

# Cardio-Oncology: The Intersection Between Cardiovascular Disease and Cancer

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## Abstract

Cardio-oncology is a rapidly emerging field, and advanced practitioners (APs) play key roles in the prevention, early detection, and optimal treatment of cardiotoxicities associated with cancer therapies. At JADPRO Live Virtual 2020, Jessica Shank Coviello, DNP, APRN, ANP-BC, and Kejal Amin, PharmD, MBA, BCOP, reviewed patient risk factors and cardiovascular therapeutic agents that APs should be aware of.

The connection between cancer and cardiovascular disease has been well established in medicine, but their shared pathophysiologic patterns remain less understood. During the JADPRO Live Virtual 2020 conference, Jessica Shank Coviello, DNP, APRN, ANP-BC, of Yale University School of Nursing, and Kejal Amin, PharmD, MBA, BCOP, of Smilow Cancer Center, identified patient risk factors common to both cancer and heart disease, explained how cardiovascular risk factors affect the risk of cardiotoxicity associated with cancer therapy, and described pharmacologic interventions available to mitigate and treat cancer therapy-related cardiotoxicity.

## RISK FACTORS FOR CHEMOTHERAPY-RELATED CARDIOTOXICITY

As Dr. Coviello explained, a number of risk factors for chemotherapy-related cardiotoxicity need to be considered before starting chemotherapy. These include current myocardial disease such as heart failure, sarcoidosis with myocardial involvement, and any significant preexisting cardiac arrhythmias (Cardinale et al., 2020). There are also demographic and other cardiovascular risk factors such as age, family history of premature cardiovascular disease, arterial hypertension, diabetes, and hypercholesterolemia. In addition, lifestyle risk factors include smoking, high alcohol intake, obesity, and sedentary lifestyle. Patients who have

had prior experience with cancer chemotherapy including anthracyclines and radiation need to be considered as well.

Another baseline risk factor that should be considered is a drop in left ventricular ejection fraction (LVEF). Patients with even a mild reduction in LVEF are at a higher risk of cardiotoxicity, said Dr. Coviello, who noted that drops in LVEF are often set within each institution. Although most institutions will consider an LVEF of less than 53% as significant, the American Heart Association defines it as less than 50% (Polansky et al., 2019).

“These patients need pretreatment evaluation as to the etiology of their low LVEF and should be treated prophylactically with an ACE inhibitor, angiotensin receptor blockers (ARBs), or a beta-blocker,” said Dr. Coviello. “They should also have aggressive reduction in other cardiovascular risk factors and begin aspirin and statin therapy.”

Pharmacogenetics is another growing area of investigation to predict which patients are at a higher risk of cardiotoxicity. Genetic factors can cause greater sensitivity to cardiotoxic agents, and cellular responses to treatment may vary based on genetic responses to other cardiovascular risks in the context of cancer therapy. The use of human-induced pluripotent stem cells also represents an opportunity to understand which patients are at the greatest risk for developing cardiotoxicities.

“The future holds promise that someday we may not only be able to target effective chemotherapeutic agents but also determine how best to minimize toxicity,” said Dr. Coviello.

Cumulative dose and choice of anthracycline are additional risk factors for chemotherapy-related cardiotoxicity. In current practice, cumulative doses of 100 to 300 mg/m<sup>2</sup> of anthracyclines are more common and less likely to cause heart failure, but some patients in this dose group have unanticipated sensitivity to anthracyclines and thus present the greatest challenge for pretreatment risk assessment.

“The first risk factor for cardiotoxicity is the chemotherapy itself,” said Dr. Coviello. “A second risk factor places the patient at higher risk, and we therefore look to treat preventively. We will also add biomarkers and imaging as patients proceed through treatment.”

## ALTERNATIVE DELIVERY METHODS/ COMBINATION CHEMOTHERAPY

Chemotherapy is often given in combination with several agents, many of which can contribute in an additive way to the risk of cardiotoxicity. In breast cancer and lymphoma patients, said Dr. Coviello, the alkylating agent cyclophosphamide, which can cause left ventricular dysfunction, is often given in combination with an anthracycline. Paclitaxel, which has a cardiac side effect of dysrhythmia, is also often given in combination. Finally, several HER2 inhibitors are in clinical use, including trastuzumab, pertuzumab, lapatinib, and trastuzumab emtansine.

According to Dr. Coviello, the importance of pretreatment cardiovascular assessment is shown in early trastuzumab plus anthracycline studies that demonstrated a 27% increase in left ventricular dysfunction in patients receiving this combination vs. 8% receiving the combination of trastuzumab and cyclophosphamide (Procter et al., 2010). Results also showed that 16% of patients receiving herceptin and anthracycline had stage III or IV heart failure.

In this early study, however, no cardiovascular risk was assessed prior to treatment, said Dr. Coviello, and no continuous monitoring was part of the surveillance. Later studies of adjuvant trastuzumab that excluded patients with abnormal LVEFs or uncontrolled cardiovascular risk and that implemented close monitoring of cardiac function demonstrated lower rates of symptomatic cardiomyopathy ranging from 2% to 4% (Polansky et al., 2019).

## RADIATION THERAPY AS A RISK FACTOR

Radiation is another risk factor due to fibrosis of the coronary arteries or valve disease. This risk increases in left chest radiation but may not appear until 18 months to several years after treatment. This risk is also increased when radiation is combined with anthracycline, said Dr. Coviello, who noted that attempts at minimizing heart exposure to radiation with current radiology techniques have actually lowered the incidence.

“Collaborative care involving cardio-oncology and oncology is essential in order to reduce the likelihood of treatment interruption and to op-

timize cancer outcomes without compromise in cardiovascular health," she added.

## PREVENTING CARDIOTOXICITY

Dr. Coviello also noted the very similar molecular underpinnings of cancer and cardiovascular disease. They both have abnormal metabolic pathways and are proinflammatory in nature. Cardiovascular medications also have pleiotropic properties, which means they treat both cardiovascular disease and certain aspects of the cancer itself. In addition, cardiovascular medications reduce morbidity and mortality for both those with cancer and with heart disease or cardiovascular risk, and they hold promise in antitumor activity.

Although evidence-based guidelines are missing, said Dr. Coviello, cardioprotective agents are recommended in patients with heart failure. Position papers from the American Heart Association, for example, recommend first-line use of beta blockers, ACE inhibitors, and ARBs (Mehta et al., 2018).

Several studies have also tried to address if preventative treatment can actually prevent heart failure when applied prior to chemotherapy. However, heterogeneity relating to the choice of drugs, the study cohorts, and the types of cancer contributes to the lack of current evidence.

A meta-analysis of randomized control trials that were published up to 2019 showed that patients treated with ACE inhibitors or ARBs alone before initiating cancer treatment had higher LVEF than controls after 6 months of chemotherapy. Although patients treated with beta-blockers also showed a mild differential when used alone, Dr. Amin noted that the data have been inconsistent.

"We would think that beta-blockers that have antioxidant properties would do great in treating cardio-protective properties, but when used with anthracyclines, beta-blockers have not demonstrated better prevention of ejection fraction drops than placebo," said Dr. Amin. "Therefore, we don't routinely use beta-blockers individually."

"ACE inhibitors, on the other hand, have shown much better results and do prevent ejection fraction drops," Dr. Amin added. "There could be a potential role in using them first."

According to Dr. Amin, the OVERCOME trial provided the most important evidence with re-

spect to combination treatment. When beta-blockers and ACE inhibitors were used together while treating with anthracyclines, they demonstrated a lower incidence of heart failure and death that was statistically significant.

"It's really important that we investigate this combination further," said Dr. Amin.

Beta-blockers could also be used with tyrosine kinase inhibitors, which have been shown to cause increases in blood pressure, to help patients with curable diseases remain on therapy, Dr. Amin added.

"I do think we can treat cardiotoxicity, but it's important to involve the cardiologist early on in the patient's management," said Dr. Amin. "That would enable us to get the appropriate tests done in a timely fashion when we suspect cardiotoxicity is occurring... and tailor the monitoring parameters to the individual patient."

Dr. Coviello emphasized the need for cardiovascular evaluation of patients before and during cancer therapy (Figure 1). Cardiovascular evaluations before entering cancer therapy would help to standardize assessment, said Dr. Coviello, which would aid in communication across disciplines, treatment decisions, and follow-up planning. Assessment of prechemotherapy risk and a physical assessment prior to starting treatment could also help stratify patients according to cardiotoxicity risk profile.

"There is a need to standardize these assessments to create stratified risk profiles," Dr. Coviello concluded. ●

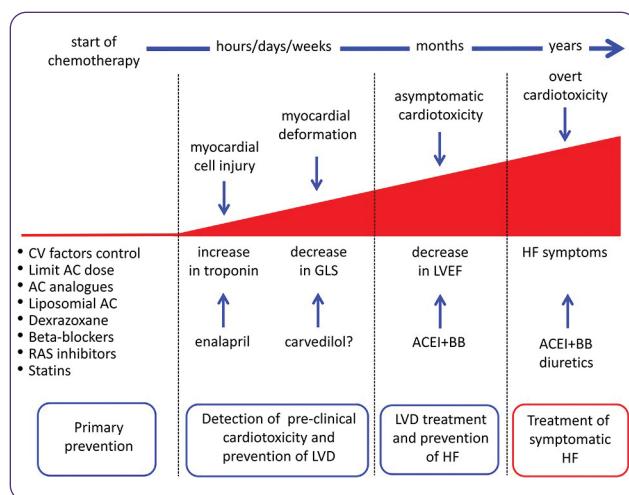


Figure 1. Preventing cardiotoxicity.

**Disclosure**

Dr. Coviello and Dr. Amin had no conflicts of interest to disclose.

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