Myocardial Protection During Cardiotoxic Chemotherapy

Ronald M. Witteles, MD; Xavier Bosch, MD, PhD

Over the last 20 years, the development of effective screening and treatment strategies has resulted in a 20% decline in cancer mortality, translating to an absolute increase of almost 1 400,000 cancer survivors in the United States. Currently, it is estimated that 60% of adults newly diagnosed with cancer will be alive 5 years later. The price to be paid for such success has varied from overt treatment toxicities (eg, bone marrow suppression) to toxicities that became obvious only with the passage of time (eg, secondary malignancies). Although cardiac complications of chemotherapy first rose to the forefront with the recognition in the 1970s of overt clinical heart failure (HF) in patients receiving anthracycline-based chemotherapy, it took several decades for the full scope of toxicity to be truly appreciated.

As cancer therapeutics have advanced, 3 points have become clear. First, cardiovascular toxicity is a widespread problem across many classes of cancer therapies. Second, it is critical to learn how to best monitor for, prevent, and treat cardiac complications of cancer therapy both to lower morbidity and mortality from the cardiac toxicity itself and to allow patients to receive their potentially life-saving/life-prolonging/palliative chemotherapy. This represents the concept of cardioprotection. Third, this is a field that at its very core is multidisciplinary, requiring the close collaboration of cardiologists and oncologists. The purpose of this article is to review the state-of-the-art evidence and to recommended practices to best protect patients against and treat patients with cardiac complications of chemotherapy with a focus on myocardial toxicity.

Mechanisms of Cardiotoxicity

A full review of the mechanisms of toxicity is beyond the scope of this article; however, a working understanding of the basic mechanisms yields important information about potential treatment strategies and the potential for myocardial recovery. Many antineoplastic drugs with broadly different mechanisms of action have cardiotoxic effects. These effects are often divided into 2 categories, depending on the reversibility of myocardial damage: Type I agents (eg, anthracyclines) cause direct cell death, leading to irreversible damage, and type II agents (eg, trastuzumab) cause ventricular dysfunction, which is reversible once the drug is withdrawn. Although the mechanisms and outcomes of cardiac toxicity from these medication classes clearly differ, caution must be used with these terms, which carry the implication that type II toxicity is regularly reversible and without long-term sequelae, a finding not consistently supported by clinical trial evidence.

For many years, anthracycline cardiotoxicity had been attributed primarily to the creation of oxygen free radicals causing oxidative stress. However, important recent research has revealed that the mechanism for anthracycline cardiotoxicity is based on DNA damage caused by disruption of the normal catalytic cycle of topoisomerase 2β, causing DNA double-strand breaks and activation of apoptosis, as well as changes in the transcriptome, leading to mitochondrial dysfunction and generation of reactive oxygen species. As discussed below, this new understanding suggests important potential therapeutic routes to pursue that may be able to limit cardiac damage while maintaining antineoplastic efficacy. Although anthracycline toxicity has often been described as acute (hours or days), early (weeks to months), and late (years), it is likely that all of the true toxicity from anthracyclines occurs close to the time of administration, with the differences merely reflecting when the toxicity was recognized and, in the case of late toxicity, reflecting gradual remodeling of the ventricle over time.

The primary mechanism of cardiac toxicity of trastuzumab occurs via blocking the ErbB2 (also known as Her2) pathway. This pathway normally acts as a response/repair mechanism to a broad range of myocardial injury. Administration of trastuzumab blocks the ErbB2 receptor, leading to potential myocardial injury via disruption of repair mechanisms. Myocardial trastuzumab uptake is particularly common shortly after anthracycline administration, providing mechanistic evidence to support the clinical observation of the high rates of cardiotoxicity when these agents are used in close temporal relationship to one another. Contrary to anthracyclines, no structural changes are observed in trastuzumab cardiotoxicity. The mechanisms of tyrosine kinase (TK) inhibitor (TKI) toxicity are likely manifold, depending on what portion of the kinome is inhibited with a given agent, with most of them targeting several TK receptors. There is likely a combination effect of increased vascular resistance with vascular endothelial growth factor (VEGF) inhibitors, along with a direct toxic myopathy.

Incidence

Table 1 summarizes the incidence of the most important cardiotoxicities caused by current chemotherapy. Hypertension is the most frequent comorbidity in cancer patients, may...
appear any time during therapy (especially when VEGF inhibitors are administered), and likely contributes to left ventricular (LV) injury, LV systolic dysfunction (LVSD), and HF. Incidence varies widely in clinical trials, likely as a result of differences in the patient population being studied and the methodology of collecting adverse event information. An 11% to 16% incidence of hypertension with sunitinib was reported in 2 trials, but the incidence was >50% when examined in real-world patients in other studies. Combined treatment with bevacizumab and sunitinib or sorafenib increases the risk of hypertension to 67% and 92%, respectively.

Cancer induces a prothrombotic state, especially in patients with metastatic disease, and the risk of thrombosis is increased in patients with known risk factors such as advanced age, immobility, and infection. Chemotherapy can further increase the risk by damaging the endothelium and the vessel walls, decreasing coagulation inhibitors, and enhancing platelet activation. Angiogenesis inhibitors such as bevacizumab, thalidomide, and lenalidomide inhibit the VEGF-induced association between cadherin 5, CD31, and β-catenin and are known to be associated with thrombosis (Table 1).

The incidence of chemotherapy-associated myocardial ischemia is not known because it has usually been based

Table 1. Incidence of Cardiotoxicity in Selected Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Class/Drug</th>
<th>Selected Indication</th>
<th>HF</th>
<th>Hypertension</th>
<th>Myocardial Ischemia</th>
<th>Thromboembolism</th>
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<td>Anthracyclines</td>
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<tr>
<td>Doxorubicin</td>
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<td></td>
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<td>Epirubicin</td>
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<td></td>
<td></td>
</tr>
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<td>Idarubicin</td>
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<td>Rare</td>
<td>Rare</td>
<td></td>
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<td>...</td>
<td>...</td>
<td>Very rare</td>
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<td>...</td>
<td>Common</td>
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<td>...</td>
<td>...</td>
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<td>...</td>
<td>Rare</td>
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<td>Rare</td>
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<td>5-Fluorouracil</td>
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<td>...</td>
<td>Very common</td>
<td>...</td>
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<td>Capecitabine</td>
<td>Colorectal, breast</td>
<td>...</td>
<td>...</td>
<td>Common</td>
<td>Rare</td>
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<td>Hormone therapies</td>
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<td>Very common</td>
<td>Very rare</td>
<td>Rare</td>
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<td></td>
<td></td>
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<td>targeted therapies</td>
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<td>Trastuzumab</td>
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<td>Very common</td>
<td>Rare</td>
<td>Very common</td>
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<td>Small molecule–targeted</td>
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<td>therapies</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Imatinib</td>
<td>Leukemia, GIST</td>
<td>Rare</td>
<td>...</td>
<td>Rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Leukemia, GIST</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
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<tr>
<td>Sunitinib</td>
<td>RCC, HCC</td>
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<td>Very common</td>
<td>Rare</td>
<td>Rare</td>
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<td>...</td>
<td>...</td>
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<td>Nilotinib</td>
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<td>Rare</td>
<td>Very common</td>
<td>Very common</td>
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<tr>
<td>Ponatinib</td>
<td>Leukemia</td>
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<td>Rare</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Multiple myeloma</td>
<td>Rare</td>
<td>Very rare</td>
<td>Very rare</td>
<td>Very rare</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>RCC</td>
<td>Common</td>
<td>Very common</td>
<td>...</td>
<td>Very rare</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>RCC</td>
<td>Common</td>
<td>Very common</td>
<td>Very common</td>
<td>Rare</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Multiple myeloma</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
<td>Very common</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Multiple myeloma</td>
<td>Rare</td>
<td>Rare</td>
<td>Common</td>
<td>Very common</td>
</tr>
</tbody>
</table>

GIST indicates gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HF, heart failure; RCC, renal cell carcinoma; ..., not well-established complication or unknown; very rare, <1%; rare, 1% to 5%; common, 6% to 10%; and very common, >10%.
on symptoms or repolarization abnormalities on the ECG. 5-Fluorouracil and its prodrug capecitabine can cause vaso-spasm-induced chest pain,\textsuperscript{19,20} with a rarer incidence for paclitaxel, tamoxifen, and first-generation TKIs.\textsuperscript{11} The risk of cardiovascular ischemic events for some second-generation TKIs is alarmingly high. Nilotinib has been associated with accelerated atherosclerosis and peripheral vascular events in 36% of patients.\textsuperscript{21} Ponatinib induced serious arterial thrombotic events in 24% of patients at a median of 1.3 years of follow-up, including severe arterial stenoses of the heart, brain, and extremities. These events increased to 48% at 2.7 years, occurred even in young patients and in patients without coronary risk factors, and prompted the US Food and Drug Administration to restrict the indication of this drug to patients with T315I mutations or in those for whom all other TKIs have failed.\textsuperscript{22}

Cisplatin can activate the arachidonic acid pathway in platelets, enhance thromboxane formation, and induce platelet aggregation, and it has been found to cause arterial and venous thromboembolism in up to 18% of patients.\textsuperscript{23} Angiogenesis inhibitors are also associated with a high risk of venous thromboembolism\textsuperscript{24} (Table 1).

### Myocardial Toxicity

The risk of cardiotoxicity with anthracyclines increases with cumulative doses, but there is not a safe dose below which cardiotoxicity is avoided.\textsuperscript{25} Other risk factors include genetic predisposition, extremes of young/old age, female sex, pre-existing cardiovascular disease, hypertension, mediastinal radiation therapy, and combination with other cardiotoxic agents.\textsuperscript{2,26,32} The risk of trastuzumab-induced cardiotoxicity increases with advanced age, previous treatment with anti-hypertensive medication, baseline reductions in LV ejection fraction (LVEF), and the concomitant administration of anthracyclines.\textsuperscript{2,5,8,33}

Much of the confusion surrounding the cardiac toxicity of cancer therapies has arisen from the multitude of definitions used.\textsuperscript{27} The Common Terminology Criteria for Adverse Events,\textsuperscript{34} used in cancer trials, was created to ensure consistency in adverse event reporting and graded on a scale of 1 to 5, with grade 3 or greater (symptomatic, life-threatening, or death) often used in publications and product labels as a threshold of reporting. This categorization is inherently prone to undergrading toxicity for conditions in which adverse outcomes are not dependent on symptom development (as is the case for severe LVEF drops). In addition, there is considerable overlap of terms for cardiac toxicity in Common Terminology Criteria for Adverse Events; the same adverse event could be graded in very different manners by different investigators\textsuperscript{27} (Figure 1). Part of the confusion also arises from the difference between an adverse event and a treatment-related adverse event. Treatment-related adverse events are coded by the investigators on the basis of the perceived likelihood that the event was treatment related, and there is potential to misattribute unexpected adverse events such as LVSD. Finally, trials often emphasize severely symptomatic cardiac events, thus not including even large asymptomatic LVEF declines. Relying on symptoms as a major arbiter of the importance of cardiotoxicity can be a particular problem because many of the signs and symptoms of HF (eg, fatigue, edema, dyspnea) are nonspecific and can easily be misattributed to noncardiac side effects of cancer therapy or to the effects of the malignancy itself.

### Anthracyclines

The US Food and Drug Administration–based doxorubicin label specifically states that “The probability of developing impaired myocardial function…is estimated to be 1 to 2% at a total cumulative dose of 300 mg/m\textsuperscript{2} of doxorubicin, 3 to 5% at a dose of 400 mg/m\textsuperscript{2}, 5 to 8% at a dose of 450 mg/m\textsuperscript{2}, and 6 to 20% at a dose of 500 mg/m\textsuperscript{2}.”\textsuperscript{28} However, these rates appear to be underestimated. In a study of 630 patients that used frequent LVEF monitoring,\textsuperscript{29} significant LVEF drops were seen at rates of 8.8% at 250 mg/m\textsuperscript{2}, 16.2% at 300 mg/m\textsuperscript{2}, 32.4% at 400

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>-</td>
<td>Asymptomatic with laboratory (e.g. BNP) or cardiac imaging abnormalities</td>
<td>Symptoms with mild to moderate activity or exertion</td>
<td>Severe with symptoms at rest or with minimal activity or exertion; intervention indicated</td>
<td>Life-threatening consequences; urgent intervention necessary</td>
</tr>
<tr>
<td>Left ventricular systolic dysfunction</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Symptomatic due to drop in ejection fraction responsive to intervention</td>
<td>Refractory or poorly controlled heart failure due to drop in ejection fraction</td>
</tr>
<tr>
<td>Ejection fraction decreased</td>
<td>-</td>
<td>-</td>
<td>Resting EF 40-50%, 10-19% drop from baseline</td>
<td>Resting EF 20-39% &lt;20% drop from baseline</td>
<td>Resting EF &lt;25%</td>
</tr>
</tbody>
</table>

Figure 1. Example demonstrating how the same event could be graded vastly differently with the use of adverse event terms from Common Terminology Criteria for Adverse Events version 4.03.\textsuperscript{24} A patient with an asymptomatic left ventricular ejection fraction (EF) drop from 60% to 35% may be graded as grade 0 (no event reported), grade 1, or grade 3 toxicity, depending on which adverse event term is used. BNP indicates brain natriuretic peptide.
has low sensitivity for the detection of early cardiac damage.\textsuperscript{25} In addition, this measure depends on preload and afterload, conditions that usually change during early treatment, and has marked intraobserver and interobserver variability.

Because LV diastolic dysfunction precedes LVSD after myocardial injury, echo-Doppler parameters of LV diastolic function may be more sensitive to detect early cardiotoxicity. However, these parameters are load dependent, the ideal assessment time has not been established, and early findings were not compared with late occurrence of HF. Tissue Doppler imaging–derived parameters such as strain and strain rate are more sensitive markers of LV function and are less dependent on loading conditions. Several studies have reported that these measurements detect early myocardial dysfunction in patients with normal LVEF and have high sensitivity but low specificity for the prediction of future LVSD.\textsuperscript{36} Two-dimensional speckle-tracking strain echocardiography has been reported in small series of patients to have less variability and good sensitivity for predicting future LVEF declines,\textsuperscript{37,38} especially with the use of peak systolic global longitudinal strain.\textsuperscript{36}

Cardiovascular magnetic resonance imaging is the gold standard to measure LVEF and to detect myocardial fibrosis. Although small studies in patients treated with chemotherapy have reported good potential for the early detection of cardiac injury, no study has reported the predictive value for HF,\textsuperscript{36} and the cost and limited availability of cardiovascular magnetic resonance imaging likely limit its broad application.

**Biomarkers**

One attractive option for the detection of cardiac toxicity is biomarker screening. Potential advantages include the ease of conducting the screening and the possibility of earlier detection of myocardial injury than with imaging. Of the various biomarker approaches that have been explored, troponin monitoring has the most evidence.

In a study of children with acute lymphoblastic leukemia, positive troponin T levels during doxorubicin treatment did not predict LVSD at a median of 3 years of follow-up\textsuperscript{39} but correlated with long-term changes in echocardiographic assessment of myocardial structure.\textsuperscript{40} Cardinale et al\textsuperscript{41} investigated the role of troponin monitoring for predominantly anthracycline-based or high-dose chemotherapy. In the most prominent study, elevation of troponin I occurred in 30% of patients, and the rate of cardiac events (mostly symptomatic HF and large asymptomatic LVEF drops of at least 25% from baseline) was 1% in the troponin-negative group, 37% in the group with initial troponin elevation but normalization at 1 month, and 84% in the group with a persistent troponin elevation. The same group reported similar findings in patients treated with trastuzumab. Troponin rises almost always occurred prior to trastuzumab invitation or very early during trastuzumab therapy, supportive of the theory that troponin rises mainly reflected anthracycline effects rather than direct effects from the trastuzumab itself. Nevertheless, troponin elevations remained predictive of outcomes in their cohort, with patients with positive troponin having a 62% incidence of a significant LVEF drop compared with 5% in patients with negative troponins.\textsuperscript{42}

Other authors have found less impressive findings.\textsuperscript{35,37,38,43} Limitations of the Cardinale et al\textsuperscript{41,42} studies include the

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**Detection of Early Myocardial Injury Imaging Techniques**

Currently, the most frequently used method to detect LVSD is the serial measurement of LVEF by echocardiography or multigated acquisition scanning. However, this measurement

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**Trastuzumab**

The initial use of trastuzumab was associated with a 16% incidence of severe New York Heart Association class III to IV HF when administered concomitantly with anthracyclines.\textsuperscript{31} In later studies in which trastuzumab was administered after the completion of anthracycline administration, rates were much lower, but trastuzumab was still permanently discontinued in 14.2% of patients for an asymptomatic decline in LVEF and in another 4.7% of patients for symptomatic HF or other adverse cardiac effects.\textsuperscript{30} In contrast, the Herceptin Adjuvant (HERA) trial reported only a 4.3% discontinuation rate for cardiotoxicity and a 3.64% incidence of symptomatic HF or LVEF drop. The difference in rates between the trials is likely attributable to the fact that HERA had a longer delay between the end of chemotherapy and the start of trastuzumab, required a high LVEF threshold to enter, and required a confirmatory LVEF assessment 3 weeks after the assessment that originally showed a drop.\textsuperscript{9}

An increasingly used trastuzumab-based regimen of docetaxel, carboplatin, and trastuzumab has been popularized largely because of the lack of anthracycline administration. In a trial comparing an anthracycline/trastuzumab–based strategy with docetaxel, carboplatin, and trastuzumab, there was a nonsignificant trend toward decreased breast cancer recurrences in the anthracycline arm, but at the cost of considerably more cardiotoxicity, with significantly higher rates of sustained, subclinical LVEF declines compared with the docetaxel, carboplatin, and trastuzumab arm (18.6% versus 9.4%).\textsuperscript{4}

**Tyrosine Kinase Inhibitors**

The largest growth in cancer therapeutics over the last decade has been the development of TKIs and VEGF inhibitors. A true estimate of myocardial toxicity of these agents has been severely limited by the lack of standardization in screening for LVEF reductions.\textsuperscript{27} A recent analysis of TKIs used for metastatic renal cell carcinoma found high rates of cardiovascular toxicity with a wide variety of agents when a prospective screening protocol was used.\textsuperscript{15} Specifically, with the use of the definitions for toxicity in Common Terminology Criteria for Adverse Events version 4.0, 73% of patients developed cardiovascular toxicity, including 33% of patients when hypertension was excluded.

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**mg/m\textsuperscript{2}, and 53.9% at 500 mg/m\textsuperscript{2}, close to a full order of magnitude higher than what is reported on the doxorubicin label. Two adjuvant breast cancer studies found similar results, with a 7.6% incidence of LVSD (148 of 1936 evaluable patients) after 240 mg/m\textsuperscript{2} doxorubicin.\textsuperscript{30} It is estimated that more than half of all patients exposed to anthracyclines will develop abnormalities of cardiac structure and function within the following 6 years; they are 5 times more likely to develop HF or LVSD than patients not treated with these drugs.**
multiple repeated troponin measurements obtained at baseline and after each cycle of chemotherapy with only the highest troponin value considered during a 3-month intensive treatment period and LVEF evaluation performed many times during follow-up. This intensity of monitoring would be impractical in most patient scenarios, particularly outside the high-dose chemotherapy subset, and the multiple sampling with repeated outcome measures is prone to bias in a non-blinded study. Finally, the predictive value of troponins has not been validated with other non-anthracycline-containing regimens, and the time point at which a troponin value reaches optimal predictive value has not been defined.

The recent finding of a key role of topoisomerase 2β in the cardiotoxicity of doxorubicin may open new possibilities for anthracycline cardioprotection. Patients with higher expression of topoisomerase 2β in cardiomyocytes may be more susceptible to doxorubicin-induced cardiotoxicity, and the measurement of circulating levels of topoisomerase 2β might predict susceptibility to anthracycline-induced cardiotoxicity. Neuregulins are growth factors that promote cell survival and growth via activation of their ErbB receptors. Since neuregulin-1/ErbB receptors-deficient mice have increased susceptibility to anthracycline-induced injury, measurement of circulating neuregulin-1β and ErbB2 has potential application for early risk stratification.

Primary Prevention Measures

Because the administration of potentially cardiotoxic chemotherapy is a risk factor for the development of HF, treated patients are currently considered to be in stage A HF. Accordingly, primary prevention includes all pharmacological and nonpharmacological measures to prevent stage B HF, whereas secondary prevention applies to interventions for stage B and beyond.

Genetic Testing

Genetic factors may explain in part the observed differences in the incidence of cardiac toxicity with different chemotherapy regimens by affecting individual susceptibility. Studies have identified common polymorphisms in genes involved in anthracycline absorption, distribution, metabolism, and elimination that have an impact on the risk of anthracycline-induced HF.

Although topoisomerase 2β is the primary mediator for anthracycline-induced toxicity, other mechanisms such as iron accumulation may increase the reactive oxygen species response. Therefore, patients with higher tissue iron concentrations may potentially have a higher risk of myocardial toxicity. Genetic mutations in the C282Y allele of the HFE gene associated with hereditary hemochromatosis have recently been reported to be associated with a 9-fold higher risk of myocardial injury in children with high-risk lymphoblastic leukemia treated with doxorubicin. Large, prospective studies are needed to validate these initial results.

Modifying Chemotherapy Administration

Several studies have investigated strategies designed to decrease the cardiotoxicity of anthracyclines and trastuzumab, including changes in the dose, the pharmacological structure, and the schedule of chemotherapy administration.

Dose limitation of anthracyclines has been adopted in almost all protocols. Modifying the structure of the drugs to improve their therapeutic and pharmacological properties is a common strategy. Epirubicin, idarubicin, and mitoxantrone are anthracycline analogs that are potentially less cardiotoxic than doxorubicin. A cumulative dose of 900 mg/m² epirubicin is believed to be equivalent to 600 mg/m² doxorubicin in efficacy but to 450 mg/m² in cardiotoxicity. A meta-analysis of 13 trials found significant differences in the incidence of HF between epirubicin and doxorubicin, although with wide confidence intervals. In the future, the development of anthracycline analogs that specifically target the topoisomerase 2α isoenzyme (rather than topoisomerase 2β) may have the potential to be less cardiotoxic. The recent finding that an engineered bivalent neuregulin-1β ligand attenuated the double-stranded DNA breaks induced by doxorubicin exposure further opens new pathways for potential cardioprotection in these patients.

Continuous intravenous anthracycline infusion instead of bolus administration has been reported to be less cardiotoxic. However, a meta-analysis of 4 trials with 410 patients showed mixed results and substantial heterogeneity between studies that precluded a definitive conclusion about their effects on LVSD. No differences were observed during an 8-year follow-up in LV diameters or function in a trial performed in children with acute lymphoblastic leukemia. In addition, this practice increases the length of hospital stay, cost, and risk of mucositis.

Liposomal encapsulation of anthracyclines can theoretically prevent myocardial endothelial absorption while allowing tumor absorption. In 2 trials that were comparable in their peak anthracycline dose that enrolled 521 women with breast cancer, 5.2% developed HF in the conventional doxorubicin group compared with only 0.8% in the liposomal-encapsulated doxorubicin group, whereas HF and LVSD occurred in 24.7% and 9.2%, respectively.

The introduction of a drug-free interval between the administrations of drugs with known cardiotoxicity, especially those with demonstrated interaction, is effective and is currently routine practice. An ongoing study is comparing the cardiac toxicity of trastuzumab when administered concurrently or sequentially to anthracycline-containing adjuvant regimen (http://www.clinicaltrials.gov; NCT01413828).

Exercise

Physical exercise at different intensities performed before, during, or after chemotherapy treatment increases cardiovascular reserve, reduces cardiotoxicity in mouse models, and increases peak VO₂ in patients treated with doxorubicin and cyclophosphamide. However, a small study reported no beneficial effects on LVEF during adjuvant trastuzumab treatment. Ongoing small trials are currently studying the effect of different levels of training and the preventive efficacy of exercise 24 hours before every chemotherapy cycle (http://www.clinicaltrials.gov; NCT02006979).

Administration of Cardioprotective Drugs

Most randomized studies to prevent cardiotoxicity have been performed in patients treated with anthracyclines; no randomized studies have been done in patients treated with novel therapies. Antioxidants may neutralize free radicals generated by anthracyclines and potentially reduce cardiotoxicity.
However, multiple clinical trials with different drugs using this strategy have been negative, probably because these drugs do not prevent DNA double-strand breaks and activation of p53.

Dexrazoxane has traditionally been thought to protect the heart from doxorubicin-associated damage by binding free iron and removing iron from the doxorubicin-iron complex, preventing the formation of oxygen radicals. Because dexrazoxane also forms a tight complex with the ATPase domain of topoisomerase 2, the most important mechanism for its cardioprotective effects is likely to be preventing anthracyclines from binding to the topoisomerase 2β-DNA complex by trapping topoisomerase 2β in a closed-clamp form.

Ten clinical trials have studied the role of dexrazoxane as a cardioprotective agent in patients receiving very high doses of anthracyclines. The incidence of HF and LVEF drop in 8 of these studies that enrolled 1561 patients was 1.4% and 10.4% in patients treated with dexrazoxane compared with 8.7% and 35.9% in control subjects, respectively, with no differences in total or progression-free survival observed. In a study performed in 205 children with acute lymphoblastic leukemia, dexrazoxane limited troponin T elevation during doxorubicin administration and prevented LV shortening fraction decline 5 years later. Mostly as a result of reports of cases of acute myeloid leukemia and myelodysplastic syndrome in children receiving dexrazoxane, the US Food and Drug Administration

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<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Disease</th>
<th>CT</th>
<th>Intervention</th>
<th>Dose, mg/d</th>
<th>n</th>
<th>Follow-Up, mo</th>
<th>Selected End Points, %</th>
<th>Other Events Prevented</th>
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<tr>
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<td>Carvedilol</td>
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ACE-I indicates angiotensin-converting enzyme inhibitor; AL, acute leukemia; ANT, anthracyclines; ARB, angiotensin receptor blocker; BNP, brain natriuretic peptide; CT, chemotherapy; FS, fractional shortening; GPSS, global peak systolic strain; hd-CT, high-dose chemotherapy; HF, heart failure; LVEDD, left ventricular diastolic diameter; LVEF, left ventricular ejection fraction; MM, multiple myeloma; NT-proBNP, N-terminal pro-brain natriuretic peptide; and SR, strain rate.
and the European Medicines Agency currently restrict the use of dexrazoxane to adult women with metastatic breast cancer who have received a cumulative dose of doxorubicin >300 mg/m² and who would benefit from additional doxorubicin treatment. Of note, a recent experimental study has shown that the cardioprotective effect of dexrazoxane is more accentuated when administered before the first dose of anthracycline rather than after a cumulative dose of 300 mg/m², suggesting that the currently recommended delayed intervention may not be able to take advantage of the full cardioprotective potential of the drug.

Enalapril did not prevent LVEF decline when administered during chemotherapy in a small study but had marked effects when administered 1 month after the end of the last chemotherapy cycle in selected high-risk patients with positive troponin levels but normal LVEF (Table 2). An ongoing trial is comparing the efficacy of both strategies (http://www.clinicaltrials.gov; NCT01968200). The evidence for cardioprotection from angiotensin receptor blocker administration is scarce because their effects have been assessed in only 2 small studies in low-risk patients, one of them during just 1 week of follow-up. An ongoing study is testing the cardioprotective effects of candesartan during trastuzumab therapy (http://www.clinicaltrials.gov; NCT00459771).

In a retrospective study of 920 women with breast cancer and normal LVEF receiving anthracyclines and trastuzumab, use of β-blockers was associated with a lower risk of new HF events. Four randomized studies including a total of 227 patients have tested their preventive effects. In 2 studies performed with carvedilol, prevention of LVEF decline and of LV fractional shortening and global peak strain rate decline were observed (Table 2). Nebivolol but not metoprolol has been reported to prevent LVEF decline in small trials. Ongoing placebo-controlled studies are testing the effect of carvedilol (http://www.clinicaltrials.gov; NCT01724450), carvedilol versus lisinopril (NCT01009918), bisoprolol versus perindopril (NCT01016886), and metoprolol versus candesartan (NCT01434134) in patients treated with trastuzumab.

Another approach is to administer combined treatment with angiotensin-converting enzyme inhibitors/β-blockers. In a recent study, the administration of enalapril and carvedilol in patients with hematological malignancies prevented LVEF decline at 6 months, especially in patients with acute leukemia, a group of patients who received more intensive chemotherapy with repeated doses of anthracyclines. Patients in the intervention group had a lower incidence of the combined event of death or HF (6.7% versus 22%) and of death, HF, or a final LVEF<45% (6.7% versus 24.4%). A recent study also found protective effects on LVEF decline with the use of a combination of candesartan and carvedilol. Finally, a study has recently reported the preventive effects of spironolactone on anthracycline-induced myocardial toxicity in patients with breast cancer.

Important limitations of all of these studies include the small number of patients treated, differences in study design, varying malignancies being studied and chemotherapy regimens used, and short follow-up times. In addition, in most studies, the mortality rate was lower than expected, and the reported beneficial effects on the incidence of HF and LVEF decline did not translate to lower mortality (Table 2). In spite of this, a recent meta-analysis did not find statistical heterogeneity between study results and concluded that prophylactic treatment with angiotensin antagonists or β-blockers prevents HF or LVEF decline in patients treated with chemotherapy.

In all of the studies, the cardioprotective effect clearly depended on the basal risk (Figure 2), emphasizing the importance of basal risk stratification to better select patients to be submitted to pharmacological cardioprevention. Large, randomized, multicenter studies performed in patients treated with and without novel therapies are clearly needed to confirm these results.

Neuregulin-1β is an ErbB receptor family ligand that is effective against anthracycline-induced injury but is also pro-neoplastic. A recent experimental study using a modified neuregulin-1β ligand with a strong preference for homodimer cardiac ErbB4 over heterodimer ErbB3/ErbB2 signaling has shown potent cardioprotective effects and provides new opportunities for effective cardioprotection in patients, although the results need to be further validated.

Management of Cardiotoxicity

At the time of cancer diagnosis, patients’ comorbidities, previous pharmacological treatment, and cardiac function should be assessed to establish or maintain an optimal treatment and to reduce the impact of drug toxicity. During cancer treatment, close cardiovascular monitoring should be applied for the early detection of cardiac toxicity, re-evaluation of the initial therapeutic plan, and early treatment of any cardiac dysfunction (Figure 3).
When VEGF inhibitors are administered, weekly home blood pressure measurements are recommended. Hypertension should be rapidly treated, as guided by current guidelines. Given their possible efficacy in preventing chemotherapy-induced LV dysfunction, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or β-blockers are frequently used as first-line agents, although there is no high-quality evidence supporting one class over another for the treatment of hypertension. Because nondihydropyridine calcium blockers such as diltiazem and verapamil inhibit cytochrome P450 3A4, they can delay the metabolism of TKIs and increase their plasma levels. Accordingly, these drugs should be administered with caution in patients with TKI-induced hypertension.

Although there are no evidence-based guidelines for cardiotoxicity monitoring during and after anticancer therapies for patients treated with anthracyclines, current European Society of Medical Oncology guidelines recommend LVEF assessment at baseline, the end of treatment, and 6 months after the completion of therapy; annually for 2 or 3 years thereafter; and then in 3- to 5-year intervals for life. For patients treated with trastuzumab, LVEF assessment is recommended at baseline and up to every 3 months while on therapy. Although these are intended only as general rules, specific cardiac monitoring guidelines have helped to remove ambiguity in a manner that to date is unique to trastuzumab. For patients treated with TKIs, similar screening monitoring may be appropriate.

In the presence of signs of LV injury or dysfunction, referral to a cardiologist is recommended with treatment/repeat imaging assessments as appropriate. Data from large, randomized trials in patients with chemotherapy-induced LVSD or HF are lacking. Although in 1 study enalapril did not prevent HF progression when administered in children a median of 4 years after completion of cancer treatment, this same treatment has proved to be very effective in adults. In the absence of new evidence, LVSD and HF should be treated as early as possible because an inverse relationship has been described between time to treatment and the degree of improvement in LVEF, with best results obtained when treatment is initiated within 2 months and no complete recovery when initiated after 6 months. One recent study of 79 patients with treatment-emergent LV dysfunction found that, with the initiation of standard HF therapy, 76% of patients were able to complete their planned cancer therapy. These results also underscore the need for active surveillance and early detection of cardiac toxicity.

Future Directions

Basic and translational studies are needed to discover more specific genetic factors for cardiotoxicity. Combined with clinical factors, genetic profile studies could be used in the future for early risk stratification at the time of cancer diagnosis. Further research is also needed to more clearly define the causative mechanisms for drugs with known cardiotoxicity to aid the development of new cardioprotective therapies.

Clinical studies should be performed to determine the natural history of patients with positive biomarkers of cardiac injury and of patients with asymptomatic LVEF drops during chemotherapy. Studies are also needed to define which biomarker or imaging technique should be used to detect early myocardial injury, as well as the highest-yield discriminating cut points and times for assessment. Large, collaborative, multicenter studies are urgently needed to define more accurately the role of potentially cardioprotective medications.

As learned from the cardiotoxic effects of second-generation TKIs, cardiology and oncology scientific societies should work together with regulatory agencies to establish uniform criteria to precisely define chemotherapy-induced cardiac toxicity, the methods to monitor the cardiovascular safety of novel cancer therapies, and a precise protocol to evaluate cardiovascular events in all randomized, controlled studies. Finally, oncologists and cardiologists should work together to develop clear clinical guidelines for the prevention and management of chemotherapy-induced cardiotoxicity.

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Disclosures

Dr Witteles is a Cardiac Review Subcommittee member for Roche (for ongoing trastuzumab emtansine trials) and Cardiology Advisory Board participant for Onyx Pharmaceuticals. Dr Bosch reports no conflicts.

References


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Witteles and Bosch  Myocardial Protection During Cardiotoxic Chemotherapy  1845
Myocardial Protection During Cardotoxic Chemotherapy
Ronald M. Witteles and Xavier Bosch

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/content/133/3/e31.full.pdf

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In the article by Witteles and Bosch, “Myocardial Protection During Cardiotoxic Chemotherapy”, which published in the November 10, 2015 issue of the journal (Circulation. 2015;132:1835–1845. DOI: 10.1161/CIRCULATIONAHA.115.010486), several corrections are needed:

1. On p 1838, the reference at the end of the first paragraph under the subheading “Trastuzumab” should be 9, not 35.
2. On p 1838, the second line under the subheading “Tyrosine Kinase Inhibitors” should read TKIs instead of TKI.
3. On p 1838, the last sentence in the second paragraph under the subheading “Biomarkers” should read: “Troponin rises almost always occurred prior to trastuzumab invitation or very early during trastuzumab therapy, supportive of the theory that troponin rises mainly reflected anthracycline effects rather than direct effects from the trastuzumab itself. Nevertheless, troponin elevations remained predictive of outcomes in their cohort, with patients with positive troponin having a 62% incidence of a significant LVEF drop compared with 5% in patients with negative troponins.”
4. On p 1839, the end of the first sentence under the subheading “Primary Prevention Measures” should read “Stage A HF” rather than “Stage A.”
5. On p 1842, in Figure 3, the third box from the left should read “Begin CT (Stage A)”.
6. On p 1842, in the third line of the second paragraph under the subheading “Future Directions”, “LVEF drop” should read “LVEF drops”.
7. On p 1842, in the second line of the third paragraph under the subheading “Future Directions”, the correct references are 21,22 rather than 8,9.

The correction has been made to the current online version of the article, which is available at http://circ.ahajournals.org/content/132/19/1835.full.