

Cardio-Oncology Considerations in Oncologic Treatment Decisions

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Abstract

At JADPRO Live Virtual 2021, presenter Anecita P. Fadol, PhD, FNP-BC, FAANP, FAAN, emphasized the critical role advanced practitioners play in the identification, monitoring, and management of the cardiac complications of cancer therapy. Dr. Fadol's presentation discussed identification of the most common cardiotoxicities associated with cancer therapy, clinical considerations related to common oncologic treatments with potential cardiotoxicity that may impact cancer treatment decisions, and the management of common cardiovascular issues in patients with cancer.

The growing awareness that many anticancer agents can be cardiotoxic to patients has led to a subspecialty field now known as cardio-oncology. As part of the interdisciplinary oncology team, advanced practitioners play a critical role in identifying, monitoring, and managing the cardiac complications of these drugs. Important issues in this area were discussed at JADPRO Live Virtual 2021 by Anecita P. Fadol, PhD, FNP-BC, FAANP, FAAN, Associate Professor in the Department of Nursing and Cardiology at The University of Texas MD Anderson Cancer Center, Houston, Texas.

“Cardiotoxicity” refers to all the cardiovascular adverse effects of cancer therapy. This includes cardiac arrhythmias, myocardial ischemia, hypertension, myocarditis,

thromboembolism, left ventricular disease, cardiomyopathy, heart failure, and more. The goal in cardio-oncology is to manage the patient's cardiac risk factors and current cardiovascular issues to prevent cardiotoxicity and optimize patient outcomes, Dr. Fadol said.

RISK FACTORS TO CONSIDER IN SELECTING TREATMENTS

“In managing patients with cancer, clinicians should consider the shared risk factors between cancer and cardiovascular disease—for example, age, smoking and genetics—that can contribute to the development of cardiotoxicity,” she said.

Also important are the presence of cardiovascular disease, such as left ventricular dysfunction, that may delay cancer treatment; the drug-to-drug interactions between cancer

medications and cardiac medications; and the potentially harmful effects of past cancer treatment that may result in cardiovascular issues, such as arrhythmia, ischemia, and left ventricular dysfunction. Early detection and management of underlying comorbidities are important to reduce these risks and resulting morbidity and mortality.

Many anticancer agents hold the potential for cardiotoxicity (Salvatorelli, 2019; Table 1). Before starting the patient on any chemotherapy, clinicians should perform a comprehensive cardiovascular assessment to determine the potential for cardiotoxicity. This may reveal risk factors, including conventional ones (age, gender, genetics); cardiovascular ones (hypertension, hyperlipidemia, diabetes); and risks related to previous cancer treatments (anthracyclines, radiotherapy involving the chest).

All cardiovascular risk factors should be optimally managed and controlled and cardiac protection instituted as needed. During treatment, surveillance and monitoring of symptoms is important, particularly in patients at high risk, and this should be continued after treatment, when delayed cardiac effects may emerge.

ATRIAL FIBRILLATION

Cardiac arrhythmia, particularly atrial fibrillation, is one of the most common clinical manifestations

of cardiotoxicity. Arrhythmia nearly doubles the risk of mortality and raises the risk of stroke almost five fold. The presence of atrial fibrillation affects the prognosis after cancer treatment and challenges the treatment strategy, Dr. Fadol said.

The two main goals for the management of atrial fibrillation are symptomatic improvement and prevention of thromboembolism. The achievement of symptomatic improvement involves a choice between rate control and rhythm control. Neither strategy has conclusively been shown to improve survival over the other, and both strategies are associated with similar benefit in preventing thromboembolism.

“The decision to anticoagulate should not be based on which strategy is chosen, but on the patient’s individual profile, such as risk for fall, GI bleeding, or brain metastasis,” she said.

For patients who are hemodynamically unstable, meaning they have hypotension or become symptomatic, a rhythm control strategy using cardioversion or antiarrhythmic medications, such as amiodarone, is preferred. For patients who are hemodynamically stable, a rate control strategy is preferred. This is accomplished with the use of medications, such as beta blockers, calcium channel blockers or digoxin, with care taken to avoid drug-to-drug interactions in choosing the drug.

Table 1. Cardiotoxic Syndromes Associated With Anticancer Agents

Left ventricular dysfunction/HF	Myocardial ischemia	Hypotension	Hypertension	QT prolongation	Myocarditis
Anthracyclines	5-FU	Etoposide	Bevacizumab	Pazopanib	Cyclophosphamide
Doxorubicin	Cisplatin	Paclitaxel	Cisplatin	Vandetanib	Nivolumab
Daunorubicin	Capecitabine	Alemtuzumab	Sorafenib	Crizotinib	Ipilimumab
Epirubicin	IL-2	Rituximab	Axitinib	Bosutinib	Pembrolizumab
Idarubicin		Cetuximab	Cabozantinib	Dasatinib	Atezolizumab
Cisplatin		IL-2	Carfilzomib	Lapatinib	Durvalumab
Imatinib		Denileukin	Pazopanib	Nilotinib	Avelumab
Mitomycin		Interferon α	Regorafenib		
Cytarabine (Ara-C)		All-trans retinoic acid	Sunitinib		
Mitoxantrone		Nilotinib	Ibrutinib		
Cyclophosphamide		Thalidomide	Nilotinib		
Trastuzumab			Ado-trastuzumab		
Ifosfamide			emtansine		
All-trans retinoic acid			Alemtuzumab		
Pazopanib			Cabozantinib		
Sorafenib			Denosumab		
Bevacizumab			Everolimus		
Paclitaxel			Ibritumomab		
Pertuzumab			tiuxetan		

Note. HF = heart failure. Information from Salvatorelli (2019).

“For example, in patients who develop atrial fibrillation secondary to the tyrosine kinase inhibitor ibrutinib (Imbruvica), we should avoid the use of calcium channel blockers, which can cause an increase in the ibrutinib level. And when digoxin is used to control the atrial fibrillation, remember that ibrutinib could increase the digoxin level,” she cautioned.

All patients should be assessed for their suitability for anticoagulation, which can be done using the CHA₂DS₂-VASc score (Lip et al., 2010) and HAS-BLED score (Pisters et al., 2010).

QT PROLONGATION

The QT interval represents the total time from ventricular depolarization to complete repolarization. QT prolongation is defined as QT interval > 450 msec for men and > 460 msec in females; an interval ≥ 60 msec increase from baseline; or an interval > 500 msec after administration of a medication. Monitoring QT interval is important because QT prolongation is associated with increased risk for polymorphic ventricular tachycardia, also known as Torsades de pointes—which without intervention can result in ventricular

tachycardia or ventricular fibrillation and subsequent sudden cardiac death.

Many tyrosine kinase inhibitors can cause QT prolongation. The incidence is generally limited to < 14% with the exception of arsenic trioxide, which carries a very high risk and mandates monitoring. Prior to starting treatment, it is recommended to obtain a baseline electrocardiogram for reference and repeat it at 2 to 4 weeks, 8 to 12 weeks, and every 3 months during treatment.

“Do not initiate treatment unless the QTc interval is < 450 msec and make sure the potassium and magnesium levels are within normal limits,” Dr. Fadol advised. “If the patient is receiving other medications that can cause QT prolongation, such as the antiemetic ondansetron, monitor the QTc more closely.”

Other commonly used noncancer medications can also cause QT prolongation and should be on the radar during cancer treatment, including other antiemetics and many antipsychotics, antiarrhythmics, antimicrobials and analgesics.

Dr. Fadol shared with listeners the algorithm used at MD Anderson Cancer Center for QT monitoring during chemotherapy (Figure 1).

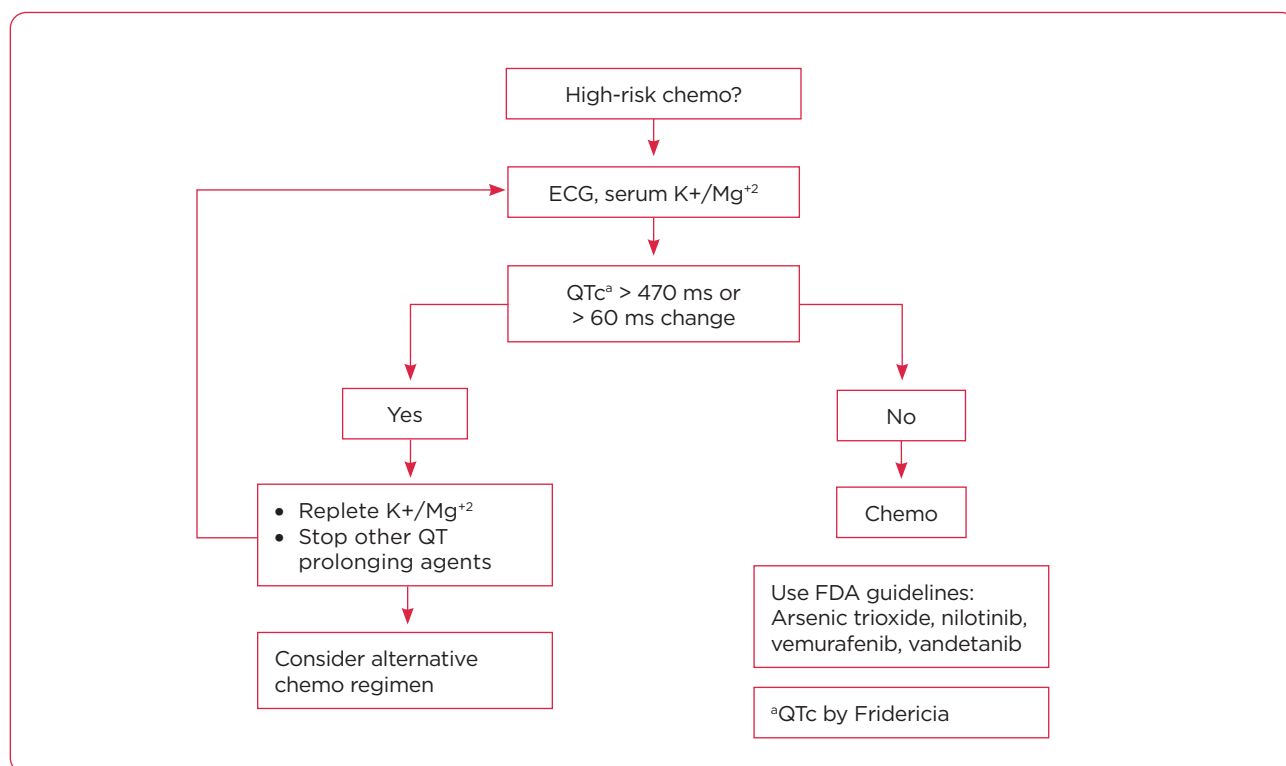


Figure 1. QT monitoring during chemotherapy. Information from Brell (2010); Kim (2014); Yeh (2016).

TREATMENT-INDUCED HYPERTENSION

Uncontrolled hypertension can lead to left ventricular hypertrophy, diastolic impairment, heart failure, kidney failure, stroke, heart attack, arrhythmia and ultimately death. The list of anticancer agents that can raise blood pressure is long and contains many targeted agents.

The most recent algorithm of the Eighth Joint National Committee (JNC 8) offers guidelines for managing hypertension in the general population, not specifically cancer patients (James et al., 2014). In cancer patients, it is most important to set blood pressure goals based on age and the presence of diabetes and chronic kidney disease, as follows: (1) for < 60 years old, < 140/90 mmHg, (2) for $\geq$ 60 years old, < 150/90 mmHg, and (3) any age with diabetes or chronic kidney disease, < 140/90 mmHg.

The choice of antihypertensive should be based on the patient's most compelling cardiac issue. For example, if it is heart failure, any antihypertensive is acceptable except calcium channel blockers. If it is coronary artery disease or the patient is post-myocardial infarction, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and aldosterone antagonist are preferred (James et al., 2014).

The Angiogenesis Task Force of the National Cancer Institute Drug Steering Committee has made recommendations for management. These are particularly applicable to patients on tyrosine kinase inhibitors (TKIs), in whom hypertension can develop soon after treatment initiation and can result in severe hypertension. The recommendations include:

- Thoroughly screen for hypertension before starting TKI.
- Measure blood pressure at baseline, weekly for the first treatment cycle and every 2 to 3 weeks for the duration of TKI treatment.
- In patients with preexisting hypertension on multiple antihypertensives, evaluate for renal dysfunction.
- Instruct patients to record their blood pressure, which can guide providers in titrating medication. Make patients aware of their risks and blood pressure goals.
- Consult with a cardiologist as needed.

CARDIOMYOPATHY AND HEART FAILURE: ANTHRACYCLINES, TRASTUZUMAB

Cardiomyopathy/heart failure is defined as a reduction in left ventricular ejection fraction (LVEF) from baseline of $\geq$ 5% to < 55% with accompanying signs and symptoms of heart failure, or LVEF reduction of > 10% to < 55% without signs and symptoms. The American College of Cardiology/American Heart Association staging system classifies exposure to cardiotoxic chemotherapy as Stage A, indicating a high risk for developing heart failure. Evolution to Stage B indicates asymptomatic heart failure; Stage C indicates symptomatic heart failure; and Stage D is refractory end-stage heart failure. Heart failure can progress forward from stage to stage but never the reverse, despite the best medical therapy, Dr. Fadol noted.

Affected patients are identified via history and physical exam, symptoms, precipitating factors, and diagnostic testing.

Cancer patients at most risk for left ventricular dysfunction, cardiomyopathy, or heart failure are those treated with (1) high-dose anthracyclines ($\geq$ 250 mg/m² doxorubicin or > 600 mg/m² epirubicin); (2) high-dose (> 30 Gy) radiotherapy with the heart in the treatment field; (3) lower-dose anthracycline (< 250 mg/m² doxorubicin) in combination with lower-dose radiotherapy (< 30 Gy) with the heart in the treatment field; (4) lower-dose anthracycline or trastuzumab alone with underlying hypertension, diabetes, coronary artery disease or older age; and (5) lower-dose anthracycline followed by trastuzumab (i.e., sequential therapy).

Anthracycline-induced cardiomyopathy can have an acute onset, can emerge within 1 year of starting treatment, or can develop a year or later after treatment ends. Acute-onset cardiomyopathy presents with abrupt clinical changes in cardiac parameters (or death) while later onset is associated with subclinical declines in myocardial function or symptoms of heart failure.

"We have to remember that because of advances in treatment we have an increasing number of survivors who have received anthracycline-based chemotherapy. Chronic anthracycline cardiotoxicity may occur even after 30 years of receiving treatment," she noted.

The condition is most likely after a higher cumulative dose ($> 300 \text{ mg/m}^2$), in concordance with other cardiotoxic drugs, in patients aged < 18 or > 65 years, after concurrent or prior radiation involving the left side of the chest, and in the setting of preexisting cardiovascular disease.

These are the general guidelines for monitoring anthracycline-induced cardiomyopathy:

- Baseline assessment of left ventricular function: echocardiography, multigated acquisition scan (MUGA), and myocardial perfusion stress test. For high-risk patients, evaluate LVEF after 200 mg/m^2 and then every one to two cycles (or if symptoms appear). For low-risk patients, evaluate LVEF after 400 mg/m^2 (or if symptoms appear), and repeat 3 months after completion of therapy.
- Cardiac biomarkers: troponin T and troponin I, B-type atrial natriuretic peptide. Mostly used in acute-care setting.
- Cardiac imaging: cardiac magnetic resonance imaging and positron emission tomography scan

Heart failure rates continue to increase up to 10 years after anthracycline-based treatment for

women > 65 years old. In the absence of progressive LVEF decline, it is reasonable for clinicians to consider annual cardiac monitoring for at least 5 years in young women and for at least 10 years in elderly women.

It is important to also understand the risks associated with trastuzumab. Table 2 describes a practical approach used by many institutions in managing these patients.

MYOCARDITIS: RELATED TO IMMUNOTHERAPY

Myocarditis is defined as an inflammatory disease of the myocardium that is diagnosed by established histological, immunological and immunohistochemical criteria; biopsy confirms the diagnosis. Treatment-related myocarditis emerged after the approval of the first immune checkpoint inhibitor, ipilimumab (Yervoy), in 2011. Although immune checkpoint inhibitor-associated myocarditis occurs in only $< 1\%$ of patients, its fatality rate is approximately 40%—much higher than that of, for example, pneumonitis, nephritis, and other immune-related adverse events (Wang et al., 2018).

Table 2. Practical Approach for the Management of Patients Receiving Adjuvant Trastuzumab

Treatment phase	Patient profile	Monitoring and management
Before starting trastuzumab	A. No cardiac history or CRF; LVEF normal ($> 50\%$)	Proceed with trastuzumab Monitor LVEF q3months
	B. With cardiac history and/or CRF; LVEF normal ($\geq 50\%$)	Proceed with trastuzumab Monitor symptoms Comprehensive PE before next cycle Cardiac biomarkers (TnI, BNP)
	C. Decreased LVEF	Treat low EF (ACE-I/ARB, BB) and reevaluate
During treatment	First decrease in LVEF ($< 50\%$)	Treat low EF (ACE-I/ARB, BB) and reevaluate a. LVEF $\geq 50\%$, restart trastuzumab b. LVEF $< 50\%$, optimize therapy, re-measure c. LVEF remains $< 50\%$, discuss with oncology
	Subsequent decrease in LVEF	a. Stop trastuzumab b. Explore other anticancer treatment options
Completion of trastuzumab therapy	No change in LVEF, no symptoms during treatment, no change in cardiac biomarkers	No monitoring post treatment completion
	LVEF decreased or HF symptoms (SOB, fatigue, LE edema, PND)	Continue HF treatment per HF guidelines

Note. CRF = cardiac risk factor; LVEF = left ventricular ejection fraction; ARB = angiotensin receptor blocker; BB = beta blocker; PE = physical exam; TnI = troponin I; BNP = B-type natriuretic peptide; SOB = shortness of breath; LE = lower extremity; PND = paroxysmal nocturnal dyspnea. Adapted from Maurea et al. (2016).

Range of clinical presentations includes the appearance of acute coronary syndrome, new-onset or worsening heart failure, chronic heart failure, life-threatening conditions such as arrhythmias, cardiogenic shock, and severely impaired left ventricular function. Risk seems highest in patients on combination immunotherapy.

“Myocarditis symptoms as an immune-related adverse event are non-specific...and signs and symptoms of immune-related adverse events overlap, making diagnosis difficult,” she said.

The National Comprehensive Cancer Network (NCCN) guidelines recommend baseline electrocardiogram, individual assessment in consultation with cardiology, and periodic testing in patients with abnormal baseline assessment or symptoms (although normal electrocardiograms and LVEF assessments should not be reassuring). Early recognition of symptoms and prompt intervention are key goals for successful management of patients.

The NCCN panel recommends methylprednisolone pulse dosing until cardiac function returns to baseline, followed by dose tapering. In the absence of improvement within 24 hours, the addition of other potential immunosuppressive agents should be considered. ●

Disclosure

The presenter had no conflicts of interest to disclose.

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