Cardiovascular Health and Risk Management in Cancer Survivors

Presented by Javid J. Moslehi, MD

ABSTRACT

Cardio-oncology is a growing field, due to several factors. These include the recognition that similar risk factors predispose people to both cardiovascular disease and cancer. In addition, certain cancers affect the heart, and cancer treatments can have short-term and long-lasting deleterious effects on the cardiovascular system. More than 40 years ago, it became evident that anthracyclines and radiation cause heart damage, and since then the list of cancer treatments that can harm the cardiovascular system has grown to include more modern treatments, such as anti-HER2 agents and angiogenesis inhibitors. Most recently, immune checkpoint inhibitors (ICIs) have been added to the list of cancer treatments that cause cardiovascular damage. ICI-associated myocarditis is a relatively rare but fatal complication that develops rapidly after initiating immunotherapy. Oncologists should be aware of the potential cardiovascular complications of cancer treatments, and should assess the cardiovascular health of all patients about to undergo therapy. Cancer survivors should be assessed and advised about prevention and treatment that may be needed to address cardiovascular disease.

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"Cardio-oncology is a new area of interest because of the increased need to recognize cardiovascular disease in patients with cancer. These 2 areas intersect: cancer itself can cause cardiovascular disease, such as amyloidosis and carcinoid cancers, and occasionally oncologists see patients with cardiac tumors," explained Javid J. Moslehi, MD, Director, Cardio-Oncology Program, and Associate Professor of Medicine, Vanderbilt-Ingram Cancer Center, who is an expert in the burgeoning field of cardio-oncology. "Common risk factors predispose people to both cardiovascular disease and cancer. This has major implications for patients about to undergo systemic cancer treatment and also implications for survivorship," he told the audience at the NCCN 2020 Virtual Annual Conference.

It is well-known that anthracyclines and radiation can have deleterious effects on the heart and blood vessels, and these effects can occur years after treatment. As new treatments have become available, there is a growing awareness of cardiotoxicity that can be associated with these treatments. HER2-targeted therapies, such as trastuzumab, for example, can lead to cardiomyopathy; antimetabolites, such as 5-FU, can cause ischemia and vasospasm; vascular endothelial growth factor (VEGF) inhibitors can cause hypertension, heart failure, and thrombosis; and later-generation tyrosine kinase inhibitors used to treat chronic myeloid leukemia can cause pulmonary arterial hypertension, vascular disease, and atherosclerosis. Additionally, androgen deprivation therapy can lead to vascular and metabolic changes.

Immune Checkpoint Inhibitors

Over the past few years as immune checkpoint inhibitors (ICIs) have been approved for treatment of different types of cancers, emerging evidence has suggested that these agents can also lead to cardiovascular disease.

To illustrate this, Dr. Moslehi presented a case of a 65-year-old woman with widespread metastatic melanoma. She received her first dose of ipilimumab/nivolumab, and 12 days later developed nonspecific symptoms (ie, chest pain and shortness of breath) and had an elevated troponin level and changes on an electrocardiogram showing ventricular tachycardia and ventricular fibrillation. She was diagnosed with myocarditis, and died of cardiac damage a few weeks after her first dose of combination immunotherapy.

"After identification of this rare complication of ICI combination therapy, in collaboration with Dr. Joe-Elie Salem in France, we started a collaborative project to gather data on patients around the world who developed myocarditis, in part through a website: www.cardioonc.org. Patient information is deidentified, and we currently have data on approximately 300 patients with ICI-associated myocarditis," he said.

Lessons Learned From www.cardioonc.org

The collaboration identified ICI-associated myocarditis as a new syndrome characterized by T-cell and macrophage infiltration in striated muscle and significant electrocardiogram abnormalities (arrhythmias). "The syndrome occurs in approximately 1% of patients treated with

combination ICI (anti–CTLA-4 and anti–PD-1) therapy. It develops early in the course of treatment and is unpredictable. Early analysis shows a 50% mortality for this fulminant condition. The main risk factor we can identify is the combination of ICI (anti–CTLA-4 and anti–PD-1) therapy," Dr. Moslehi continued. "It can also be accompanied by concomitant myositis and myasthenia gravis, for reasons that are not clear to us. Fortunately, ICI-associated myocarditis is not very frequent," he added.

Researchers at Vanderbilt University are currently studying the pathophysiology and molecular characteristics of this syndrome, starting with basic research in genetic knockout mice. As more data are gathered, it will be possible to understand the long-term consequences of myocarditis. "It is useful to remember that not every chest pain or shortness of breath [in patients on ICIs] will be myocarditis," he noted. "Also, not every EKG abnormality is myocarditis. In some patients, a cardiac biopsy may be necessary."

"I don't have a full answer for what to do in terms of surveillance of patients with cancer treated with ICIs," Dr. Moslehi continued. In his practice, patients at high risk who are being treated with combination immunotherapy undergo an electrocardiogram and have their troponin levels measured weekly for the first 4 to 6 weeks after initiating treatment.

Treatment of ICI-associated myocarditis is an evolving area. High-dose steroids are initiated after a patient is diagnosed with myocarditis. Anecdotal evidence and experience with small numbers of patients who develop severe ICI-associated myocarditis suggest that abatacept may be useful, he said.

ICI-associated fatal toxicities have been reported in approximately 1.2% of all patients, he said. Of these, myocarditis has the highest death rate.[1] "It is not the most frequent [of fatal toxicities], but it does have the highest fatality. However, other immune-related toxicities such as pneumonitis and myositis can also be fatal. The challenge is how does a treating oncologist know how to diagnose these fatal toxicities, including myocarditis, and knowing how to treat the patient," he continued. At Vanderbilt, Dr. Moslehi, in collaboration with Dr. Douglas Johnson, a melanoma specialist, lead a multidisciplinary program called the Vanderbilt Program for Optimizing Immuno-oNcology Therapy (V-POINT), with the goal of safer treatment of patients treated with ICIs, with a multidisciplinary team in place to treat ICI-associated toxicities (Figure 1). "Hopefully, we can work together to better care for our patients," Dr. Moslehi stated.

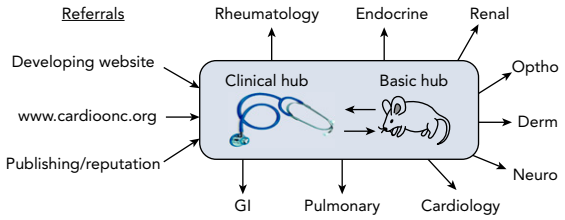

Figure 1. Vanderbilt Program for Optimizing Immuno-oNcology Therapy (V-POINT).

Cardiovascular Risk and Survivorship

"Many times, the number one cause of death in cancer survivors is heart disease," Dr. Moslehi said. A very large study of >10,000 cancer survivors and 1,014 siblings showed that over time more survivors developed congestive heart failure, coronary artery disease, and cerebrovascular accident than second cancers.[2] "Although second cancers are a big consideration in survivors, cardiovascular disease represents a major health problem for them," he emphasized.

In some cases, the treatment for cancer can increase the risk of cardiovascular disease. For example, patients with breast cancer who underwent radiation had a significantly increased risk of heart attack in one study.[3]

"We have to put this in context. This is a good problem to have, because cancer treatments have allowed patients to become survivors in the first place," he said. "But it is very important that we think about prevention. We don't do a good enough job [with prevention] in the general population, but we should certainly focus on disease prevention in the 17 million cancer survivors in the United States. We have to think about these issues that can arise later on. It shouldn't have to be an after-thought."

NCCN has developed a new guideline for Cardiovascular Disease Risk Assessment and Anthracycline-Induced Cardiac Toxicity within the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Survivorship that addresses the prevention and assessment of cardiovascular disease in cancer survivors (Figure 2).[4]

"We have to be aware of these risks and assess all patients," he said. "We have to debate what constitutes high-risk. Consider history and a physical examination, and I recommend an echocardiogram for anyone who has completed anthracycline therapy with at least one risk factor. In that instance, an echocardiogram would help identify patients with early cardiac damage and start appropriate cardioprotective medications," Dr. Moslehi said. "We increasingly recognize asymptomatic patients with structural heart disease on echocardiogram. It is important to pick this up before it becomes full-blown congestive heart failure."

Dr. Moslehi encouraged all oncologists to employ the "ABCDEs" of cardiovascular disease prevention in cancer survivors. This simple checklist can prevent the development of cardiovascular disease in cancer survivors:

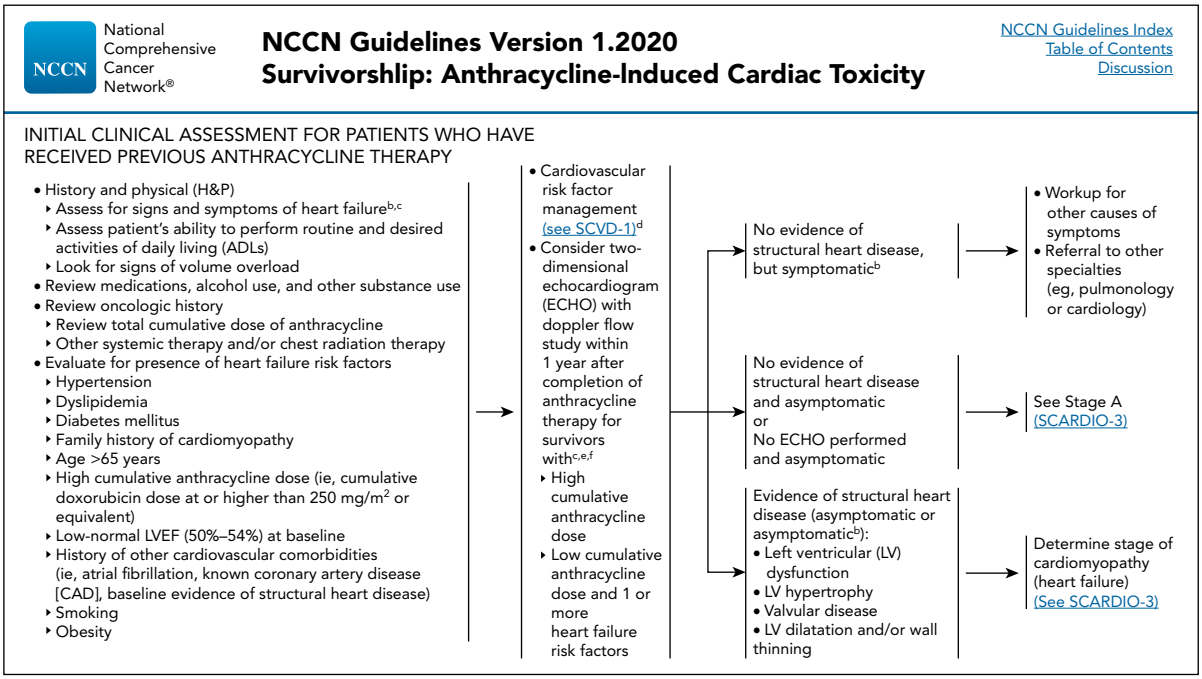

Figure 2. NCCN Guidelines for Survivorship: Anthracycline-Induced Cardiac Toxicity. Version 1.2020. ©NCCN. All rights reserved.

A = Awareness of signs and symptoms, assessment, aspirin when indicated

B = Blood pressure monitoring and treatment if indicated

C = Cholesterol—lipid panel for every patient; cigarettes—smoking cessation

D = Diet and weight management

E = Exercise; EKG in some cases

More recently, it has become recognized that common risk factors for cardiovascular disease predispose people for developing cancer, such as obesity and diabetes. This has major implications for public health strategies, he noted. In addition, certain genetic mutations carry a risk of hematologic malignancies, such as clonal hematopoiesis of indeterminant potential (*CHIP*). People with *CHIP* have a 40% increased risk of cardiovascular disease, and the main cause of death in this group is cardiovascular disease, Dr. Moslehi explained.

Disclosures: Dr. Moslehi has disclosed that he is a scientific advisor for Nektar Therapeutics, Novartis Pharmaceuticals Corporation, Bristol-Myers Squibb, Pfizer Inc., and Takeda Pharmaceuticals North America, Inc.

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