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New field booms but awareness lags

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Cardio-oncology is expanding, fed by a steadily increasing population of cancer survivors at elevated risk for a range of cardiovascular diseases and complications because of the anticancer treatments they received. Cardio-oncology's quick growth has also been driven by the rapidly expanding universe of cancer treatments with direct or indirect adverse effects on a diverse range of cardiovascular DR.

functions.

During the past year, the field's rapid evolution has featured the first formal diagnostic and care standards in two iterations: A position paper on the cardiovascular toxicities of cancer treatment from the European Society of Cardiology (ESC), released in August 2016 (*Eur Heart J.* 2016 Sep 21;37[36]:2766-801); and a guideline for preventing and monitoring cardiac dysfunction in adult cancer survivors, issued last December by the American Society of Clinical Oncology (ASCO) and endorsed by the American Heart Association (*J Clin Oncol.* 2017 Mar 10;35[8]:893-913), but notably not endorsed by the American College of Cardiology, despite having an ACC representative on the guideline panel. In 2015, the ACC started a Cardio-Oncology Section, one of 20 special-interest sections it maintains, and by mid-2017 the section had some 500 members.

Despite these milestones and spread of the cardio-oncology concept, the cardiovascular consequences of cancer treatment remain underappreciated and incompletely understood by many cardiologists and primary care physicians, experts say. Other current limitations include the absence of a well defined cardio-oncology subspecialty and training infrastructure and significant gaps in the field's evidence base, including no direct proof of the clinical value of

screening for the earliest signs of cardiovascular adverse effects in cancer patients. “I’ve had



recent conversations with cardiologists who said ‘I’m not sure what cardio-oncology is,’ ” said Tomas G. Neilan, MD, (pictured left) director of the cardio-oncology program at Massachusetts General Hospital in Boston. “The No. 1 priority for cardio-oncology is to raise awareness about it at every level: patients, their support people, oncologists, cardiologists, and primary care physicians,” said Daniel J. Lenihan, MD, until recently professor of medicine and a cardio-oncologist at Vanderbilt University in Nashville, Tenn., who in September moved to Washington University in St. Louis to start a cardio-oncology program there.

#### **More than just heart failure**

A few decades ago, the concept of cardiovascular damage during cancer therapy focused entirely on myocardial damage caused by anthracyclines and chest radiation, a concern that eventually

expanded to include trastuzumab (Herceptin) and other agents that target the human epidermal growth factor receptor 2 (HER2). These treatments cause significantly reduced left ventricular ejection fractions and heart failure (HF) in a significant minority of treated patients. Patients who receive combined treatment with an anthracycline and trastuzumab are at the highest risk for developing HF with reduced ejection fraction, but even among patients treated with this combination, fewer than 5% develop outright HF.

While this parochial view of cardio-oncology has recently shifted, it remains true that myocardial damage from a relatively large cumulative anthracycline dose, or from radiation, causes some of the most extreme cases of cardiovascular adverse effects and remains an ongoing problem as these treatments stay front line for selected cancer patients.

But some of the recent burgeoning of cardio-oncology has followed the recognition that many other drugs and drug classes can cause a spectrum of adverse cardiovascular effects...

“There has been a significant focus on heart failure and cardiomyopathy due to anthracyclines and HER2-targeted therapies. I think the field will continue to evolve over the next 5 years to focus on other cardiovascular complications, including arrhythmias and vascular disease,” observed Michael Fradley, MD, director of cardio-oncology at Moffitt Cancer Center in Tampa. “In addition, there will be an increased focus on targeted drugs and immunotherapies,” agents that Dr. Fradley said “have many unique cardiovascular complications. We need additional guidelines regarding the management of a variety of cardiotoxicities as well as long-term monitoring strategies...”

In his own recent review, Dr. Fradley highlighted adverse cardiovascular effects from additional anticancer drug classes, including proteasome inhibitors, which can trigger hypertension and cardiomyopathy; immunomodulators, implicated in causing both venous and arterial thromboembolism; and the immune checkpoint inhibitors, linked with myocarditis, arrhythmias, hypotension, and myocardial ischemia (Eur Heart J. 2016 Sept 21;37[36]:2740-2). A similarly broad spectrum of adverse cardiovascular effects linked with a wide range of anticancer treatments also appeared in the ESC 2016 position paper on cancer treatments.

But while the range of cancer treatments that can have some impact on the cardiovascular system is strikingly large, experts uniformly caution that far from every patient treated for cancer needs an immediate cardiology consult and workup, especially when the cancers appear in young adults.

“We’re not quite at the point where every cancer patient needs to be seen by a cardiologist or cardio-oncologist,” Dr. Fradley noted in an interview.

The most common cardiology referrals made by Sandra M. Swain, MD, are for patients with either breast cancer or lymphoma who undergo treatment with an anthracycline. “If a patient receiving this treatment has a history of any cardiovascular disease, I’ll refer them. But if a patient is just undergoing adjuvant chemotherapy with another drug, and if everything looks fine and an echocardiogram shows everything is normal, then I don’t refer. I refer [to a cardiologist] any patient with a cardiac history just in case they experience toxicity, but that’s not every patient. It’s not feasible to refer every patient,” said Dr. Swain, a medical oncologist who is professor of medicine and associate dean for research development at Georgetown University in Washington.

### **Cardio-oncology centers**

The rise of cardio-oncology has given rise to a new academic niche, the cardio-oncology clinic. Starting from almost no programs a few years ago, by 2016 one tally put the total number of U.S. self-designated cardio-oncology centers at about 40 (Heart Fail Clin. 2017 Apr;13[2]:347-55), and that number undoubtedly grew even more during the year since. While these programs promote and advance the nascent subspecialty of cardio-oncology, and provide a foundation for development of formalized training programs, many experts see a clear hierarchy of risk that distinguishes the patients who should ideally be managed at these focused, multidisciplinary programs from the lower-risk patients who probably do fine under the care of just their oncologist or their oncologist in collaboration with a community cardiologist or primary care physician.

“The cardio-oncology community recognizes that it is nice to have programs at academic centers but it’s more important to deliver this care in the community,” said Dr. Lenihan. “Many cancer patients have no prior history of cardiovascular disease. These low-risk patients don’t necessarily need a cardio-oncologist. They may need to have their blood pressure managed more effectively or receive other preventive care, but that can certainly be done locally. There are low-risk patients who don’t need to go to a major center.”

But it’s different when patients receive an anthracycline or an anthracycline plus trastuzumab. “This high-risk population is best seen at a cardio-oncology center.” Dr. Lenihan (pictured below) also included in this high risk subgroup patients treated with mediastinal radiation, an option often used during the 1980s-2000s.

“Any time a patient receives treatment with the potential to cause a cardiovascular effect, which is pretty much any drug that now comes out, you need an accurate baseline assessment. ...But it does not need to be done at a cardio-oncology center,” Dr. Lenihan said in an interview.

“For the vast majority of patients, care can be at community hospitals, similar to the delivery of oncology care. Some patients need referral to tertiary cardiology centers for advanced HF or to undergo advanced procedures, but that is a very small percentage of patients,” said Ana Barac, MD, director of the cardio-oncology program at the MedStar Heart Institute in Washington, and chair of the ACC’s Cardio-Oncology Section.

“Cardio-oncology centers are good for patients with type I damage from anthracycline treatment, especially patients who already had underlying heart disease,” said Michael S. Ewer, MD, a cardiologist and professor of medicine at MD Anderson Cancer Center in Houston. Specialist centers are also for patients with cardiovascular risk factors: older age, diabetes, preexisting coronary artery disease, and patients who receive cardiotoxic type I therapy (J Clin Oncol. 2005 May;23[13]:2900-2). Also, patients with a significant, immediate cardiac reaction to treatment, and those with an unexpected cardiac reaction, Dr. Ewer said.

A somewhat more expansive view of the typical cardio-oncology patient came from Dr. Neilan, based on the patients he sees at his program in Boston. Dr. Neilan estimated that roughly 60%-70% of his patients first present while they undergo active cancer treatment, with another 20% coming to the program as cancer survivors, and a small percentage of patients showing up for cardiology assessments and treatments without a cancer history. Among those with a cancer history, he guessed that perhaps 10%- 20% were treated with an anthracycline, at least 10% received trastuzumab, and about 10% received radiation treatment. “I also see a lot of patients with complications from treatment” with tyrosine kinase inhibitors, VEGF inhibitors, and immunotherapies. “I don’t see a lot of patients for cardiovascular disease assessment before they start cancer therapy,” Dr. Neilan added.

#### **A new cardiology subspecialty?**

These views of how cardio-oncology is practiced in the real world raise a question about the role of the growing roster of U.S. cardio-oncology programs. If most cancer patients can have their cardiology needs taken care of in the community, how do all the academic programs fit in? The answer seems to be that they model successful oncology and cardiology collaborations, provide a training ground for physicians from both specialties to learn how to



collaborate, and serve as the home for research that broadens the field's evidence base and moves knowledge forward.

"Education and partnerships with oncology teams is the key," said Dr. Barac. "Our traditional subspecialty training focused on 'treating cancer' and 'treating cardiovascular disease.' Learning about and seeing effective partnerships during training" is the best model to foster cardiology and oncology partnerships among early-career physicians, she suggested.

"What is the spectrum of knowledge required to be proficient in cardio-oncology, and how do we enhance training at the resident or fellowship level? How do we get [all cardiology] trainees exposed to this knowledge?" wondered Dr. Lenihan, who viewed cardio-oncology programs as a way to meet these needs. "Cardio-oncology is not an established subspecialty. A goal is to establish training requirements and expand training opportunities. And the whole field



needs to contribute to clinical research. We need cardio-oncologists to share their experience."

ASCO's cardiac dysfunction practice guideline, first released last December and formally published in March, is likely helping to further entrench cardio-oncology as a new subspecialty. The guideline was "a remarkable step forward," said Dr. Barac (pictured left). In addition to establishing a U.S. standard of care for preventing and monitoring cardiac dysfunction in cancer patients, "I use it as a guide for creation of referral pathways with my oncology colleagues, as well as in education of cardiovascular and oncology trainees," she said in an interview.

Though produced primarily through ASCO's leadership, the target audience for the guideline seems to be as much cardiologists as it is oncologists. Dissemination of the

guideline to cardiologists snagged when it failed to appear in the cardiology literature. That wasn't the original plan, said guideline participants.

"Before we started, it was agreed that both ASCO and the ACC would publish it. We had a [letter] signed by the president of the ACC saying the ACC would publish it," recalled Dr. Lenihan, a guideline coauthor. "After all the details were settled, the ACC bailed. They said that they had changed their organizational structure and that they wouldn't publish the guideline even though they had agreed to." Not having the guideline appear simultaneously in the cardiology literature hinders getting the message to cardiologists, he said.

"I served as the ACC representative on the guideline, and the lack of ACC endorsement was the unfortunate consequence of approval and publication timing that coincided with restructuring of the ACC committees," said Dr. Barac. "It absolutely does not reflect a lack of

interest from the ACC.” As an example of the College’s commitment example, she cited an ACC 1.5-day educational course on cardiovascular care of oncology patients held for the first time in February 2017 and scheduled for a second edition next February.

Further advancing awareness of patients with cardio-oncology issues, what Dr. Moslehi has called “an emerging epidemic,” seems the most fundamental of the goals currently advanced by many active in this field.

One step to grow the subspecialty that he and his associates at Vanderbilt have taken is to start this year a formally recognized fellowship program in cardio-oncology; an initial class of three cardiologists started in the program this summer. The Vanderbilt group also plans to launch a website before the end of 2017 that will include an oncology-drug database that compiles all available information on each agent’s cardiovascular effects. The planned website will aggregate links to all existing cardio-oncology programs.

“We will absolutely see the field grow,” said Dr. Swain. “It has only sprung up in the past 10 or so years. It is now getting recognition, people are being trained in cardio-oncology, and it will grow as a subspecialty. It’s very exciting, and it’s better for patients.”

“What oncologists and cardiologists want to do is to optimize oncologic outcomes but with an acceptable adverse event profile. The cardio-oncologist helps push that envelope. The goal is not to eliminate cardiac events at the expense of oncologic outcomes, but to shift the balance to fewer and less severe cardiac events without unduly compromising oncologic outcomes,” explained Dr. Ewer. Cardio-oncology grapples with one of the core challenges of medicine: how to balance the potential risks from treatment against its potential benefits, he observed.

Dr. Neilan is a consultant to Ariad and Takeda. Dr. Lenihan is a consultant to Janssen and Roche and has received research funding from Takeda. Dr. Moslehi is a consultant to Acceleron, Ariad, Bristol-Myers Squibb, Incyte, Pfizer, Takeda/ Millennium, Verastem and Vertex. Dr. Ewer, Dr. Fradley, and Dr. Barac had no relevant disclosures. Dr. Swain has been a consultant to Genentech and Roche. [mzoler@frontlinemedcom.com](mailto:mzoler@frontlinemedcom.com) On Twitter [@mitchelzoler](https://twitter.com/mitchelzoler)