermath as one of the most devastating consequences of cancer therapies\(^2,3\), being most prevalent in adult survivors of breast cancer and hematological malignancies\(^4,5\).

In this work, we define cancer therapeutics-induced cardiotoxicity (CTIC) as the direct or indirect cardiovascular injury or injurious effect caused by cancer therapies, such as mediastinal radiotherapy\(^6\) and/or some chemotherapeutic agents\(^7\). These incipient toxic changes (e.g. cardiomyocyte apoptosis, cardiac ion-channel alteration, endothelial damage, etc.) can further develop into complex cardiovascular conditions, such as heart failure (HF), valvular heart disease, coronary artery disease (CAD), pericardial disease, systemic and pulmonary hypertension, arrhythmias, and thromboembolic disease, among others\(^8,9\). Concomitant pre-existent cardiovascular risk factors have been shown to foment this pathogenesis\(^10\).

**Pathogenesis of cancer therapeutics-induced cardiotoxicity**

**Cardiotoxic chemotherapy**

Doxorubicin (and other agents in the anthracycline family) is the archetype chemotherapeutic leading to CTIC, historically called anthracycline-induced cardiotoxicity or anthracycline-induced cardiomyopathy (AIC)\(^11\). The hallmark of this condition is a HF syndrome arising from dilated cardiomyopathy (DCM)\(^11\); supraventricular and ventricular arrhythmias have also been described during anthracycline administration but seldom require intervention\(^12\). Its prevalence has not been thoroughly studied owing to lack of a uniform definition, inconsistent diagnostic criteria, and underreporting; in modern times, it is thought to affect 17–23% of survivors of pediatric hematological malignancies\(^13–15\) and accounts for 2.6% of all patients with non-ischemic cardiomyopathy undergoing cardiac transplantation\(^16\).

In addition to anthracyclines, an increasing number of chemotherapeutic agents have been labeled as “cardotoxic”, with particular mechanisms of action that lead to distinctive cardiovascular effects, and in turn various degrees of frequency and severity (see Table 1 for a list of the most important cardiotoxic chemotherapeutic agents currently available in the US)\(^17,18\). Because historical cardiotoxicity was mediated by non-specific agents such as anthracycline and alkylating agents, it was believed that the novel “targeted therapeutics” (e.g. monoclonal antibodies, tyrosine kinase inhibitors, etc.) would provide fewer off-target adverse effects. However, an increasingly systematic evaluation and reporting of cardiovascular safety, along with a concomitant explosion of basic\(^19\), translational\(^19\), and clinical research in the area of CTIC\(^20\), have progressively revealed that a large number of these targeted agents are mechanistically determined to cause cardiotoxicity\(^21\). Based on the weight of the evidence, the US Food and Drug Administration has recently issued several cardiovascular box warnings for some of these agents, such as myocardial toxicity for anthracyclines, cardiomyopathy for ERBB2 inhibitors, QT prolongation and sudden cardiac death for certain tyrosine kinase inhibitors, and immune-mediated adverse reactions (i.e. myocarditis) for CTLA-4 inhibitors, among others (see Table 1)\(^22\).

**Cardiotoxic radiotherapy**

The significant delay between exposure to mediastinal radiotherapy and manifestation of heart disease, reporting bias, and the frequent concomitant use of cardiotoxic chemotherapy precludes an accurate determination of the incidence of radiation-induced cardiotoxicity\(^23\). Having said that, it is believed that cancer survivors who have undergone chest radiotherapy have a 23% increase in absolute risk of cardiovascular morbidity and mortality after 20 years\(^24\). When considering the risk of radiotherapy-induced cardiomyopathy, for example, Hodgkin lymphoma survivors who received mediastinal radiotherapy have a fivefold increase after 30 years\(^25\), whereas the greatest risk for breast cancer survivors belongs to those who received left-sided chest radiation and concomitant anthracycline chemotherapy\(^26\). This laterality risk factor is likely related to the higher incidence of severe CAD in the mid and distal left anterior descending and distal diagonal arteries that is also present in this population, which could contribute to left ventricular (LV) dysfunction\(^27\).

Myocardial injury induced by radiotherapy has the hallmark of increased interstitial myocardial fibrosis\(^8\), which in turn leads to diastolic LV dysfunction\(^28\) and subtle contractile impairment\(^29\). These pathological changes may also account for the higher incidence of conduction abnormalities, cardiovascular autonomic dysfunction, impaired exercise performance, and overall mortality\(^30\). Additionally, cardiac radiation is associated with complex stenotic and regurgitant valvular lesions\(^31\), pericardial disease\(^4\), and carotid artery disease\(^10\), among other conditions.

**Stages of cancer therapeutics-induced cardiotoxicity**

Patterened after an established classification of disease progression\(^32\), we have divided CTIC into four distinct stages, i.e. A, B, C, and D (see Figure 1). Stage A CTIC refers to cancer patients with cardiovascular health. Stage B CTIC designates cancer patients with high risk of developing CTIC. Risk factors for CTIC can be broadly divided into those pertaining to the patient and those pertaining to the cancer therapies implemented (see Table 2)\(^33,32,33\). Stage C CTIC denotes “incipient” cardiotoxicity; this is the early stages of the cardiotoxic process before it becomes clinically apparent. This stage is characterized by the appearance of abnormal biomarkers that precede the clearly defined diseased entities (e.g. QTc prolongation precedes Torsade de Points and sudden cardiac death, and sarcomeric protein or natriuretic peptide serum elevations precede LV dysfunction and overt heart failure, etc.). Finally, stage D CTIC refers to established cardiotoxicity, which is manifested by cardiovascular syndromes in early or late stages, that requires standard diagnostic modalities and medical and surgical therapies derived from expert consensus guidelines\(^34,35,36\).

**Levels of prevention**

Preventive strategies for CTIC can also be divided into four standard levels, i.e. primordial, primary, secondary, and tertiary,
| Table 1. | Chemistry agents associated with cancer therapeutics-induced cardiotoxicity. |
|---|---|
| **Chemotherapy agents associated with cancer therapeutics-induced cardiotoxicity.** | Text in bold represents US Food and Drug Administration box warnings. 5-FU, 5-fluorouracil; ALK, anaplastic lymphoma kinase; CSF-1R, colony-stimulating factor 1 receptor; ECG, electrocardiogram; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; FLT3, FMS-like tyrosine kinase 3; GIST, gastrointestinal stromal tumor; GVHD, graft-versus-host disease; LT3, Lymphotoxin 3; HDAC, histone deacetylase; HGFR, hepatocyte growth factor receptor; mTOR, mammalian target of rapamycin; NK, natural killer; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PNET, primitive neuroectodermal tumor; SCD, sudden cardiac death; TdP, Torsades de Pointes; TIL, tumor-infiltrating lymphocyte; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor. |
| **Family** | **Agent** | **Approved uses** | **Mechanism of action** | **Cardiovascular toxicities** |
|---|---|---|---|---|
| **Anthracyclines** | Doxorubicin | Breast cancer, non-Hodgkin lymphoma, Burkitt lymphoma, mantle cell lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, mantle cell lymphoma, follicular lymphoma, Burkitt lymphoma, Hodgkin lymphoma, Waldenstrom macroglobulinemia, acute lymphocytic leukemia, small cell lung cancer, multiple myeloma, gastrointestinal stromal tumor | Anthracyclines bind directly to DNA (intercalation) and also inhibit DNA repair (via topoisomerase II inhibition), resulting in blockade of DNA and RNA synthesis and fragmentation of DNA. Doxorubicin is also a p53 inhibitor and powerful iron chelator; the iron–doxorubicin complex binds to DNA and cell membranes, producing free radicals that cleave the DNA and cell membranes. | Acute myocarditis, cardiomyopathy, heart failure, bradyarrhythmias and tachyarrhythmias, non-specific ST or T wave changes. |
| | Daunorubicin | Acute myelocytic leukemia, acute lymphocytic leukemia, Kaposi sarcoma, non-Hodgkin lymphoma | | |
| | Epirubicin | Breast cancer, soft tissue sarcoma, bone sarcoma | Acute myelogenous leukemia, acute lymphoblastic leukemia, Kaposi sarcoma, acute lymphocytic leukemia, bone sarcoma, breast cancer | |
| | Mitoxantrone | Non-Hodgkin lymphoma, bone cancer, esophageal cancer, acute myelogenous leukemia, breast cancer | | |
| **Alkylating agents** | Cyclophosphamide | Breast cancer, colon cancer, soft tissue sarcoma, bone sarcoma, gastrointestinal cancer, breast cancer, acute myelogenous leukemia | Alkylating agents prevent cell division by cross-linking DNA strands and binding to DNA and cell membranes, resulting in cell death. | |
| | Etoposide | Breast cancer, soft tissue sarcoma, bone sarcoma, esophageal cancer, acute myelogenous leukemia | Acute promyelocytic leukemia, acute lymphoblastic leukemia, Kaposi sarcoma, acute lymphoblastic leukemia, bone sarcoma | |
| | Ifosfamide | Hodgkin lymphoma, non-Hodgkin lymphoma, Burkitt lymphoma, neuroblastoma, small cell lung cancer, bone sarcoma, soft tissue sarcoma | | |
| | Mitomycin | Breast cancer, colon cancer, soft tissue sarcoma, bone sarcoma, gastrointestinal cancer, breast cancer, acute myelogenous leukemia | Alkylating agents prevent cell division by cross-linking DNA strands and binding to DNA and cell membranes, resulting in cell death. | |
| **Cisplatin** | Trabectedin | Breast cancer, colon cancer, soft tissue sarcoma, bone sarcoma, gastrointestinal cancer, breast cancer, acute myelogenous leukemia | Alkylating agents prevent cell division by cross-linking DNA strands and binding to DNA and cell membranes, resulting in cell death. | |
| **Bleomycin** | | | | |
| | | | | |
| **Melphalan** | | | | |
| | | | | |
| **Carboplatin** | | | | |
| | | | | |
| **Cisplatin** | | | | |
| | | | | |
| **Docetaxel** | | | | |
| | | | | |
| **Paclitaxel** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Carboplatin** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Cyclophosphamide** | | | | |
| | | | | |
| **Etoposide** | | | | |
| | | | | |
| **Ifosfamide** | | | | |
| | | | | |
| **Mitomycin** | | | | |
| | | | | |
| **Cisplatin** | | | | |
| | | | | |
| **Docetaxel** | | | | |
| | | | | |
| **Paclitaxel** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Cyclophosphamide** | | | | |
| | | | | |
| **Etoposide** | | | | |
| | | | | |
| **Ifosfamide** | | | | |
| | | | | |
| **Mitomycin** | | | | |
| | | | | |
| **Cisplatin** | | | | |
| | | | | |
| **Docetaxel** | | | | |
| | | | | |
| **Paclitaxel** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Cyclophosphamide** | | | | |
| | | | | |
| **Etoposide** | | | | |
| | | | | |
| **Ifosfamide** | | | | |
| | | | | |
| **Mitomycin** | | | | |
| | | | | |
| **Cisplatin** | | | | |
| | | | | |
| **Docetaxel** | | | | |
| | | | | |
| **Paclitaxel** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Cyclophosphamide** | | | | |
| | | | | |
| **Etoposide** | | | | |
| | | | | |
| **Ifosfamide** | | | | |
| | | | | |
| **Mitomycin** | | | | |
| | | | | |
| **Cisplatin** | | | | |
| | | | | |
| **Docetaxel** | | | | |
| | | | | |
| **Paclitaxel** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Cyclophosphamide** | | | | |
| | | | | |
| **Etoposide** | | | | |
| | | | | |
| **Ifosfamide** | | | | |
| | | | | |
| **Mitomycin** | | | | |
| | | | | |
| **Cisplatin** | | | | |
| | | | | |
| **Docetaxel** | | | | |
| | | | | |
| **Paclitaxel** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Cyclophosphamide** | | | | |
| | | | | |
| **Etoposide** | | | | |
| | | | | |
| **Ifosfamide** | | | | |
| | | | | |
| **Mitomycin** | | | | |
| | | | | |
| **Cisplatin** | | | | |
| | | | | |
| **Docetaxel** | | | | |
| | | | | |
| **Paclitaxel** | | | | |
| | | | | |
| **Vincristine** | | | | |
| | | | | |
| **Gemcitabine** | | | | |
| | | | | |
| **Cyclophosphamide** | | | | |
| | | | | |
| **Etoposide** | | | | |
| | | | | |
## Chemotherapy agents associated with cancer therapeutics-induced cardiotoxicity

| Family | Agent | Approved uses | Mechanism of action | Cardiovascular toxicities |
|--------|-------|---------------|---------------------|--------------------------|
| Antimetabolites | 5-FU | Breast cancer, anal cancer, gastric cancer, esophageal cancer, colorectal cancer, cervical cancer, bladder cancer, head and neck cancer, pancreatic cancer | Antimetabolites inhibit DNA polymerase, interfering with DNA and, to a lesser degree, RNA synthesis. Some agents also inhibit ribonucleotide reductase, DNA primase, and DNA ligase I. | Angina pectoris, vasospasm, myocardial infarction, non-specific ECG changes, atrial and ventricular bradyarrhythmias and tachyarrhythmias, cardiomyopathy, heart failure, pericardial effusion, cerebrovascular accident, local thrombophlebitis, periarditis |
| | Capcitabine | Colorectal cancer, breast cancer, biliary cancer, esophageal cancer, pancreatic cancer, gastric cancer | | |
| | Fludarabine | Chronic lymphocytic leukemia, acute myeloid leukemia, hematopoietic stem cell transplant, non-Hodgkin lymphoma, Waldenstrom macroglobulinemia | | |
| | Cytarabine | Acute myelocytic leukemia, acute promyelocytic leukemia, acute lymphocytic leukemia, primary central nervous system lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma, meningial leukemia | | |
| Anti-ERBB monoclonal antibodies | Trastuzumab | Breast cancer and gastric cancer (ERBB2+) | Binds to ERBB1 (EGFR) or ERBB2 (HER-2), mediating antibody-dependent cellular cytotoxicity of cells that overexpress EGFR or HER-2 proteins. | Cardiomyopathy, heart failure, peripheral edema, hypertension, arrhythmias. BOX WARNING: CARDIOMYOPATHY |
| | Pertuzumab | Non-small cell lung cancer (ERBB1+) | | |
| | Nectumumab | Non-small cell lung cancer, cervical cancer, ovarian cancer, breast cancer, endometrial cancer, renal cell cancer, glioblastoma, soft tissue sarcoma, colorectal cancer | Binds to and neutralizes VEGF-A, preventing its association with the endothelial receptors VEGFR1 and VEGFR2, inhibiting angiogenesis and thus retarding the growth of all tissues (including metastatic tissue). | Hypertension, cardiomyopathy, heart failure, peripheral edema, hypotension, venous and arterial thromboembolism, ischemia. BOX WARNING: CARDIOPULMONARY ARREST |
| Anti-VEGF monoclonal antibodies | Bevacizumab | Colorectal cancer | Inhibits VEGFR1 and VEGFR2 | |
| | Aflibercept | Colorectal cancer | Inhibits VEGFR2 | |
| | Ramucirumab | Colorectal cancer, gastric cancer, non-small cell lung cancer | | |
| Immune checkpoint inhibitors (monoclonal antibodies) | Ipilimumab | Melanoma, small cell lung cancer | Human IgG1 that blocks CTLA-4, which is a downregulator of T-cell activation pathways, enhancing their activation and proliferation. | Acute myocarditis, cardiogenic shock. BOX WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS (including autoimmune myocarditis) |
| | Nivolumab | Head and neck cancer, Hodgkin lymphoma, melanoma, non-small cell lung cancer, renal cell cancer, urothelial carcinoma, small cell lung cancer | Human IgG4 that inhibits PD-1, enhancing T-cell activation and proliferation. It potentiates the effects of CTLA-4 inhibitors | Peripheral edema, acute myocarditis, cardiogenic shock, pulmonary embolism |
| | Pembrolizumab | Non-small cell lung cancer, urothelial carcinoma | | |
| | Atezolizumab | Non-small cell lung cancer, urothelial carcinoma | Human IgG1 that inhibits PD-L1 and CD80, enhancing T-cell activation and proliferation. It potentiates the effects of CTLA-4 inhibitors | Peripheral edema, venous thromboembolism |
| | Avelumab | Merkel cell carcinoma, urothelial carcinoma | | |
| | Durvalumab | Urothelial carcinoma | | |

---

Page 5 of 21

F1000Research 2018, 7(F1000 Faculty Rev):1566 Last updated: 28 SEP 2018
| Family                                      | Agent      | Approved uses                                                                 | Mechanism of action                                                                                                                                                                                                                                                                                                                                 | Cardiovascular toxicities                                                                 |
|--------------------------------------------|------------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Multi-targeted (VEGFR) tyrosine kinase inhibitors | Sunitinib  | Renal cell cancer, soft tissue sarcoma, GIST                                  | Inhibits multiple receptor tyrosine kinases (VEGFR1, VEGFR2, and VEGFR3 mainly; also inhibits PDGFRβ, FGFR1/3; cKIT; IL-2R; Lck; c-Fms; RET/PTC; CRAF; BRAF), preventing tumor growth and angiogenesis.                                                                                                | Hypertension, QTc prolongation, bradycardia, peripheral edema, cardiomyopathy, heart failure, chest pain, venous and arterial thromboembolism, ischemia, myocardial infarction, arrhythmias. BOX WARNING: QTc PROLONGATION, TdP, AND SCD (vandetanib) |
|                                            | Pazopanib  | Renal cell cancer, soft tissue sarcoma, thyroid cancer                       |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Sorafenib  | Renal cell cancer, hepatocellular cancer, soft tissue sarcoma, GIST, thyroid cancer |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Axitinib   | Renal cell cancer, thyroid cancer                                              |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Lenvatinib | Renal cell cancer, thyroid cancer                                              |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Regorafenib| Colorectal cancer, GIST, hepatocellular carcinoma                            |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Vandetanib | Thyroid cancer (medullary)                                                   |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
| Multi-targeted (BCR-ABL) tyrosine kinase inhibitors | Imatinib   | Acute lymphocytic leukemia, acute myelocytic leukemia, GIST                  | Inhibits multiple receptor tyrosine kinases (Bcr-Abl mainly; also VEGFRs, PDGFRβ, SRC, LCK, YES, FYN, cKIT, EPHA2, among others), inducing apoptosis.                                                                                                                                                                                                         | Edema (anasarca, ascites, pericardial and pleural effusion, peripheral edema, pulmonary edema, and superficial edema), hypertension, hypotension, chest pain, cardiomyopathy, heart failure, QTc prolongation, tachyarrhythmias and bradyarrhythmias, pulmonary hypertension, myocardial ischemia and infarction. BOX WARNING: QTc PROLONGATION, TdP, AND SCD (nilotinib). BOX WARNING: HEART FAILURE; ARTERIAL AND VENOUS THROMBOEMBOLISM (ponatinib) |
|                                            | Dasatinib  | Acute lymphocytic leukemia, chronic myelocytic leukemia, GIST                |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Nilotinib  | Chronic myelocytic leukemia, GIST                                             |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Bosutinib  | Chronic myelocytic leukemia                                                    |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Ponatinib  | Acute lymphocytic leukemia, chronic myelocytic leukemia                      |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
| Multi-targeted (ALK) tyrosine kinase inhibitors | Brigatinib | Non-small cell lung cancer (EML4-ALK)                                       | Inhibits multiple receptor tyrosine kinases (ALK, HGF, c-MET, ROS1, IGF-1R, FLT-3, EGFR, etc.), blocking cell proliferation.                                                                                                                                                                                                                          | Sinus bradycardia, hypertension, QTc prolongation, edema, pulmonary embolism, syncope       |
|                                            | Crizotinib |                                                                    |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
|                                            | Ceritinib  |                                                                    |                                                                                                                                                                                                                                                                                                                                                         |                                                                                          |
| Multi-targeted (MEK) tyrosine kinase inhibitors | Cobimetinib | Melanoma and non-small cell lung cancer (BRAF V600E and V600K mutations)     | MEK1 and MEK2 inhibitors (BRAF pathway), causing decreased proliferation, cell cycle arrest and apoptosis. Some also inhibit RAS, RAF, and ERK.                                                                                                                                                                                                                  | Sinus bradycardia, hypertension, QTc prolongation, edema, pulmonary embolism, syncope       |
|                                            | Trametinib |                                                                    |                                                                                                                                                                                                                                                                                                                                                         | Cardiomyopathy, hypertension                                                                 |
|                                            | Vemurafenib|                                                                    |                                                                                                                                                                                                                                                                                                                                                         | Peripheral edema, hypotension, atrial fibrillation, QTc prolongation, retinal vein occlusion, vasculitis                                                                                                                                         |
| Multi-targeted (ERBB) tyrosine kinase inhibitors | Lapatinib  | Breast cancer (ERBB2+)                                                       | Inhibits EGFR (ERBB1) and HER2 (ERBB2), regulating cellular proliferation and survival.                                                                                                                                                                                                                                                                   | Peripheral edema, cardiomyopathy, heart failure, hypertension, arrhythmias                 |
|                                            | Osimertinib| Non-small cell lung cancer (ERBB1 T790M mutation)                           | Inhibits EGFR (ERBB1 T790M and L858R mutations), regulating cellular proliferation and survival.                                                                                                                                                                                                                                                     | Cardiomyopathy, QTc prolongation, venous thromboembolism, stroke                           |
|                                            | Carfilzomib| Multiple myeloma                                                             | Inhibits the 20S proteasome, leading to cell cycle arrest and apoptosis.                                                                                                                                                                                                                                                                                           | Hypotension, acute pulmonary edema, cardiomyopathy, heart failure, cardiogenic shock, bradyarrhythmias and tachyarrhythmias, angina pectoris, cerebrovascular accident, venous thromboembolism, hemorrhagic stroke, myocardial infarction, pericardial effusion, periarditis, peripheral edema, pulmonary embolism. |
| Proteasome inhibitors                      | Bortezomib | AL amyloidosis, follicular lymphoma, mantle cell lymphoma, Waldenstrom macroglobulinemia, multiple myeloma | Inhibits the 26S proteasome, leading to cell-cycle arrest, and apoptosis                                                                                                                                                                                                                                                                                            |                                                                                          |
| Family             | Agents                                      | Approved uses                                                                 | Mechanism of action                                                                                                                                                                                                 | Cardiovascular toxicities                                                                 |
|--------------------|---------------------------------------------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| Antimicrotubule agents | Vinblastine                                | Hodgkin lymphoma, breast cancer, bladder cancer, soft tissue sarcoma           | Binds to tubulin and inhibits microtubulin formation; it is specific of M and S phases.                                                                                                                                 | Angina, hypotension, arrhythmias, peripheral edema, deep vein thrombosis, pulmonary embolism, syncope, stroke, heart failure, myocardial infarction, arterial hypertension, cardiomyopathy, pericardial effusion, myocardial infarction, angina pectoris, limb ischemia |
|                   | Paclitaxel                                  | Breast cancer, bladder cancer, cervical cancer, esophageal cancer, gastric cancer, head and neck cancer, testicular cancer, small cell lung cancer, ovarian/salivary gland cancer, penile cancer, prostate cancer, soft tissue sarcoma, thymoma/thymic carcinoma, melanoma | Inhibits microtubule disassembly, interfering with the M mitotic phase, and inhibits cell replication. In addition, it can distort mitotic spindles, resulting in breakage of chromosomes. | Hypotension, edema, arrhythmias, hypertension, syncope, cardiomyopathy, heart failure, venous thrombosis |
|                   | Docetaxel                                    | Breast cancer, breast cancer, bone sarcoma, esophageal cancer, gastric cancer, head and neck cancer, non-small cell lung cancer, small cell lung cancer, uterus cancer, thymoma/thymic carcinoma, melanoma | Inhibits microtubule disassembly, interfering with the M mitotic phase, and inhibits cell replication. In addition, it can distort mitotic spindles, resulting in breakage of chromosomes. | Hypotension, cardiomyopathy, heart failure. |
|                   | Eribulin                                    | Breast cancer, liposarcoma                                                     | Promotes proliferation, differentiation, and recruitment of T and B cells, NK cells, and dendritic cells.                                                                                                                                 | Capillary leak syndrome, angina pectoris, edema, hypotension, QTc prolongation |
| Immunomodulators  | IL-2                                        | Melanoma, neuroblastoma, renal cell cancer                                     | Increases NK cell number and levels of IL-2 and interferon gamma. Also inhibits angiogenesis, increases cell-mediated cytotoxicity of lymphocytes.                                                                                       | Chest pain, myocardial ischemia, and infarction, atrial and ventricular tachyarrhythmias, edema, ventricular tachyarrhythmias, BOX WARNING: CARDIOPULMONARY DISEASE, CAPILLARY LEAK SYNDROME (including infarction) |
|                   | Interferon                                  | Melanoma, renal cell cancer                                                    | Inhibits secretion of proinflammatory cytokines; enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells, resulting in increased IL-2 and interferon gamma secretion; inhibits toxic signals in angiogenic factors in cells. | Edema, deep vein thrombosis, arterial hypertension, cardiomyopathy, myocardial infarction, syncope, stroke, heart failure, cardiogenic shock, heart failure, cardiac arrest, cardiogenic shock, stroke |
|                   | Lenalidomide                                | Mantle cell lymphoma, multiple myeloma, chronic lymphocytic leukemia, multiple myeloma, AL amyloidosis | Inhibits secretion of proinflammatory cytokines; enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells, resulting in increased IL-2 and interferon gamma secretion; inhibits toxic signals in angiogenic factors in cells. | Edema, deep vein thrombosis, arterial hypertension, cardiomyopathy, myocardial infarction, syncope, stroke, heart failure, cardiogenic shock, heart failure, cardiac arrest, cardiogenic shock, stroke |
|                   | Thalidomide                                 | AL amyloidosis, Waldenstrom macroglobulinemia, multiple myeloma, lymphoproliferative disorders, lymphoproliferative disorders, multiple myeloma, AL amyloidosis, renal cell cancer, non-Hodgkin lymphoma | Increases NK cell number and levels of IL-2 and interferon gamma. Also inhibits angiogenesis, increases cell-mediated cytotoxicity of lymphocytes.                                                                                       | Chest pain, myocardial ischemia, and infarction, atrial and ventricular tachyarrhythmias, edema, ventricular tachyarrhythmias, BOX WARNING: CARDIOPULMONARY DISEASE, CAPILLARY LEAK SYNDROME (including infarction) |
|                   | Lenalidomide                                | Mantle cell lymphoma, multiple myeloma, chronic lymphocytic leukemia, multiple myeloma, AL amyloidosis, renal cell cancer, non-Hodgkin lymphoma | Inhibits secretion of proinflammatory cytokines; enhances cell-mediated immunity by stimulating proliferation of anti-CD3 stimulated T cells, resulting in increased IL-2 and interferon gamma secretion; inhibits toxic signals in angiogenic factors in cells. | Edema, deep vein thrombosis, arterial hypertension, cardiomyopathy, myocardial infarction, syncope, stroke, heart failure, cardiogenic shock, heart failure, cardiac arrest, cardiogenic shock, stroke |
| Family       | Agent       | Approved uses                                  | Mechanism of action                                                                                                                                                                                                 | Cardiovascular toxicities                                                                 |
|-------------|-------------|------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| mTOR inhibitors | Sirolimus   | GVHD, renal angiomyolipoma                    | Reduces protein synthesis and cell proliferation by binding to FKBP-12 and subsequently inhibiting mTOR activation, halting the cell cycle at the G1 phase. Also reduces angiogenesis by inhibiting VEGF and HIF-1 expression. Temsirolimus is the prodrug of sirolimus, the active metabolite. Everolimus is a sirolimus derivative. | Peripheral edema, hypertension, angina pectoris, atrial fibrillation, cardiomyopathy, heart failure, deep vein thrombosis, hypotension, pulmonary embolism, renal artery thrombosis, syncope |
|             | Everolimus  | Breast cancer, renal cell cancer, astrocytoma, PNET |                                                                                                                                                                                                                      |                                                                                           |
|             | Temsirolimus| Renal cell cancer                             |                                                                                                                                                                                                                      |                                                                                           |
| Differentiation agents | Tretinoin (ATRA) | Acute promyelocytic leukemia | Binds to nuclear receptors, decreasing proliferation and inducing differentiation of primitive promyelocytes                                                                                                         | Peripheral and facial edema, arrhythmias, pericardial effusion/tamponade, myocardial ischemia and infarction, hypertension, cardiomyopathy, stroke, myocarditis, pericarditis, retinoic acid syndrome |
|             | Arsenic trioxide |                                             |                                                                                                                                                                                                                      | Tachycardia, QTc prolongation, angina, hypotension. BOX WARNING: QTc PROLONGATION, TdP, AND SCD |
| HDAC inhibitors | Vorinostat  | Cutaneous T-cell lymphoma                     | Inhibits HDAC1, HDAC2, HDAC3, and HDAC6, resulting in the accumulation of acetyl groups, which alters chromatin structure and transcription factor activation, leading to cell growth arrest and apoptosis                                                                     | Peripheral edema, QTc prolongation, hypotension, tachyarrhythmias, pulmonary embolism, hypertension. BOX WARNING: SEVERE FATAL CARDIAC ISCHEMIC EVENTS AND ARRHYTHMIAS (panobinostat) |
|             | Romidepsin  | Cutaneous and peripheral T-cell lymphoma      |                                                                                                                                                                                                                      |                                                                                           |
|             | Panobinostat| Multiple myeloma                              |                                                                                                                                                                                                                      |                                                                                           |
which correspond with the stages of CTIC; each level of prevention has a particular goal, focus, and means (see Figure 1).

Primordial prevention is principally focused on the education of both patients and providers and on the implementation of general best practices to impede the emergence and development of risk factors for CTIC. This is being accomplished by the explosion of expert consensus guidelines in the last decade (see “expert consensus guidelines” below) as well as a growing presence of cardio-oncology programs in major oncology and cardiology scientific meetings. Moreover, there has been an increasing number of continuing medical education materials and public health education programs in this topic, all serving to raise awareness and educate on the cardiovascular effects of cancer therapies. Furthermore, the International Cardio-Oncology Society and the Canadian Cardiac Oncology Network have recently partnered in the writing of a cardio-oncology multidisciplinary training proposal to formally educate physicians in this developing field.

Primary prevention has the goal of impeding the emergence of CTIC. The diagnosis and control of modifiable risk factors (see Table 2) and the promotion of cardiovascular health in the cancer population are of utmost importance. In addition, the administration of cardioprotective therapies to selected patients with unavoidable moderate and high risk of CTIC is a means of primary prevention (see “cardioprotectants” below).

Secondary prevention is enforced once cardiac toxicity is incipient; early diagnosis and surveillance (see “blood biomarkers and diagnostic modalities” below), implementation of cardioprotective strategies, and administration of cardioprotective and basic therapies have the overarching goal to mitigate the progression of cardiotoxicity, restore cardiovascular health, and prevent complications. As in most health conditions, earlier diagnosis and treatment of CTIC seem to translate into improved outcomes. Inspired by the American Society of Clinical Oncology (ASCO) clinical practice guideline on the prevention and monitoring of cardiac dysfunction in survivors of adult cancers, as well as by other recent expert consensus guidelines that include recommendations on the prevention of CTIC, we have constructed a table summarizing the general evidence-based recommendations for the prevention of cardiotoxicity before, during, and after cancer therapies (see Table 3).

Lastly, once CTIC has progressed sufficiently to be manifest in cardiovascular syndromes (e.g. HF, arrhythmias, acute coronary syndromes, etc.), tertiary prevention aims to limit further progression and disability, and promote rehabilitation, by both basic and advanced cardiovascular therapeutics. The evaluation

---

Figure 1. Prevention of cancer therapeutics-induced cardiotoxicity.
and management of these defined CTIC syndromes are similar to those encountered in non-cancer patients. There are several clinical practice guidelines for the evaluation and management of these conditions in the literature, and some specifically address the cancer population; these tertiary prevention strategies will not be further detailed in this work.

**Expert panel consensus guidelines**

As mentioned above, the prevention of cardiotoxicity induced by cancer therapies has increasingly been the focus of several clinical cardiovascular and oncolgical societies, demonstrating the increasing relevance that this field has taken in the latest decade. In 2012, the European Society for Medical Oncology published a basic set of clinical practice guidelines for the prevention, monitoring, and management of CTIC. The American Society of Echocardiography and the European Society of Cardiovascular Imaging joined forces to create expert consensus guidelines for the multimodality imaging evaluation of cardiovascular complications of radiotherapy in adult patients in 2013, and as well as evaluation during and after cancer therapies in 2014. These efforts aim to standardize the indications, acquisition protocols, definitions, limitations, and vendor variability for the different cardiac imaging modalities usually employed in the diagnosis and surveillance of CTIC. In 2016, the American Heart Association (AHA) released a comprehensive scientific statement describing the mechanism, magnitude, onset, and likelihood of direct myocardial toxicity of several anti-cancer medications, among other clinically approved drugs, “to assist healthcare providers in improving the quality of care for these patients”.

### Table 2. Risk factors of cancer therapeutics-induced cardiotoxicity

| Risk factors of cancer therapeutics-induced cardiotoxicity | Age | Sex |
|----------------------------------------------------------|-----|-----|
| Health behaviors                                          | Smoking/tobacco use | Overweigt and obesity |
|                                                          | Physical inactivity | Poor nutrition |
| Health factors                                            | Hypertension |
|                                                          | Diabetes mellitus |
|                                                          | Hyperlipidemia |
|                                                          | Metabolic syndrome |
|                                                          | Kidney disease |
| Risk factors of SCD                                        | QTc prolongation |
|                                                          | Electrolyte abnormalities |
|                                                          | Proarrhythmic drugs |
| Pre-existent CVD                                          | e.g. CAD, HF, arrhythmias, etc |

| Cancer therapies | Risk Factors of CVD |
|------------------|---------------------|
| Cardiotoxic chemotherapy | High-dose anthracycline therapy | e.g. doxorubicin ≥250 mg/m² or epirubicin ≥600 mg/m² |
|                   | Low-dose anthracycline or trastuzumab therapy in high-risk patients | e.g. low normal LVEF (<53%), two or more general CVD risk factors, age 60 or over, established moderate to severe CVD |
|                   | Low-dose anthracycline and trastuzumab sequential therapy | e.g. doxorubicin <250 mg/m² or epirubicin <600 mg/m² + trastuzumab |
|                   | Other chemotherapy | e.g. US FDA box warning agents |
| Cardiotoxic radiotherapy | High-dose cardiac radiation therapy | e.g. cardiac RT ≥30 Gy or ≥2 Gy/day |
|                   | Inability of cardiac avoidance | e.g. anterior or left chest radiation, tumor in cardiac proximity, lack of shielding, etc. |
| Combination of cardiotoxic cancer therapies | Low-dose anthracycline + low-dose radiation therapy | e.g. doxorubicin <250 mg/m² or epirubicin <600 mg/m² + cardiac RT <30 Gy |
Society published a set of best practice guidelines for the management of cancer patients, focusing on the identification of the high-risk population and the detection and prevention of cardiotoxicity. This was followed by a position paper from the European Society of Cardiology summarizing the available evidence on the pathophysiology, prevention, diagnosis, therapeutic management, and long-term surveillance of the most common forms of cardiotoxicities induced by cancer therapies. Most recently, as mentioned above, the ASCO published a clinical practice guideline outlining general recommendations for the prevention of cardiac dysfunction in survivors of adult cancers. It was developed by an expert multidisciplinary physician panel using a systematic review (1996–2016) of 104 articles (meta-analyses, randomized clinical trials, and observational trials) and their clinical experience. Finally, the AHA has just published a scientific statement specifically and comprehensively dealing with the prevention of CVD in breast cancer patients, including that caused by cancer therapies.

Cardioprotectants

The development and investigation of cardioprotective agents has been exponentially increasing since the early days of anthracycline cardiotoxicity. To date, only one cardioprotectant is approved for clinical use, i.e. dexrazoxane; many others have been tested in the clinical setting, and an even larger number are on preclinical stages of investigation (see Table 4 for a succinct list of cardioprotective agents for CTIC that have been shown to be useful at different stages of research). The vast majority of cardioprotectants have been tested in the setting of anthracycline administration, either alone or in combination with other chemotherapeutic agents; a small number has been tested in trastuzumab-only administration.

**Dexrazoxane**

In the US, dexrazoxane is the only approved cardioprotective agent consistently shown to reduce the incidence or severity of AIC. It is recommended to be given intravenously, in a 10:1 ratio of dexrazoxane:doxorubicin (e.g. dexrazoxane 500 mg/m²; doxorubicin 50 mg/m²) in the context of normal renal function; cardiac monitoring should be continued during dexrazoxane therapy. Its use has been associated with statistically significant risk reductions for most doxorubicin-related cardiotoxic outcomes (other than survival), without compromising its therapeutic efficacy, in both pediatric and adult populations. Although currently dexrazoxane use is strictly restricted to women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and need continued treatment to maintain tumor control, its use in the treatment of other malignancies has been endorsed by expert guidelines. Having said that, dexrazoxane is not currently recommended for routine use with the initiation of doxorubicin therapy for either primary or metastatic disease. It needs to be noted that dexrazoxane was associated with a potential increased risk of acute myeloid leukemia, myelodysplastic syndrome, and second malignant neoplasms in a pediatric population with Hodgkin

| Table 3. Preventive strategies for cancer therapeutics-induced cardiotoxicity. DM, diabetes mellitus; HL, hyperlipidemia; HTN, hypertension. |
|---|
| **Preventive strategies for cancer therapeutics-induced cardiotoxicity** |
| **Before cardiotoxic cancer therapy** | Prioritize non-cardiotoxic cancer therapies without compromising cancer-specific outcomes |
| | Diagnosis and control of modifiable cardiovascular risk factors (e.g. HTN, DM, HL, etc.) |
| | Establish cardiovascular health (e.g. clinical examination, imaging, biomarkers) |
| | Referral to specialist as appropriate |
| **During cardiotoxic cancer therapy** | Diagnosis and control of modifiable cardiovascular risk factors (e.g. HTN, DM, HL, etc.) |
| | Evaluate and maintain cardiovascular health (e.g. clinical examination, imaging, biomarkers) |
| | Referral to specialist as appropriate |
| | Cardiotoxic chemotherapy |
| | Prioritize liposomal formulation and continuous infusion of doxorubicin |
| | Prioritize the use of dexrazoxane administration when considered appropriate (e.g. high-dose anthracyclines) |
| | Discontinue chemotherapy when considered appropriate |
| | Mediastinal radiotherapy |
| | Prioritize lowest clinically effective radiation dose |
| | Deep-inspiration breath holding radiotherapy techniques |
| | Intensity-modulated radiotherapy |
| | Discontinue radiotherapy when considered appropriate |
| **After cardiotoxic cancer therapy** | Diagnosis and control of modifiable cardiovascular risk factors (e.g. HTN, DM, HL, etc.) |
| | Monitor cardiovascular health (e.g. clinical examination, imaging, biomarkers) |
| | Referral to specialist as appropriate |
Table 4. Cardioprotectants in cancer therapeutics-induced cardiotoxicity. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; NSAID, non-steroidal anti-inflammatory drug; PC-SOD, lecithinized human recombinant super oxide dismutase.

| Antidotes | Dexrazoxane | Lipshultz et al.\textsuperscript{59} |
|-----------|-------------|-------------------------------------|
| N-acetylcysteine | Myers et al.\textsuperscript{54} |
| Beta-blockers | Carvedilol | Avila et al.\textsuperscript{55} |
| Nebivolol | Kaya et al.\textsuperscript{56} |
| Bisoprolol | Pituskin et al.\textsuperscript{57} |
| Metoprolol | Georgakopoulos et al.\textsuperscript{58} |
| ACEIs | Enalapril | Cardinale et al.\textsuperscript{59} |
| Ramipril | Jensen et al.\textsuperscript{56} |
| Perindopril | Pituskin et al.\textsuperscript{57} |
| ARBs | Valsartan | Nakamae et al.\textsuperscript{53} |
| Candesartan | Gulati et al.\textsuperscript{52} |
| MRAs | Spironolactone | Akpek et al.\textsuperscript{59} |
| Statins | Atorvastatin | Acar et al.\textsuperscript{54} |
| Natural supplements | Melatonin | Lissoni et al.\textsuperscript{55} |
| Ubiquinone | Iarussi et al.\textsuperscript{56} |
| Vitamins C and E | Wagdi et al.\textsuperscript{57} |
| Levocarnitine | Waldner et al.\textsuperscript{58} |
| ACEIs | Temocapril | Tokudome et al.\textsuperscript{59} |
| Delapril | Maeda et al.\textsuperscript{70} |
| Zofenopril | Sacco et al.\textsuperscript{71} |
| ARBs | Losartan | Matouk et al.\textsuperscript{72} |
| Statins | Fluvastatin | Riaad et al.\textsuperscript{73} |
| Biguanides | Metformin | Kobashigawa et al.\textsuperscript{74} |
| Prostacyclins | Iloprost | Neilan et al.\textsuperscript{75} |
| NSAIDs | Meloxicam | Hassan et al.\textsuperscript{76} |
| Vasodilators | Diazoxide | Hole et al.\textsuperscript{77} |
| Molsidomine | Disli et al.\textsuperscript{78} |
| Nicorandil | Ahmed et al.\textsuperscript{79} |
| Iron salts | Ferric carboxymaltose | Tobili et al.\textsuperscript{80} |
| Neuropeptides | Ghrelin | Wang et al.\textsuperscript{81} |
| Natural antioxidants | Dihydromyricetin | Zhu et al.\textsuperscript{82} |
| Hydroxytyrosol | Granados-Principal et al.\textsuperscript{83} |
| Sesame oil | Saleem et al.\textsuperscript{84} |
| Sesamin | Su et al.\textsuperscript{85} |
| Salidroside | Wang et al.\textsuperscript{86} |
| Glutathione | Mohamed et al.\textsuperscript{87} |
| Quercetin | Matouk et al.\textsuperscript{72} |
| Isorhamnetin | Sun et al.\textsuperscript{88} |
| Cannabidiol | Fouad et al.\textsuperscript{89} |
| Resveratrol | Dolinsky et al.\textsuperscript{90} |
| indole-3-carbinol | Hajra et al.\textsuperscript{91} |
| α-Linolenic acid | Yu et al.\textsuperscript{92} |
| Synthetic antioxidants | Didox | Al-Abd et al.\textsuperscript{93} |
| Other | Mdivi-1 | Gharanei et al.\textsuperscript{94} |
lymphoma in a single study a decade ago\textsuperscript{85}. Many later studies have not been able to reproduce these initial results\textsuperscript{86,87,88}. Furthermore, a recent large clinical trial in a pediatric population corroborated these latter findings, suggesting that dexrazoxane was indeed cardioprotective, did not interfere with antitumor efficacy, did not result in an increased occurrence of toxicities, and had no association with a significant rise in second malignancies\textsuperscript{89}.

**Cardiovascular pharmacotherapy**

Given their consistent benefit in other cardiovascular conditions (e.g. HF and CAD), beta-blockers, angiotensin converting-enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), and HMG-CoA reductase inhibitors (statins) have been extensively studied in the clinical setting, in the context of both anthracycline and trastuzumab therapy, for the prevention of LV dysfunction.

Beta-blocker agents with antioxidant properties such as carvedilol\textsuperscript{60,61} and nebivolol\textsuperscript{62} have shown the most promising results in early small clinical trials investigating their cardioprotective effects. Regrettably, in the so far largest clinical trial of beta-blockers for the prevention of cardiotoxicity under contemporary anthracycline dosage, carvedilol monotherapy had no impact on the incidence of early onset of LV ejection fraction (LVEF) reduction when compared to placebo in a breast cancer population\textsuperscript{63}. Similarly, ACEI monotherapy with enalapril\textsuperscript{59} and ramipril\textsuperscript{64} has also been shown to be beneficial in early small clinical trials; however, the administration of enalapril monotherapy either before chemotherapy or during or after chemotherapy in selected patients with elevated serum troponin levels failed to have a significant impact on outcomes in the most recent multicenter clinical trial\textsuperscript{65}. As for ARBs, valsartan was shown to be beneficial in small clinical trials over a decade ago\textsuperscript{66}; however, the use of candesartan as a cardioprotectant has recently provided conflicting results in well-conducted randomized placebo-controlled clinical trials\textsuperscript{67,68}. The cardioprotective effects of spironolactone monotherapy have also been promising in early small clinical settings\textsuperscript{69}; however, there is no impact on the incidence of early onset of LV dysfunction in patients receiving high-dose doxorubicin and/or radiotherapy, respectively\textsuperscript{70,71}. Melatonin\textsuperscript{65} and levocarnitine\textsuperscript{68} have also been tested in the clinical setting with positive results. Larger randomized placebo-controlled trials are lacking as to draw firm conclusions relevant to the clinical practice.

Several clinical trials have investigated the cardioprotective effects of combined neurohormonal inhibition, i.e. beta-blockers plus ACEIs/ARBs, as is recommended in the general population with HF\textsuperscript{34}. Over a decade ago, early initiation of combined beta-blockers and ACEIs was shown to provide benefit in a small population of established AIC, albeit the effect was thought to be mediated mainly by beta-blockers\textsuperscript{72}. Since then, the role of combined neurohormonal inhibition in cardioprotection has been repeatedly evaluated up to this day in the settings of anthracycline, trastuzumab, or sequential chemotherapy. In the only positive trial to date, the combination of enalapril and carvedilol was shown to prevent deterioration of LV function in adult patients with hematological malignancies undergoing anthracycline therapy\textsuperscript{73}. However, there are significant concerns regarding this trial, including lack of blinding and differing results based on the methods used to quantify LVEF, making it difficult to conclusively interpret\textsuperscript{74}. In other clinical settings, metoprolol has been tested in combination with enalapril\textsuperscript{75} and with candesartan\textsuperscript{76}, with disappointing results. Similarly, the combination of bisoprolol and perindopril failed to prevent trastuzumab-induced LV remodeling in a modern cohort of ERBB-positive breast cancer patients\textsuperscript{77}. Finally, in the as-yet-unpublished work by Guglin et al. presented at the 2018 American College of Cardiology annual meeting, both lisinopril and carvedilol failed to prevent cardiotoxicity in breast cancer patients treated with trastuzumab monotherapy, whereas both drugs prevented cardiotoxicity in patients who received both anthracycline and trastuzumab sequential therapy\textsuperscript{78}.

The cardioprotective role of statins has also been evaluated in small retrospective and prospective analyses, both with non-specific statins\textsuperscript{79,80} and atorvastatin monotherapy\textsuperscript{64}, and was found to be beneficial. These findings are very promising but are yet to be corroborated in larger randomized placebo-controlled trials (simvastatin NCT02096588; atorvastatin NCT02674204).

**Natural supplements**

Clinical cardioprotective data involving natural supplements are scarce but growing. Ubiquinone (coenzyme Q10) administration in children receiving anthracyclines was associated with a lesser degree of LV dysfunction and remodeling\textsuperscript{81}. N-acetylcysteine, administered either alone or with vitamins E and C, averted LV dysfunction from developing in patients receiving high-dose doxorubicin and/or radiotherapy, respectively\textsuperscript{82,83}. Melatonin\textsuperscript{84} and levocarnitine\textsuperscript{85} have also been tested in the clinical setting with positive results. Larger randomized placebo-controlled trials are lacking as to draw firm conclusions relevant to the clinical practice.

**Preclinical agents**

Many other agents have been shown to ameliorate anthracycline cardiotoxicity in small animal models of CTIC. Clinically available agents such as losartan\textsuperscript{86}, fluvastatin\textsuperscript{87}, metformin\textsuperscript{88}, iloprost\textsuperscript{89}, and meloxicam\textsuperscript{90} as well as other clinically unavailable ACEIs\textsuperscript{91,92} have been shown to have cardioprotective results in vivo. Vasodilators\textsuperscript{74,75}, neuropeptides\textsuperscript{80}, and iron salts\textsuperscript{81} have also been found to be useful. Finally, given that the pathogenesis of anthracyclines is in part related to increased oxidative stress\textsuperscript{93}, several natural antioxidants (e.g. sesamin\textsuperscript{94} and sesame oil\textsuperscript{95} and hydroxytyrosol\textsuperscript{96}, among others\textsuperscript{97,98}) have been tested and shown various degrees of cardioprotective effects. Didox, a synthetic antioxidant, was also shown to significantly potentiate the cytotoxicity of doxorubicin in liver cancer cells while at the same time protecting the murine model from cardiotoxicity\textsuperscript{99}. Mdvi-1, a mitochondrial division/mitophagy inhibitor, was also shown to lessen AIC\textsuperscript{100}.

**Other cardioprotective strategies**

Within a family of cardiotoxic agents, there are variations in terms of cardiac safety. For example, the use of pegylated liposomal doxorubicin has been associated with a lower incidence of CTIC and HF\textsuperscript{101,102}. Similarly, epirubicin or mitoxantrone are also believed to cause less cardiotoxicity compared with doxorubicin\textsuperscript{103}. When considering the large family of
multitargeted tyrosine kinase inhibitors, vandetanib, nilotinib, and ponatinib seem to possess the highest cardiotoxicity risk\(^{17}\). The role of exercise therapy in the prevention of CTIC remains controversial because of conflicting results\(^{114,115}\).

In summary, with the exception of dexrazoxane, no conclusive recommendations can be made on the clinical use of cardioprotectants for either stage B or stage C CTIC\(^{5}\).

**Blood biomarkers**

Blood biomarkers, in particular myocardial natriuretic peptides (i.e. NTproBNP and BNP) and sarcomeric proteins (i.e. troponin I and T), have been an integral part of the diagnostic and prognostic armamentarium in common cardiovascular conditions, such as HF and CAD. As it would seem natural, they have been progressively adopted in clinical practice to assist in the diagnosis or surveillance of patients with incipient and established CTIC, in particular LV dysfunction and HF (see **Table 5** for a list of various clinical and preclinical biomarkers shown to predict CTIC\(^{5}\)).

Troponin I\(^{10,116,117}\) and troponin T\(^{18}\) have been shown to be clinically useful in several clinical trials of cardiotoxicity prediction. Modern, more-sensitive assays of troponin I and T

| Blood biomarkers in cancer therapeutics-induced cardiotoxicity | Clinical Myocardial natriuretic peptides | NTproBNP De Iuliis et al.\(^{119}\) |
| --- | --- | --- |
|  |  | BNP Lenihan et al.\(^{37}\) |
|  |  | ANP Nousiainen et al.\(^{120}\) |
| Myocardial sarcomere proteins | cTnI Cardinale et al.\(^{117}\) |
|  | cTnT Kilickap et al.\(^{118}\) |
|  | hs-cTnI Sawaya et al.\(^{121}\) |
|  | hs-cTnT Katsurada et al.\(^{122}\) |
|  | us-cTnI Ky et al.\(^{123}\) |
| Other biomarkers | cTnAAbs Ylänen et al.\(^{124}\) |
|  | Hb Garrone et al.\(^{125}\) |
|  | hsCRP Onitilo et al.\(^{126}\) |
|  | MPO Ky et al.\(^{123}\) |
|  | PI GF Putt et al.\(^{127}\) |
|  | GDF15 Arslan et al.\(^{128}\) |
|  | Arginine-NO metabolites Finkelman et al.\(^{129}\) |
|  | GPBB Horacek et al.\(^{130}\) |
|  | ROS Mercuro et al.\(^{131}\) |
|  | IMA Ma et al.\(^{132}\) |
| Single nucleotide polymorphisms (GWAS) | rs2229774 Aminkeng et al.\(^{133}\) |
|  | rs1786814 Wang et al.\(^{134}\) |
|  | rs28714259 Schneider et al.\(^{135}\) |
| DNA Doxorubicin DNA adducts Hahm et al.\(^{136}\) |
|  | Spp1, Fht1, Tmp1, Ccl7 and Reg3b Mori et al.\(^{137}\) |
| MicroRNA | miR-34a Desai et al.\(^{138}\) |
|  | miR-34c Vacchi-Suzzi et al.\(^{139}\) |
|  | miR-146a Horie et al.\(^{140}\) |
| Preclinical Proteins | S100A1 Eryilmaz et al.\(^{141}\) |
|  | cMLC1 ElZarrad et al.\(^{142}\) |
|  | Cathepsin B Bao et al.\(^{143}\) |
| Proteomics pattern diagnostics | Petricoin et al.\(^{144}\) |
| Metabolomics pattern diagnostics | Li et al.\(^{145}\) |
| Transcriptome profiling | Todorova et al.\(^{146}\) |
to be clinically predictive of CTIC\textsuperscript{12,13}, Early studies have suggested that troponin I elevation predicted severity of CTIC\textsuperscript{11,17}, and refractoriness to HF therapy in the case of trastuzumab-induced cardiomyopathy\textsuperscript{37}, but response to enalapril monotherapy in the case of AIC\textsuperscript{39}. However, in a recent large multicenter randomized clinical trial, these findings could not be corroborated\textsuperscript{83}. Interestingly, the presence of troponin-specific autoantibodies also predicted cardiac dysfunction by cardiac magnetic resonance (CMR) imaging in the absence of elevated traditional troponin levels\textsuperscript{24}. Myocardial natriuretic peptides, such as NTproBNP\textsuperscript{19}, BNP\textsuperscript{47}, and ANP\textsuperscript{30,39,20}, have also been shown to be clinically useful predictors of CTIC, albeit to a lesser extent.

Although the use of these blood biomarkers is currently recommended in the evaluation and surveillance of patients with CTIC\textsuperscript{5,8}, their helpfulness remains disputed owing to inconsistent results in terms of sensitivity, accuracy, and reliability\textsuperscript{48}. Hence, various other alternative blood biomarkers have been studied in recent years, either alone or in combination, and shown also to be clinically predictive of CTIC, e.g. hsCRP\textsuperscript{26}, MPO\textsuperscript{23}, and arginine-NO metabolites (arginine, citrulline, ornithine, asymmetric dimethylarginine, symmetric dimethylarginine, and N-monomethylarginine)\textsuperscript{29}, among others\textsuperscript{5,8,12,13,10,32}. Likewise, many other predictive biomarker strategies are currently being developed in the preclinical arena. Proteomics\textsuperscript{44} and metabolomics\textsuperscript{46} pattern diagnostics, as well as transcriptome profiling\textsuperscript{40}, have been shown to be useful in animal models of AIC as well as the detection of doxorubicin DNA adducts (HM-dUMP, 8-OH-dGMP, HM-dCMP, and Me-dCMP)\textsuperscript{39} and other particular genes that are overexpressed during incipient cardiotoxicity\textsuperscript{17}. Cellular proteins such as S100A\textsuperscript{41,42}, cMLC1\textsuperscript{14}, and cathepsin B\textsuperscript{41,43} have also been shown to have predictive value. Some microRNAs (e.g. miR-34a\textsuperscript{39,44}, miR-34c\textsuperscript{39,45}, and miR-146a\textsuperscript{46}) have been shown to be useful in predicting CTIC in small animal models; however, a recent clinical trial involving miR-208a measurement in breast cancer patients failed to have a predictive impact\textsuperscript{49}.

Finally, research efforts to identify the genetic susceptibility of AIC have been increasing in the last decade, with the purpose of risk stratifying patients before they receive anthracycline chemotherapy. To date, three main single-nucleotide polymorphisms (SNPs: rs28714259, rs17868143, and rs2229774) have been identified as being strongly associated with AIC by means of genome-wide association studies (GWAS) from pediatric and adult case-controlled clinical trial populations.

### Diagnostic modalities

Non-blood diagnostic modalities are also an integral part of the evaluation of CVDs. For the purpose of early diagnosis and surveillance of CTIC, several imaging modalities have been studied since the late 1970s and shown to be of value (see Table 6). Historically, electrocardiography\textsuperscript{150} was used to diagnose arrhythmias during anthracycline infusion, and radionuclide cineangiography (MUGA)\textsuperscript{51,32} was the first technique used to detect falls in LV systolic function in patients receiving anthracyclines\textsuperscript{13}. Although MUGA is still considered widely available and highly reproducible, it carries the main disadvantage of submitting cancer patients to small, but potentially significant, radiation exposure (5–10 mSv)\textsuperscript{50,43}. Additionally, 2D-echocardiogram\textsuperscript{54} and stress 2D-echocardiogram\textsuperscript{55} have been shown to be beneficial in the serial evaluation of cancer patients undergoing cardiotoxic chemotherapies. Newer echocardiographic modalities, such as 3D-echocardiography\textsuperscript{16} and LV global longitudinal strain (LVGLS) measurement by speckle-tracking echocardiography (STE)\textsuperscript{37}, have demonstrated superiority over 2D-echocardiography in terms of reproducibility and predictability, respectively. CMR is currently considered the gold standard modality in the assessment of LV and right ventricular volumes and function\textsuperscript{58}. Secondary modalities such as CMR strain imaging\textsuperscript{59}, T1 mapping\textsuperscript{60}, and extracellular volume fraction (ECV)\textsuperscript{61} have also been clinically studied in recent years and found to be of great value in the assessment of subclinical cardiotoxicity. Among various non-imaging techniques, cardiopulmonary exercise testing was shown to detect abnormalities in peak oxygen consumption in cancer patients with apparently normal LV function\textsuperscript{62}, suggesting subclinical impairments of contractile reserve and chronotropic incompetence\textsuperscript{23}. Finally, many other imaging modalities are currently being studied in the preclinical arena to help detect incipient cardiotoxicity with high specificity and sensitivity. For example, 18F-labeled tetrapeptide caspase positron emission tomography (PET) is able to specifically diagnose doxorubicin-induced myocardial apoptosis in a murine model by detection of overexpressed myocardial caspase 3 resulting from anthracycline chemotherapy\textsuperscript{63}.

According to current guidelines, echocardiography (ideally 3D-echocardiography) is the method of choice for the evaluation of patients before, during, and after cancer therapies\textsuperscript{64}. CMR and MUGA scan (in that order) should be utilized as alternative modalities whenever the echocardiographic image quality is deficient. When available, measurement of LVGLS by STE is also recommended as a complementary modality. CMR should also be considered for the evaluation of chronic “constrictive” pericarditis, when the diagnosis remains uncertain after a careful echocardiographic evaluation\textsuperscript{51}.

To date, there is little evidence to guide the indication, timing, and frequency of use of imaging modalities in patients undergoing cancer therapies. The ASCO expert consensus recommends an echocardiographic evaluation prior to the initiation of potentially cardiotoxic cancer therapies\textsuperscript{3}. Routine imaging surveillance in asymptomatic patients should be offered to patients based on the healthcare provider’s perceived risk of CTIC, and the frequency of it needs to be individualized based on clinical judgment and patient circumstances\textsuperscript{3}. Subsequent to cardiotoxic cancer therapies, it is recommended that high-risk patients undergo a follow up LVEF evaluation between 6 and 12 months after completion of therapy\textsuperscript{3}.

### Conclusions

In this work, we have attempted to comprehensively and concisely survey the most relevant available literature pertaining to cardioprotection during cancer therapy. We have briefly
summarized the pathophysiology of CTIC, describing the mechanisms of cardiotoxicity of various agents, and risk factors that promote this phenomenon. For didactic purposes, we have classified CTIC into four progressive stages, in which four levels of prevention are applied, each having a specific goal, focus, and means of prevention. We have subsequently reviewed the available data on cardioprotective agents, blood biomarkers, and imaging diagnostic modalities, which are the core of primary and secondary prevention strategies. Finally, we have provided general evidence-based preventive recommendations for CTIC following the most current expert consensus guidelines. The promotion of the cardiovascular health of cancer patients and cancer survivors is paramount, requiring the diligent and knowledgeable effort of a multidisciplinary team of healthcare providers; as in all medical disorders, prevention is better than cure.

Grant information

W. H. Wilson Tang is supported by grants from the National Institutes of Health (R01HL103866, P20HL113452, R01DK106000, and R01HL126827).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

1. Miller KD, Siegel RL, Lin CC, et al.: Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin. 2016; 66(4): 271–89. PubMed Abstract | Publisher Full Text | F1000 Recommendation
2. Patnaik JL, Byers T, DiGuiseppi C, et al.: Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011; 13(3): R64. PubMed Abstract | Publisher Full Text | Free Full Text
3. Tashakkor AY, Moghaddamjo A, Chen L, et al.: Predicting the risk of cardiovascular comorbidities in adult cancer survivors. Curr Oncol. 2013; 20(5): e360–70. PubMed Abstract | Publisher Full Text | Free Full Text
4. Oetfinger KC, Merrana AC, Sklar CA, et al.: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006; 355(15): 1572–82. PubMed Abstract | Publisher Full Text
5. Armenian SH, Lacchetti C, Barac A, et al.: Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017; 35(8): 893–911. PubMed Abstract | Publisher Full Text | F1000 Recommendation
6. Jaworski C, Mariani JA, Wheeler G, et al.: Cardiac complications of thoracic irradiation. J Am Coll Cardiol. 2013; 61(23): 2319–28. PubMed Abstract | Publisher Full Text
7. Page RL 2nd, O’Byrne CL, Cheng D, et al.: Drugs That May Cause or Exacerbate Heart Failure: A Scientific Statement From the American Heart Association. Circulation. 2016; 134(9): e50–69. PubMed Abstract | Publisher Full Text | F1000 Recommendation
8. Zamorano JL, Lancetelli P, Rodriguez Muñoz D, et al.: 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016; 37(36): 2768–801. PubMed Abstract | Publisher Full Text | F1000 Recommendation
chemotherapy and a combination with L-carnitine on oxidative metabolism in patients with non-Hodgkin lymphoma. J Cancer Res Clin Oncol. 2006; 132(2): 121–8.

59. Cardinale D, Colombo A, Sandri MT, et al.: Prevention of doxorubicin (adriamycin)-induced cardiomyopathy by simultaneous administration of angiotensin-converting enzyme inhibitor assessed by acoustic densitometry. J Cardiovasc Pharmacol. 2000; 36(3): 361–8.

60. Maeda A, Honda M, Kuramochi T, et al.: An angiotensin-converting enzyme inhibitor protects against doxorubicin-induced impairment of calcium handling in neonatal rat cardiac myocytes. Clin Exp Pharmacol Physiol. 1997; 24(9–10): 720–6.

61. Secco G, Bigoni M, Evangelista S, et al.: Cardioprotective effects of zofenopril, a new angiotensin-converting enzyme inhibitor, on doxorubicin-induced cardiotoxicity in the rat. Eur J Pharmacol. 2001; 414(1): 71–8.

62. Matsouk AI, Tave A, Heeby GH, et al.: Quercetin augments the protective effect of losartan against chronic doxorubicin cardiotoxicity in rats. Cancer Chemother Pharmacol. 2013; 67(2): 443–50.

63. Riad A, Bens S, Westermann D, et al.: Pretreatment with statin attenuates the cardiotoxicity of Doxorubicin in mice. Cancer Res. 2009; 69(3): 695–9.

64. Koushaghawa LC, Xu YC, Pedin JD, et al.: Metformin protects cardiomyocyte from doxorubicin induced cytotoxicity through an AMP-activated protein kinase dependent signaling pathway: an in vitro study. PLoS One. 2014; 9(8): e104388.

65. Neilen TG, Jassal DS, Scully MI, et al.: Ipropost attenuates doxorubicin-induced cardiac injury in a murine model without compromising tumour suppression. Eur Heart J. 2006; 27(10): 1251–6.

66. Hassan MH, El-Beshbishy HA, Aly H, et al.: Modulatory effects of meloxicam on cardiotoxicity and antitumor activity of doxorubicin in mice. Cancer Chemother Pharmacol. 2014; 74(3): 559–69.

67. F1000Research 2018, 7(F1000 Faculty Rev):1566 Last updated: 28 SEP 2018

68. Takudome T, Mizugishi K, Noma T, et al.: Prevention of doxorubicin-induced cardiomyopathy and non-Hodgkin lymphoma. N Engl J Med. 2004; 351(2): 145–53.

69. Choi HS, Park ES, Kang HJ, et al.: Dose-optimization of L-carnitine for the prevention of doxorubicin-induced cardiomyopathy. Jpn J Pharmacol. 2000; 86: 63–9.

70. Flemming S, Hagerly K, et al.: American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy for prostate cancer. J Urol. 2008; 180(2): 481–99.

71. Holder BD, Pande SP, et al.: Decreased toxicity and increased efficacy of doxorubicin-containing therapy in advanced breast cancer. J Clin Oncol. 1997; 15(4): 1333–40.

72. Kaya MG, Ozkan M, Gunebalamoz, et al.: Protective effects of nevibolol on doxorubicin-induced cardiomyopathy: a randomized control study. Int J Cardiol. 2013; 167(5): 2006–10.

73. Gulati G, Heck SL, et al.: Ferric carboxymaltose-mediated attenuation of doxorubicin-induced cardiotoxicity in an iron deficiency rat model. Chemother Res Pract. 2014; 2014: 570241.

74. Wang X, Wang XL, et al.: Hydroxytyrosol ameliorates doxorubicin-induced cardiotoxicity in rats with breast cancer. Biochem Pharmacol. 2014; 89(9): 1301–10.

75. Toblli JE, Rivas C, et al.: Protective effects of sesamin against doxorubicin-induced cardiotoxicity in rats. Toxicon. 2003; 42: 265–76.

76. Akpek M, Ozdogru I, et al.: Protective effects of spironolactone against anthracene-induced cardiomyopathy. Eur J Heart Fail. 2015; 17(1): 81–9.

77. Lisoni P, Barni S, et al.: Decreased toxicity and increased efficacy of chemotherapy using the pineal hormone melatonin in metastatic solid tumour patients with poor clinical status. Eur J Cancer. 1999; 35(12): 1688–92.

78. Israels D, Aurichio U, et al.: Protective effect of coenzyme Q10 on anthracelines cardiotoxicity: Control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma. Mol Aspects Med. 1994; 15 Suppl: s207–12.
128. Arslan D, Cihan T, Kose D, et al.: Growth-differentiation factor-15 and tissue doppler imaging in detection of asymptomatic anthracycline cardiomyopathy in childhood cancer survivors. Clin Biochem. 2013; 46(13–14): 1239–43. Published Abstract | Publisher Full Text

129. Frickhimer BS, Puot M, Wang T, et al.: Apamin-Nitric Oxide Metabolites and Cardiac Dysfunction in Patients With Breast Cancer. J Am Coll Cardiol. 2017; 70(2): 152–62. Published Abstract | Publisher Full Text | Free Full Text

130. Horacek JM, Vasatova M, Tichy M, et al.: The use of cardiac biomarkers in detection of cardiotoxicity associated with conventional and high-dose chemotherapy for acute leukemia. Exp Oncol. 2010; 32(2): 97–9. Published Abstract | Publisher Full Text | Free Full Text

131. Mercuro G, Cadeddu C, Piras A, et al.: Early epirubicin-induced myocardial dysfunction revealed by serial tissue Doppler echocardiography: correlation with inflammatory and oxidative stress markers. Oncologist. 2007; 12(5): 1124–33. Published Abstract | Publisher Full Text | Free Full Text

132. Ma Y, Kang W, Bao Y, et al.: Clinical significance of ischemia-modified albumin in the diagnosis of doxorubicin-induced myocardial injury in breast cancer patients. PLoS One. 2013; 8(11): e79426. Published Abstract | Publisher Full Text | Free Full Text

133. Amingnek F, Bhavsar AP, Visscher H, et al.: A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. Nat Genet. 2015; 47(9): 1079–84. Published Abstract | Publisher Full Text | Free Full Text

134. Wang X, Sun CL, Quirones-Lombraña A, et al.: CELF4 Variant and Anthracycline-Related Cardiomyopathy: A Children’s Oncology Group Genome-Wide Association Study. J Clin Oncol. 2016; 34(8): 863–70. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

135. Schneider BP, Shen F, Gardiner L, et al.: Genome-Wide Association Study for Anthracycline-Induced Congestive Heart Failure. Cancer Res. 2017; 77(1): 43–51. Published Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

136. Hahn S, Dreiser HS, Podwall D, et al.: DNA biomarkers antecedent semiannualanthraceline cardiomyopathy. Cancer Invest. 2003; 21(1): 53–67. Published Abstract | Publisher Full Text

137. Koy Y, Kondo C, Tomomura Y, et al.: Identification of potential genomic biomarkers for early detection of chemically induced cardiotoxicity in rats. Toxicology. 2010; 271(1–2): 36–44. Published Abstract | Publisher Full Text

138. Desai VG, C Kwekel J, Vijay V, et al.: Early biomarkers of doxorubicin-induced heart injury in a mouse model. Toxicol Appl Pharmacol. 2014; 281(2): 221–9. Published Abstract | Publisher Full Text

139. Vacchi-Suzzi C, Bauer Y, Berridge BR, et al.: Perturbation of microRNAs in rat heart during chronic doxorubicin treatment. PLoS One. 2012; 7(7): e40095. Published Abstract | Publisher Full Text | Free Full Text

140. Horie T, Ono K, Nishi H, et al.: Acute doxorubicin cardiotoxicity is associated with miR-146b-5p inhibition of the neuregulin-ErbB pathway. Cardiovasc Res. 2010; 87(4): 656–64. Published Abstract | Publisher Full Text | Free Full Text

141. Eryilmaz U, Demiro J, Aksum B, et al.: S100A1 as a Potential Diagnostic Biomarker for Assessing Cardiotoxicity and Implications for the Chemotherapy of Certain Cancers. PLoS One. 2015; 10(12): e0145418. Published Abstract | Publisher Full Text | Free Full Text

142. ElGazaar MK, Mukhopadhyay P, Mohan N, et al.: Trastuzumab alters the expression of genes essential for cardiac function and induces ultrastructural changes of cardiomyocytes in mice. PLoS One. 2013; 8(11): e79543. Published Abstract | Publisher Full Text | Free Full Text

143. Bao GY, Wang HZ, Wang YJ, et al.: Quantitative proteomic study identified cathepsin B associated with doxorubicin-induced damage in H9c2 cardiomyocytes. Biostat Trends. 2012; 6(6): 283–7. Published Abstract | Publisher Full Text

144. Petrocin EF, Rajapakse V, Herman EH, et al.: Toxicoproteomics: serum proteomic pattern diagnostics for early detection of drug induced cardiac toxicities and cardioprotection. Toxicol Pathol. 2004; 32 Suppl 1: 122–30. Published Abstract | Publisher Full Text | Free Full Text

145. Li J, Yu L, Hou Z, et al.: Screening, verification, and optimization of biomarkers for early prediction of cardiotoxicity based on metabolomics. J Proteome Res. 2015; 14(5): 4247–50. Published Abstract | Publisher Full Text | Free Full Text

146. Todorova VK, Beggs ML, Delongchamp RR, et al.: Transcriptome profiling of peripheral blood cells identifies potential biomarkers for doxorubicin cardiotoxicity in a rat model. PLoS One. 2012; 7(11): e46398. Published Abstract | Publisher Full Text | Free Full Text

147. Lenihan DJ, Stevens PL, Massey M, et al.: The Utility of Point-of-Care Biomarkers to Detect Cardiotoxicity During Anthracycline Chemotherapy: A Feasibility Study. J Clin Oncol. 2016; 34(8): 435–38. Published Abstract | Publisher Full Text | F1000 Recommendation

148. Kim YH, Kinjo J, Tang WH: Alternative Biomarkers for Combined Biology. Heart Fail Clin. 2017; 13(2): 381–401. Published Abstract | Publisher Full Text | Free Full Text

149. Oliveira-Carvalho V, Ferreira LR, Bocchi EA: Circulating mir-208a fails as a biomarker of doxorubicin-induced cardiotoxicity in breast cancer patients. J Appl Toxicol. 2015; 35(9): 1071–2. Published Abstract | Publisher Full Text

150. Steinberg JS, Cohen AJ, Wasserman AG, et al.: Acute arrhythmogenicity of doxorubicin administration. Cancer. 1987; 60(6): 1213–8. Published Abstract | Publisher Full Text | Free Full Text

151. Schwartz RG, McKenzie WB, Alexander J, et al.: Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. Am J Med. 1987; 82(6): 1109–18. Published Abstract | Publisher Full Text

152. McGibb-jh, Bristro MR, Goits ML, et al.: Sensitivity and specificity of radionuclide ejection fractions in doxorubicin cardiotoxicity. Am Heart J. 1983; 106(5 Pt 1): 1048–56. Published Abstract | Publisher Full Text

153. Goddard JS, Mathison DJ, Bone JS, et al.: Doxorubicin cardiotoxicity: assessment of late left ventricular dysfunction by radionuclide cineangiography. Ann Intern Med. 1981; 94(4 pt 1): 430–5. Published Abstract

154. Thavendranathan P, Grant AD, Negishi T, et al.: 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(1): 77–84. Published Abstract | Publisher Full Text

155. Khouri MG, Hornsby WE, Rism N, et al.: Utility of 3-dimensional echocardiography, global longitudinal strain, and exercise stress echocardiography to detect cardiac dysfunction in breast cancer patients treated with doxorubicin-containing adjuvant therapy. Breast Cancer Res Treat. 2014; 143(3): 531–9. Published Abstract | Publisher Full Text | Free Full Text

156. Walker J, Bhalar N, Fallah-Rad N, et al.: Role of three-dimensional echocardiography in breast cancer: comparison with two-dimensional echocardiography, multiple-gated acquisition scans, and cardiac magnetic resonance imaging. J Clin Oncol. 2010; 28(21): 3429–36. Published Abstract | Publisher Full Text | Free Full Text

157. Negishi K, Negishi T, Haliuska BA, et al.: Use of speckle strain to assess left ventricular responses to cardiotoxic chemotherapy and cardioprotection. Eur Heart J Cardiovasc Imaging. 2014; 15(3): 324–31. Published Abstract | Publisher Full Text

158. Armstrong GT, Piana JC, Zhang N, et al.: Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. J Clin Oncol. 2012; 30(23): 2876–84. Published Abstract | Publisher Full Text | Free Full Text

159. Drafts BC, Tsvangay VM, D’Agostino R Jr, 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(8): 877–85. Published Abstract | Publisher Full Text | Free Full Text | Free Full Text

160. Lightfoot JC, D’Agostino RB Jr, Hamilton CA, et al.: Novel approach to early detection of doxorubicin cardiotoxicity by gadolinium-enhanced cardiovascular magnetic resonance imaging in an experimental model. Circ Cardiovasc Imaging. 2010; 3(5): 550–8. Published Abstract | Publisher Full Text | Free Full Text | Free Full Text

161. Jordan JH, D’Agostino RB Jr, Hamilton CA, et al.: Longitudinal assessment of concurrent changes in left ventricular ejection fraction and left ventricular myocardial tissue characteristics after administration of cardiotoxic chemotherapies using T1-weighted and T2-weighted cardiovascular magnetic resonance. Circ Cardiovasc Imaging. 2014; 7(6): 812–20. Published Abstract | Publisher Full Text | Free Full Text | Free Full Text

162. Jones LW, Courmay KA, Mackey JR, et al.: Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. J Clin Oncol. 2012; 30(20): 2530–7. Published Abstract | Publisher Full Text | Free Full Text

163. Su H, Gorody N, Gomez LF, et al.: Noninvasive molecular imaging of apoptosis in a mouse model of anthracyline-induced cardiotoxicity. Circ Cardiovasc Imaging. 2015; 8(5): e001952. Published Abstract | Publisher Full Text | Free Full Text
Open Peer Review

Current Referee Status:  

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1 Ana Barac Medstar Washington Hospital Center, Medstar Heart and Vascular Institute, Washington, USA
   Competing Interests: No competing interests were disclosed.

2 Edimar A Bocchi Monica S Ávila Heart Failure Department, Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil
   Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

• Your article is published within days, with no editorial bias
• You can publish traditional articles, null/negative results, case reports, data notes and more
• The peer review process is transparent and collaborative
• Your article is indexed in PubMed after passing peer review
• Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com