


# Cancer Therapy-Related Cardiac Dysfunction: An Overview for the Clinician

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**ABSTRACT:** Cancer therapy-related cardiac dysfunction (CTRCD) is one of the most feared and undesirable side effects of chemotherapy, occurring in approximately 10% of the patients. It can be classified as direct (dose-dependent vs dose-independent) or indirect, either case being potentially permanent or reversible. Risk assessment, recognition, and prevention of CTRCD are crucial.

**KEYWORDS:** Cardiotoxicity, cardiac dysfunction, heart failure, cardio-oncology

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## Introduction

With the increased prevalence of cancer over the last decade, there has been a parallel increase in the number of cancer survivors due to both early detection and advances in treatment.<sup>1</sup> Despite these advances, cancer therapy-related cardiac dysfunction (CTRCD) is one of the most feared and undesirable side effects of chemotherapy, occurring in approximately 10% of the patients.<sup>2</sup>

There are numerous proposed definitions for CTRCD (Table 1), although an official American College of Cardiology (ACC) consensus statement is still needed. The most accepted definition comes from the cardiac image societies, such as the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI), which define it as a decrease in left ventricular ejection fraction (LVEF) of more than 10% to below the lower limit of normal, which is considered an LVEF of 53%, despite symptoms.<sup>3</sup> If these definitions were not met, then a decrease greater than 15% in global longitudinal strain (GLS) compared with a baseline GLS was considered subclinical left ventricular (LV) dysfunction.

## Cardiotoxicity Classifications

Historically, CTRCD classifications were described after introduction of trastuzumab for breast cancer in 1998. With the growth in use of this drug, there was an increase in the reported cardiotoxic events,<sup>4</sup> which was initially considered to be the same clinical picture of anthracycline cardiotoxicity, but then classified as different entities: Type 1 for anthracycline-related cardiotoxicity and Type 2 cardiotoxicity for trastuzumab.<sup>5</sup> These are pathophysiologic-derived definitions, however, with no clinical implication, as permanent cardiac dysfunction could be seen in both types.

It is important to emphasize that chemotherapy may also have an indirect effect on the heart while interplaying with

various facets of the cardiovascular system (ie HTN, vascular or endothelial damage, and arrhythmias) (Table 2).

Type 1 cardiotoxicity is characterized by irreversible myocardial damage due to the cumulative administered dose. Anthracyclines are the best representation of this type of cardiotoxicity. Many mechanisms have been proposed for their dose-dependent cardiac dysfunction, such as the generation of reactive oxygen species, accumulation of anthracycline metabolites which disrupt sarcomere structure and function, and mitochondrial biogenesis.<sup>6</sup> Anthracyclines are considered to have increased potential for long-term cardiac dysfunction.

Type 2 cardiotoxicity is characterized by dose-independent reversible myocardial damage, and the best representation of this is trastuzumab. Trastuzumab plays a central role in breast cancer treatment by binding to the human epidermal growth factor receptor 2 (HER2) and inhibiting downstream-associated signaling cascades.<sup>7</sup>

With the advent of immunotherapy, there is a new set of mechanisms in which patients with cancer may suffer cardiovascular injury and the need for an updated classification. Therefore, this review will arbitrarily expand the prior classification to further incorporate mechanisms not previously categorized (Table 3) such as coronary disease-related (radiation exposure, endothelial damage, and/or spasm), myocarditis-related, takotsubo's cardiomyopathy, and secondary electrical abnormalities (such as conduction abnormalities and arrhythmias).

## Risk Factors

Risk factors can be classified as patient-related or therapy-related.

Patient-related risk factors include the already known factors for coronary artery disease (CAD), such as advanced age, hypertension, diabetes, smoking, female sex, and postmenopausal state.<sup>8</sup> Genetic polymorphism might contribute to an



**Table 1.** Proposed definitions for cancer therapy-related cardiac dysfunction (CTRCD).

| AGENCY  | DEFINITIONS  |
|---|--|
| The American Society of Echocardiography (ASE) and the European Association of cardiovascular Imaging (EACVI) | <ol style="list-style-type: none"> <li>1. <math>\geq 10\%</math> decline in LVEF to a final value less than 53% confirmed on subsequent imaging performed 2 to 3 weeks after the initial measurement.</li> <li>2. <math>&gt;15\%</math> relative decline in global longitudinal strain (GLS) compared with baseline strain.</li> </ol>   |
| US Food and Drug Administration (FDA)   | Doxorubicin-mediated cardiotoxicity was defined as either: <ol style="list-style-type: none"> <li>1. <math>\geq 20\%</math> absolute decline in LVEF.</li> <li>2. <math>\geq 10\%</math> decrease in LVEF to less than the lower limit of normal or absolute value of less than 45%.</li> </ol>  |
| Cardiac review and evaluation committee in trastuzumab trials   | Trastuzumab-mediated cardiomyopathy was either: <ol style="list-style-type: none"> <li>1. <math>\geq 10\%</math> decline in the absence of symptoms.</li> <li>2. <math>\geq 5\%</math> decrease in symptomatic patients to a final LVEF of less than 55%.</li> </ol>   |
| Herceptin Adjuvant (HERA) trial   | <ol style="list-style-type: none"> <li>1. LVEF decline by at least 10% from baseline to a value of <math>&lt;50\%</math> was considered a significant LVEF decrease.</li> </ol>  |
| The Breast Cancer International Research Group (BCIRG)  | <ol style="list-style-type: none"> <li>1. <math>&gt;10\%</math> reduction from baseline LVEF assessment to define asymptomatic left ventricular dysfunction.</li> </ol>  |
| The National Cancer Institute (NCI)   | Proposes the Common Terminology Criteria for Adverse Events (CTCAE) that define left ventricular dysfunction and HF based on severity into grades 1 to 5. <ol style="list-style-type: none"> <li>1. Grade 1 is asymptomatic elevations in biomarkers or abnormalities on imaging.</li> <li>2. Grades 2 and 3 consist of symptoms with mild and moderate exertion.</li> <li>3. Grade 4 includes severe, life-threatening symptoms requiring hemodynamic support.</li> <li>4. Grade 5 involves death.</li> </ol> |

Abbreviations: HF, heart failure; LVEF, left ventricular ejection fraction.

**Table 2.** Indirect cardiovascular effects of chemotherapy.

|                            |   |
|----------------------------|---|
| Hypertension               | TKIs, proteasome inhibitors, platinum-based therapy, ibrutinib, and VEGF  |
| Vascular toxicity          | Radiation (CAD), platinum therapy (CAD), 5-FU (spasm), capecitabine (spasm), BCR-ABL, and immunomodulators  |
| Arrhythmias                | Ibrutinib (atrial fibrillation, atrial flutter, and ventricular tachyarrhythmias), TKI (QT prolongation), fluorouracil, platinum-based therapy (bradycardia/SVT), taxanes (bradycardia, ventricular arrhythmias, and SVT), and ALK inhibitors (bradycardia and QT prolongation) |
| Takotsubo's cardiomyopathy | 5-FU  |
| Myocarditis                | TKIs/ICPis  |
| Ventricular dysfunction    | Anthracyclines, HER2 inhibitors, proteasome inhibitors, TKIs, and immunotherapy   |

Abbreviations: 5-FU, 5-fluorouracil; ALK, anaplastic lymphoma kinase; CAD, coronary artery disease; HER2, human epidermal growth factor receptor 2; TKIs, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; ICPis, immune checkpoint inhibitors.

increased risk for cardiomyopathy at lower anthracycline dose, implying that genetic variations could predict cardiac risk. These patients might be sensitive to anthracyclines independent of the dose given.<sup>9</sup> Patients with cancer might have elevated levels of cardiovascular peptides at baseline like high-sensitive troponin T (hsTnT), N-terminal pro-BNP (NT-proBNP),

**Table 3.** Proposed cardiotoxicity classifications.

|        |  |
|--------|--|
| Type 1 | Irreversible myocardial damage, dose dependent (ie anthracyclines)   |
| Type 2 | Reversible myocardial damage, dose independent (ie trastuzumab)  |
| Type 3 | Coronary disease related such as radiation exposure and spasm (ie radiation therapy and 5-FU)  |
| Type 4 | Miscellaneous related to myocarditis or takotsubo's cardiomyopathy (ie 5-FU and TKIs)  |
| Type 5 | Indirect which are secondary to conduction abnormalities, arrhythmias, and hypertension (ie ibrutinib, fluorouracil, and platinum-based therapy) |

Abbreviations: 5-FU, 5-fluorouracil; TKIs, tyrosine kinase inhibitors.

mid-regional pro-atrial natriuretic peptide (MR-proANP), mid-regional pro-adrenomedullin (MR-proADM), and C-Terminal pro-endothelin-1. In an unselected population of patients with cancer prior to cardiotoxic chemotherapy, elevations of these peptides were strongly associated with all-cause mortality, suggesting subclinical myocardial damage linked to disease progression.<sup>10</sup>

Therapy-related risk factors include high-dose chemotherapy, administration as a bolus or in combination with other cancer therapy, prior anthracycline use, mediastinal radiation, and using specific agents linked to higher incidence of cardiotoxicity, such as anthracyclines, trastuzumab, and cyclophosphamide.<sup>11</sup>

**Table 4.** Cardiotoxicity risk score (CRS).

|  |  |
|--|--|
| Patient-related risk factors   | HTN, CAD/PAD, heart failure, diabetes, age < 15 or >65 years, female sex, anthracycline exposure, and chest radiation.   |
| Chemotherapy-related risk factors  | High (risk score of 4): anthracyclines, trastuzumab, cyclophosphamide, ifosfamide, and clofarabine<br>Moderate (risk score of 2): docetaxel, pertuzumab, sorafenib, and sunitinib<br>Low (risk score of 1): imatinib, lapatinib, bevacizumab, and dasatinib<br>Rare (risk score of 0): rituximab, etoposide, and thalidomide |
| Overall risk for CRS (number of patient-related risk factors plus chemotherapy-related risk factors) | Very high: CRS > 6<br>High: CRS 5 to 6<br>Moderate: CRS 3 to 4<br>Low: CRS 1 to 2<br>Very low: CRS 0   |

Abbreviation: CAD, coronary artery disease; HTN, hypertension; PAD, peripheral arterial disease.

Source: adapted from the study by Herrmann et al.<sup>12</sup>

### Risk Prediction

Many risk prediction models have been published in the literature; however, none have been actually validated in prospective studies. Therefore, their clinical significance is yet to be determined.

Herrmann et al<sup>12</sup> proposed the cardiotoxicity risk score (CRS), which takes both patient and cancer therapy risk factors into consideration. It assigns one point to each of the patient-related risk factors, including hypertension, CAD or CAD equivalent, cardiomyopathy or heart failure, diabetes mellitus, prior or current anthracycline, prior or current chest radiation, age < 15 or >65 years, and female sex. It also assigns 0 for rare risk, 1 for low risk, 2 for moderate risk, and 4 for high medication-related risk. Anthracyclines, cyclophosphamide, trastuzumab, and 5-fluorouracil (5-FU) are considered to be of high risk. Pertuzumab, vinblastine, capecitabine, and ponatinib are considered to be of moderate risk, whereas imatinib and bevacizumab are considered to be of low risk. Paclitaxel, rituximab, carboplatin, and fludarabine are considered to be of rare risk. If the overall risk is >6, it is considered very high, 5 to 6 as high, 3 to 4 as intermediate, 1 to 2 as low, and 0 as very low (Table 4).

### Chemotherapy Agents Associated with CTRCD

*Anthracyclines (eg, doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone)*

Anthracyclines are a class of very effective chemotherapy used for the treatment of hematologic cancers (eg, lymphoma and leukemia) and solid tumors (eg, breast adenocarcinoma and sarcoma).<sup>13</sup> The therapeutic effect of anthracyclines against cancer cells is mediated through inhibition of topoisomerase II alpha. Cardiotoxicity is an undesired complication from

anthracyclines. The exact mechanism is unclear but there are many theories behind anthracycline-induced cardiomyopathy. It includes intercalation into nuclear DNA, which impairs protein synthesis, inhibition of topoisomerase II beta to inhibit DNA repair, and production of reactive oxygen species. Reactive oxygen species levels may also be increased by free cellular iron. The doxorubicin-iron complexes form toxic radical and reactive nitrogen species, producing increased stress and mitochondrial dysfunction.<sup>14</sup> It is believed that cardiac toxicity might be mediated by binding of anthracycline products to DNA, resulting in a complex formation with ultimate cardiac myocyte cell death.<sup>15</sup>

The presence of cardiovascular risk factors, concomitant therapy with agents known to cause CTRCD (ie, cyclophosphamide, trastuzumab, and paclitaxel), and mediastinal radiation increase the risk of anthracycline toxicity.<sup>16</sup> Previous studies indicate an association between the cumulative anthracycline dosing and cardiotoxicity. Diastolic dysfunction had been reported at doses of 200 mg/m<sup>2</sup> of doxorubicin and systolic dysfunction at 400 to 600 mg/m<sup>2</sup>.<sup>17</sup> More recent data described that LV dysfunction could be seen with doxorubicin doses of 240 mg/m<sup>2</sup> when combined with cyclophosphamide.<sup>18</sup> The American Society of Clinical Oncology (ASCO) classifies as increased risk of developing cardiac dysfunction those who receive: (1) high-dose anthracycline (doxorubicin > 250 mg/m<sup>2</sup> or epirubicin > 600 mg/m<sup>2</sup>); (2) lower-dose anthracycline in combination with lower-dose radiation therapy (RT < 30 Gy) where the heart is in the treatment field; (3) treatment with lower-dose anthracycline or trastuzumab alone with the presence of multiple cardiovascular risk factors, older age (>60 years), or structural heart disease; and (4) treatment with lower-dose anthracycline followed by trastuzumab (sequential therapy).<sup>19</sup>

Liposomal doxorubicin and epirubicin are modified analogs of doxorubicin, which are relatively less cardiotoxic than conventional doxorubicin. In a meta-analysis, liposomal doxorubicin had lower rates of clinical cardiotoxicity (odds ratio [OR] 0.18, 0.08-0.38;  $P < .001$ ;  $I^2 = 0\%$ ) and subclinical cardiotoxicity (OR 0.31, 0.20-0.48;  $P < .01$ ;  $I^2 = 48.5\%$ ) than doxorubicin without compromising efficacy.<sup>20</sup> Epirubicin also had lower rates of clinical cardiotoxicity (OR 0.39, 0.2-0.78;  $P = .008$ ;  $I^2 = 0.5\%$ ) and subclinical cardiotoxicity (OR 0.30, 0.16-0.57;  $P < .001$ ;  $I^2 = 1.7\%$ ).<sup>20</sup>

The method of administration of doxorubicin is also important to attempt to reduce cardiotoxicity. Continuous infusion aims to decrease peak plasma levels by increasing its duration of infusion;<sup>21</sup> therefore, replacing bolus administration with continuous infusion over 48 to 96 hours reduces early cardiotoxicity in adults but not in children.<sup>22,23</sup>

Anthracycline toxicity may be: (1) acute (within 1 week), which is uncommon (approximately 1%), but usually reversible when discontinued; (2) sub-acute (1.6%-2.1%); and (3) chronic (1.6%-5%), which are likely irreversible.<sup>24</sup> This classification is controversial as there is possible progression of one phenomenon

to another. The most common presentation occurs before 1 year of therapy and carries mortality that exceeds 50%. Late onset occurs within 1 to 20 years and may also be seen after a second insult. The late onset presentation tends to improve with guideline-directed medical therapy. Overall, 2% to 20% of the patients who receive anthracycline will have a decrease in LVEF.<sup>2</sup>

The initial cardiovascular work up prior to initiation of anthracycline use based on the consensus guidelines includes baseline evaluation of LVEF (preferred 3-dimensional [3D] echocardiography or 2-dimensional [2D] with contrast), GLS, and troponin. If the LVEF is <53%, GLS below the lower limit of normal, and elevated troponins, cardiology consultation would be recommended. If these parameters are all normal, follow-up is needed with reassessment of LVEF, GLS, and troponin at completion of therapy and 6 months later. For patients receiving >250 mg/m<sup>2</sup> of doxorubicin, screening should occur after every 50 mg/m<sup>2</sup>.<sup>3</sup> The ASCO guidelines for surveillance recommend an echocardiogram 6 to 12 months after completion of therapy in asymptomatic high-risk patients. There is no specific guidance on routine surveillance in asymptomatic patients with normal echocardiography.<sup>19</sup>

#### *HER2 inhibitors (eg, trastuzumab, pertuzumab, and lapatinib)*

Human epidermal growth factor receptor 2-targeted agents are the standard of treatment for both early and metastatic HER2-positive breast cancers, which are marked by the overexpression of HER2 gene in malignant cells.<sup>25</sup> Human epidermal growth factor receptor 2 is expressed in myocytes and might play a protective role against myocardial stress. Therefore, the proposed mechanism of cardiotoxicity involves binding of HER2-targeted agents with disruption of this cardioprotective pathway.<sup>17</sup>

Trastuzumab cardiotoxicity is not dose-related (“random” effect) and appears to be highly reversible.<sup>5</sup> The reported rate of CTRCD without concomitant anthracycline use is approximately 3%, and this risk increases to 5% when anthracycline is given before trastuzumab.<sup>26</sup> Cancer therapy-related cardiac dysfunction increases significantly up to 27% when trastuzumab is used in combination with doxorubicin and cyclophosphamide.<sup>26</sup> Risk factors for CTRCD are underlying heart disease, advanced age, renal dysfunction, and diabetes.<sup>27</sup>

Cardiac function should be assessed prior to initiation of trastuzumab therapy. Patients with normal LV function and no signs of heart failure may start therapy. If the LV dysfunction is mildly suppressed (40%–53%), therapy may be stated with at a cost of increased vigilance. Thereafter, assessment of LVEF should be evaluated at regular 3-month intervals during therapy, and this should be followed by LVEF assessment every 6 months for 2 years after completion of therapy. Trastuzumab should be held for at least 4 weeks if either there is a >15% decrease in LVEF from baseline or >10% decrease in LVEF from baseline to <50%. Resume trastuzumab within 4 to 8 weeks if LVEF

returns to normal and the absolute decreased from baseline is <15%. Consider permanent discontinuation of trastuzumab for a persistent (>8 weeks) LVEF decline or for suspension of trastuzumab on >3 occasions for cardiomyopathy (based on a discussion between cardiology and oncology).<sup>19</sup>

#### *Alkylating agents (eg, cyclophosphamide, ifosfamide, busulfan, mitomycin, and melphalan)*

Alkylating agents are a fundamental component of combination chemotherapy for the treatment of solid tumors, leukemias, and lymphomas.<sup>28</sup> It works by negatively affecting DNA transcription, therefore, resulting in protein production down-regulation.<sup>28</sup> The mechanism of cardiotoxicity is unknown, but the most accepted theory is endothelial layer injury causing leakage of potentially toxic metabolites into the myocardium, resulting in myocyte injury and capillary microthrombi promoting ischemia.<sup>29</sup> The incidence of symptomatic cardiomyopathy is around 22% and fatal cardiotoxicity is approximately 11%.<sup>29</sup> This cardiotoxicity is also dose dependent. A dose of around 180 to 200 mg/kg within a period of 2 to 4 days was associated with major risk. The dose based on body surface area is also a good predictor for cardiotoxicity: 1.5 g/m<sup>2</sup>/d or higher was associated with 25% risk for LV dysfunction.<sup>29</sup> Left ventricular dysfunction has been reported with ifosfamide at high dose exceeding 12.5 g/m<sup>2</sup>.<sup>30</sup>

#### *Taxanes (eg, paclitaxel and docetaxel)*

Antimicrotubule agents are used for the treatment of solid tumors (eg, breast adenocarcinoma, ovarian cancer, and head and neck tumors).<sup>31</sup> The mechanism of action involves interrupting cell division by binding to and inhibiting disassembly of microtubules.<sup>31</sup> The incidence of LV dysfunction with taxanes is 0.7%, which is comparatively low in comparison with other agents.<sup>32</sup> Taxanes increase the risk of anthracyclines cardiotoxicity by affecting their metabolism and excretion.<sup>33</sup> The combination of paclitaxel and high-dose anthracyclines increases the risk of LV dysfunction to 20%. Avoiding simultaneous administration of paclitaxel and doxorubicin minimizes cardiac dysfunction. Limiting the dose of doxorubicin to <360 mg/m<sup>2</sup> also reduces the risk.<sup>34</sup> Furthermore, taxanes have high incidence of cardiovascular reactions, including asymptomatic bradycardia (30%), ventricular arrhythmias (0.26%), and supraventricular tachycardia (0.24%).<sup>29</sup>

#### *Platinum-based therapies (eg, cisplatin, carboplatin, and oxaliplatin)*

A weak association had been described, but it is unclear whether a causal relation exists. Cisplatin-related cardiotoxicity might be related to electrolyte abnormalities secondary to cisplatin-induced nephrotoxicity. It could be manifested by hypertension, ischemic cardiomyopathy, myocardial infarction,



left bundle branch block, supraventricular tachycardia, and bradycardia.<sup>35,36</sup>

#### *Fluoropyrimidines (eg, FU and capecitabine)*

Fluorouracil is the third most used chemotherapy agent in solid malignancies, including head and neck, colon, and breast cancers.<sup>37</sup> Fluoropyrimidines have radiosensitizing properties and, therefore, are concurrently used with external beam RT.<sup>38</sup> Fluoropyrimidine-associated cardiomyopathy remains a poorly understood entity. The mechanism of toxicity is possibly explained by coronary vasospasm, which is supported by in vitro evidence of vasoconstriction by FU on vascular smooth muscle cells.<sup>39</sup> The incidence of FU cardiomyopathy ranges from 1% to 19%.<sup>40,41</sup> The presence of underlying CAD, RT, and anthracycline use increases the risk of cardiotoxicities. The most frequent cardiotoxicities include heart failure, angina with possible myocardial infarction, arrhythmias, cardiac arrest, pericarditis, and recently reported takotsubo cardiomyopathy. The risk of cardiotoxicity is also dependent on the route of administration and on the schedule. The risk is higher with infusion (2%-18%) as opposed to bolus regimens (1.6%-3%).<sup>38,40</sup>

Capecitabine is an orally available fluoropyrimidine that is metabolized to FU in tissues. Daily administration of capecitabine mimics continuous infusion of FU. The incidence of cardiotoxicity is 3% to 9%. The incidence increases to 12% when administered in combination with oxaliplatin.<sup>42</sup> Fluoropyrimidine cardiotoxicity tends to most commonly occur during the first cycle of administration and the median time to initiation of symptoms is 12 hours after infusion administration and as late as 48 hours.<sup>43</sup>

Cardiac symptoms usually resolve with discontinuation of FU and vasodilators.<sup>38</sup> The cardiotoxicity appears to be reversible after cessation of therapy.<sup>38</sup>

#### *Tyrosine kinase inhibitors (eg, dasatinib, imatinib, sorafenib, nilotinib, ponatinib, osimertinib)*

Tyrosine kinase inhibitors (TKIs) are selective for inhibiting tyrosine phosphorylation. There are currently more than 30 TKIs that are classified into 2 main classes: (1) small molecule TKIs (imatinib, sorafenib, dasatinib, sunitinib, nilotinib, etc) and (2) tyrosine kinase monoclonal antibodies (trastuzumab, rituximab, alemtuzumab, etc). Tyrosine kinase inhibitors were expected to be less toxic as they target specific proteins involved in cancer cell proliferation.<sup>44</sup> They are currently used in a wide array of malignancies including chronic myelogenous leukemia.<sup>45</sup>

Tyrosine kinase inhibitors have a large spectrum of cardiovascular toxicities including hypertension, acute coronary syndrome, heart failure, and arrhythmias with QT prolongation. The risk of cardiotoxicity is increased with previous cardiovascular history.<sup>44</sup> There are several mechanisms of

cardiotoxicities, which involve inhibiting angiogenesis by the vascular endothelial growth factor (VEGF) pathway and also by acting on erythroblastic leukemia viral oncogene B (commonly referred to as HER).<sup>44</sup> Hypertension incidence ranges from 15% to 47% with sunitinib and 17% to 42% with sorafenib. Left ventricular dysfunction is seen frequently among TKIs: sunitinib (2.7%-19%), sorafenib (4%-8%), pazopanib (7%-11%), imatinib (0.2%-2.7%), and lapatinib (0.2%-1.5%).<sup>44</sup>

#### *Bruton's TKIs (eg, ibrutinib)*

Ibrutinib is an inhibitor of Bruton's tyrosine kinase, which was approved for the treatment of mantle cell lymphoma, chronic lymphocytic leukemia, and Waldenstrom's macroglobulinemia.<sup>46</sup> The known significant cardiac events for this medication are hypertension, atrial fibrillation, atrial flutter, and ventricular tachyarrhythmias. As of now, there is only one case reported for new onset cardiomyopathy in a patient taking ibrutinib for relapsed mantle cell lymphoma.<sup>47</sup>

#### *VEGF signaling pathway inhibitors (eg, bevacizumab, aflibercept, ramucirumab, sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, and lenvatinib)*

Vascular endothelial growth factor signaling pathway inhibitors include small molecule TKIs and monoclonal antibodies. These agents used in solid tumors (eg colorectal cancer, renal cell carcinoma, and ovarian cancer)<sup>48</sup> work by inhibiting VEGF-mediated angiogenesis<sup>49</sup> and are known to cause hypertension, ischemia, and LV dysfunction.<sup>50</sup> The mechanism leading to cardiotoxicity might be related to microvascular dysfunction, adenosine triphosphate (ATP) depletion in the mitochondria, myocardial proapoptotic kinases, microvascular dysfunction, and profound vasoconstriction.<sup>51</sup>

Bevacizumab is associated with more than 4-fold increase in heart failure risk.<sup>52</sup> Around 14% of the patients receiving sunitinib experienced >10% decrease in ejection fraction.<sup>53</sup>

#### *Immune checkpoint inhibitors (eg, pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab, and ipilimumab)*

Immune checkpoint inhibitors (ICPis) are immunomodulatory antibodies used to enhance the immune system. They are used in multiple malignancies (melanoma, renal cell carcinoma, and non-small cell lung cancer) and substantially improve the prognosis for patients with advanced malignancy. Their primary targets are programmed cell death receptor 1 (PD-1, pembrolizumab, and nivolumab), programmed cell death ligand 1 (PD-L1, avelumab, atezolizumab, and durvalumab), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4, ipilimumab).<sup>54</sup>

There is a significant amount of fulminant cases of ICPi-related myocarditis. The incidence is unclear, but it has been reported to range from 0.06% to 1%.<sup>55</sup> In a recent study of 101 cases of ICPi-related myocarditis, the reported incidence is early on during monotherapy, and with increased with combination PD-1 and CTLA-4.<sup>56</sup>

The American Society of Clinical Oncology Clinical Practice Guideline recently published grading scale for organ involvement with ICPi. Myocarditis, pericarditis, arrhythmias, impaired ventricular function with heart failure, and vasculitis are graded as: G1 if there are abnormal cardiac biomarkers or ECG, G2 if there are abnormal screening tests with mild symptoms, G3 if moderately abnormal testing or symptoms with mild activity, and G4 if moderate to severe (including life-threatening). Different from other organ involvement, discontinuation of ICPi is recommended with G1 involvement and treatment with corticosteroids (1–2 mg/kg of prednisone oral or intravenous [IV] depending severity). Anecdotal use of pulse doses of methylprednisolone and the addition of antirejection therapy (mycophenolate, infliximab, or antithymocyte globulin) and mechanical circulatory support have been reported in fulminant and refractory cases.<sup>57</sup>

#### *Anaplastic lymphoma kinase inhibitors (eg, crizotinib and ceritinib)*

Crizotinib and ceritinib are inhibitors of the anaplastic lymphoma kinase (ALK) and are approved for the treatment of metastatic non-small cell lung cancer if the tumor contains a characteristic EML4-ALK fusion oncogene. Anaplastic lymphoma kinase inhibitors are associated with profound sinus bradycardia and prolongation of the QT interval and therefore should be avoided in patients on atrioventricular (AV) nodal blockers.<sup>58,59</sup>

#### *Proteasome inhibitors (eg, bortezomib and carfilzomib)*

Proteasome inhibitors are approved for the treatment of mantle cell lymphoma and multiple myeloma. They target the 26S and 20S proteasome leading to apoptosis of the affected cells. Bortezomib forms reversible stable interactions with the chymotrypsin-like site of the complex, whereas carfilzomib is irreversible. Malignant plasma cells have very high rates of proteasome activity making it great targets, but unfortunately, cardiac myocytes also have high rates of proteasome activity and protein turnover. Their mechanism to cardiotoxicity is through apoptosis.<sup>60</sup> There are conflicting data regarding cardiotoxicity in patients on bortezomib. One meta-analysis of the 5718 subjects demonstrated that there was no increased risk of cardiotoxicity,<sup>61</sup> whereas reports suggest otherwise.<sup>62,63</sup> As carfilzomib forms irreversible interactions, its risk of cardiomyopathy is higher. In the landmark ASPIRE trial, 3.8% of the patients developed cardiomyopathy compared with 1.8% in the control

group, as well as higher rate of uncontrolled hypertension in the carfilzomib group (4.3%) vs controls (1.8%).<sup>64</sup>

### **Radiation Therapy**

Radiation therapy is an effective adjuvant therapy in many malignancies. In fact, more than 50% of the cancer patients undergo RT. Exposure to radiation causes damage to DNA interfering with cell proliferation. Malignant cells have high proliferation rates, therefore, making them susceptible to RT.<sup>65</sup> Cardiac myocytes are relatively resistant to radiation damage because of their post-mitotic state. However, cardiac endothelial cells remain sensitive to radiation, and the pathophysiology of most forms of radiation-induced cardiovascular disease appears to be associated with damage to endothelial cells.<sup>66</sup>

Cardiovascular complications from thoracic RT include: (1) CAD (microvascular injury with accelerated atherosclerosis), (2) valvular disease (leaflet fibrosis, thickening, and calcification), (3) pericardial disease (increased pericardial permeability with consequent adhesions and thickening), (4) cardiomyopathy (diffuse myocardial interstitial fibrosis and restrictive cardiomyopathy), and (5) conduction system disease (direct radiation to the conduction system or from ischemia).<sup>67</sup> These cardiovascular complications might manifest from 5 years to as long as 20 to 30 years after initial exposure.<sup>68</sup>

Cardiotoxicity secondary to radiation is dependent on dose, volume of body area exposed, location of exposure, and adjuvant therapies. Hodgkin lymphoma survivors who received mediastinal radiotherapy and breast cancer survivors who received left-sided chest radiation along with anthracyclines are at particularly high risk.<sup>69</sup> The ASCO classifies at increased risk of developing cardiac dysfunction those who receive high-dose radiotherapy (RT > 30 Gy) where the heart is contained within the treatment field.<sup>19</sup>

### **Biomarkers and Cardiotoxicity**

#### *Troponins*

Cardinale et al<sup>70</sup> conducted one of the initial studies correlating elevation in troponins and LV dysfunction. Patients who had elevated troponins had decreased ejection fraction on follow-up echocardiograms. Inversely, patients with negative troponins had better outcomes and, therefore, established good sensitivity and specificity for CTRCD. Four years later, a new study by the same author showed that 22.6% of the patients had at least a 15% decrease in ejection fraction. Among this group, 59.1% had increased troponin levels. The study demonstrated a negative predictive value of 99% and a positive predictive value of 84%.<sup>71</sup> In a recent study, troponin was abnormal in 94% of the patients with ICPi myocarditis and discharge troponin T of >1.5 ng/mL was associated with a 4-fold increased risk of major adverse cardiovascular events, which makes troponin a crucial biomarker to screen for this type of myocarditis and reasonable predictor of adverse events.<sup>72</sup> Current evidence suggests troponin evaluation before initiation of anthracycline

therapy, for patients receiving  $> 250 \text{ mg/m}^2$  of doxorubicin, screening should occur after every  $50 \text{ mg/m}^2$ , at completion of therapy, and 6 months later.<sup>3</sup>

### *Brain natriuretic peptide*

The role of brain natriuretic peptide (BNP) and NT-pro-BNP as biomarkers for CTRCD is unclear. It is a less sensitive biomarker of CTRCD and more of a marker of subclinical LV dysfunction in asymptomatic patients. Brain natriuretic peptide increase correlated with decline in LVEF but change in BNP did not precede deterioration of LVEF.<sup>73</sup> Lipshultz et al<sup>74</sup> demonstrated the correlation between elevated BNP levels and subsequent LV dysfunction in patients on doxorubicin treatment. On the contrary, another study by Sawaya et al<sup>75</sup> failed to prove this association.

### *Novel biomarkers*

Higher levels of high-sensitivity C-reactive protein, interleukin 6, fatty acid-binding protein, and neuregulin-1 have independently been correlated with a greater decline in LVEF with exposure to anthracyclines. Further studies are required before establishment of clear recommendations.<sup>76</sup>

## **Imaging**

### *Echocardiography*

Echocardiography is the mainstay modality for the assessment of cardiac function in oncology patients because of its widespread availability, reproducibility, and lack of radiation exposure.<sup>3</sup> It is the first-line screening tool to assess cardiac function in this patient population.<sup>3</sup> As per the ASE, accurate calculation of LVEF should be done with the best method available in the echocardiography laboratory (ideally 3D echocardiography) and when using 2D echocardiography, the method of choice is the modified biplane Simpson's technique. Certainly, 3D echocardiography has shown to be more accurate with an error  $< 5\%$  when compared with Simpson's technique, which has shown 10% variation in LVEF calculation.<sup>77</sup> A study published in 2016 showed that 3D echocardiogram was comparable with cardiac magnetic resonance imaging (MRI) for the detection of subclinical myocardial dysfunction.<sup>78</sup>

More recent studies have shown that strain and speckle tracking allows earlier detection of more subtle changes in myocardial function. GLS reduction anticipates myocardial dysfunction. A change in GLS of  $> 11\%$  was the strongest predictor of cardiotoxicity in patients receiving trastuzumab alone or with anthracyclines.<sup>79</sup> A GLS of less than  $-17.5\%$  before starting anthracycline therapy was linked to a 6-fold higher risk for cardiac events and may tailor treatments to decrease CTRCD.<sup>80</sup> A reduction in GLS less than  $-19\%$  at the end of breast cancer therapy anticipated CTRCD.<sup>75</sup> This technique is limited by the lack of universal definitions, availability, image quality, and variability of quantification between vendors.

### *Cardiac magnetic resonance imaging*

Cardiac magnetic resonance imaging (CMR) is the gold standard to evaluate cardiac function. Its advantages include lack of ionizing radiation, flexible scanning planes, LV/RV functional determination, LV/RV volume/mass, true 3D volumetric coverage, and excellent discrimination of the endocardial/epicardial borders.<sup>3</sup> CMR detects early changes in tissue damage after chemotherapy (inflammation, edema, changes in LV strain, and changes in LV mass).<sup>81</sup> LV mass index is an independent predictor of major adverse cardiac events in patients with anthracycline-induced cardiomyopathy.<sup>82</sup>

### *Multiple-gated acquisition scan*

In the past, multiple-gated acquisition scan (MUGA) was the mainstay modality for the assessment of cardiac function in oncology patients<sup>83</sup> due to its availability and excellent reproducibility.<sup>84</sup> However, the exposure to radiation ( $\sim 5\text{--}10 \text{ mSv/scan}$ ) is a major concern. In patients undergoing serial assessments, such as patients receiving MUGAs before trastuzumab therapy and once every 3 months as established by the Dutch Guidelines for breast cancer, could receive a cumulative radiation exposure of  $\sim 25$  to  $50 \text{ mSv}$  per year, which is comparable to 4 to 8 CT angiography procedures and 250 to 500 chest radiographs.<sup>85</sup> Unfortunately, MUGA can only provide a LVEF, which is less sensitive for early detection of CTRCD.

## **Pharmacological Prevention**

All patients exposed to cardiotoxins should be treated as if they were American Heart Association (AHA) heart failure stage A—patients at high risk for heart failure but without structural heart disease. Many different preventive strategies have been proposed, which include primordial prevention (initiation of cardioprotective medications after the diagnosis of cancer) and primary prevention (initiation of medical therapy with cancer treatment in patients with cardiovascular risk factors and increased risk for CTRCD).<sup>86</sup>

### *Beta blockers*

There is evidence of the cardioprotective role of beta blockers in the prevention of anthracycline cardiotoxicity. Carvedilol is a beta-adrenergic receptor antagonist with strong antioxidant properties and abilities to chelate iron, proven against doxorubicin-induced mitochondrial-mediated cardiotoxicity.<sup>87</sup> The Carvedilol for Prevention of Chemotherapy-related Cardiotoxicity (CECCY) trial demonstrated that anthracycline-based chemotherapy in patients with invasive breast cancer, carvedilol, was not effective in preventing a reduction in LVEF but it was associated with a lower frequency of detectable troponin I values and abnormal diastolic dysfunction.<sup>88</sup> The study was underpowered to be able to detect a difference in outcomes between treatment groups. Nebivolol at the initiation of anthracyclines was also associated with a higher degree



of LV function preservation.<sup>89</sup> Metoprolol had a marginal benefit in a single study,<sup>90</sup> whereas propranolol was found to be cardiotoxic in this setting.<sup>91</sup> The use of beta blockers during anthracycline and trastuzumab regimen was associated with a decreased incidence of LV dysfunction over a 5-year period.<sup>92</sup>

#### *Renin angiotensin inhibitors and aldosterone antagonist therapy*

Enalapril treatment a week before anthracycline was administered and continued for about a month after the last dose prevented mitochondrial dysfunction and downregulated the generation of free radicals.<sup>93</sup> Using enalapril after troponin I elevation in patients on anthracycline therapy prevented cardiotoxicity.<sup>94</sup> Aldosterone antagonists might attenuate trastuzumab-induced cardiomyopathy through inhibition of the epidermal growth factor receptor (EGFR).<sup>95</sup> A recent study suggested that the administration of spironolactone during anthracycline chemotherapy demonstrated an antioxidative effect, protected the myocardium against anthracycline-related myocardial damage, consequently preserving both myocardial systolic and diastolic functions.<sup>96</sup>

#### *Combination therapy*

The Multidisciplinary Approach to Novel Therapies in Cardio-oncology Research (MANTICORE) trial evaluated the combined use of bisoprolol and perindopril in patients receiving trastuzumab. It showed that the combination therapy could prevent CRCD but did not prevent LV remodeling, which was the primary endpoint of the study.<sup>97</sup> The prevention of left Ventricular dysfunction with Enalapril and carvedilol in patients submitted to intensive Chemotherapy for the treatment of Malignant Hemopathies (OVERCOME) trial used a combination of enalapril and carvedilol in patients with leukemia or those planned for stem cell transplantation and demonstrated that patients on combination therapy had no reduction in LV function and lower incidence of death compared with placebo.<sup>98</sup> The Prevention of Cardiac Dysfunction during an Adjuvant Breast Cancer Therapy (PRADA) trial showed that candesartan prevented a modest short-term decline in LV function during anthracycline therapy for breast cancer.<sup>99</sup>

#### *Dexrazoxane*

It is a derivative of the metal chelating agent ethylenediaminetetraacetic acid (EDTA). Dexrazoxane decreases anthracycline-related cardiac dysfunction through iron chelation and by decreasing the production of free radicals. In addition, it binds to topoisomerase 2, preventing anthracycline complexes.<sup>100</sup> The ASCO recommends dexrazoxane use only in patients with metastatic breast cancer and other malignancies who have received >300 mg/m<sup>2</sup> and who might benefit of additional anthracycline use.<sup>101</sup> In patients treated with anthracyclines,

dexrazoxane decreases cardiac event-free survival and decreases LV dysfunction risk. There has been concern that this agent may attenuate doxorubicin anti-tumor activity but a Cochrane review demonstrated no difference in efficacy against the primary malignancy with the addition of dexrazoxane.<sup>14</sup>

#### *Statins*

Statins exert cardioprotective effects through pleiotropic mechanism. In patients without preexisting cardiovascular disease, prophylactic atorvastatin led to an increased preservation of the LV systolic function.<sup>102</sup> Studies suggest the benefit of statins in reducing anthracycline-mediated cardiomyocyte death.<sup>103</sup>

#### **Future Direction**

Human-induced pluripotent stem cells (hiPSCs) have made it conceivable to experimentally validate the hypothesis that certain drug-induced cardiovascular adverse events are genetically determined. Human-induced pluripotent stem cells are uniquely suitable for pharmacogenomics research as they are genetically identical to the patients from whom they are derived and can be obtained non-invasively. Therefore, this technology is exceptionally suited to investigate the pharmacogenomics of chemotherapy-induced adverse cardiovascular effects, potentially could identify toxicities, mechanism of toxicities, and both to identify and validate causal genetic variants that contribute to such toxicities.<sup>104</sup>

#### **Conclusions**

Cancer therapy-related cardiac dysfunction affects an increasing population of oncology patients. It can be classified as direct (dose-dependent vs dose-independent) or indirect, either case being potentially permanent or reversible. Risk assessment, recognition, and prevention of CTRCD are crucial.

Traditional cardiac risk factors, as well as therapy-related risk factors, may be predictive of CTRCD. Anthracyclines, alkylating agents, HER-2 inhibitors, taxanes, and fluoropyrimidines are traditional cancer therapies with the risk of cardiotoxicity, with more targeted therapies including TKIs and immunotherapy more recently being described as culprits.

Troponin assessment has been shown to be of high negative predictive value and positive predictive value for CTRCD. Although cardiac MRI is the gold standard to evaluate cardiac function, echocardiography is the first-line screening tool and may be of greater value when GLS and 3D echocardiography for EF are used.

We recommend screening all patients before starting cancer therapeutics with the potential for cardiac dysfunction with an electrocardiogram, troponin level, and LV function assessment with an echocardiogram including GLS, echo contrast, and, if possible, 3D EF.

Beta-blockers, renin angiotensin inhibitors, aldosterone antagonist therapy, and statins can preserve LV systolic function in patients at risk. Dexrazoxane in patients who are



planned to exceed the recommended cumulative dose of anthracyclines and steroids in the event of immunotherapy-related cardiac dysfunction are important cancer therapy-specific considerations.

Finally, we propose an additional classification including a new set of mechanisms in which cancer patients may suffer cardiovascular injury.

### Author Contributions

IP, ST, GH, and RS conceived and designed this review article. IP and GH analyzed the data and reviewed the literature.

IP wrote the first draft of the manuscript. IP, GH, ST, and RS contributed to the writing of the manuscript. IP, ST, GH, and RS agree with manuscript results and conclusions. IP, ST, GH, and RS jointly developed the structure and arguments for the paper. IP, ST, GH, and RS made critical revisions and approved final version. All authors reviewed and approved of the final manuscript.

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