Advanced Heart Failure Therapies for Cancer Therapeutics–Related Cardiac Dysfunction

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KEYWORDS

• Heart failure • Right ventricular failure • Chemotherapy-induced cardiomyopathy
• Cancer therapeutics–related cardiac dysfunction • Anthracyclines
• Mechanical circulatory support devices • Heart transplant • Cardiac resynchronization therapy

KEY POINTS

- Cancer survivors who undergo advanced therapies for heart failure (HF) are predominantly young women with low prevalence of traditional cardiovascular comorbidities.
- Valvular disease is common especially among patients with chest radiation and may require surgical intervention.
- Mechanical circulatory support (MCS) is safe in carefully selected patients with chemotherapy-induced cardiomyopathy (CCMP).
- Careful assessment of right ventricular (RV) function should be performed in patients with CCMP given the high rates of RV failure in patients undergoing left ventricular assist device (LVAD) implantation.
- Orthotopic heart transplant (OHT) in patients with CCMP is associated with comparable outcomes to other causes of HF.

INTRODUCTION

Over the past decade, evolving cancer treatments have resulted in improved overall survival. It is estimated that there are approximately 15 million cancer survivors in the United States today and this number is expected to reach 20 million by 2026.[1] Thus, many cancer survivors in the current era die from noncancer causes, such as cardiovascular diseases.[2–4]

Although novel cancer therapies are increasingly used, anthracyclines remain the cornerstone of cancer treatment, especially in hematologic malignancies, sarcomas, and breast cancer. Anthracyclines have long been known to predictably cause cardiotoxicity, which may progress to long-term HF.[5] In addition, new targeted therapies (namely, human epidermal growth factor receptor 2 antagonists as well as other tyrosine kinase inhibitors) have also been associated with HF.[6] Thus, unsurprisingly, many cancer survivors are living with and dying from progressive HF.

Moreover, other treatment modalities, such as radiation, further increase this risk through direct

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myocardial effects, valvulopathy, and accelerated vascular disease.[7] Therefore, 2 main types of cardiomyopathies that result from the cardiotoxic effects of cancer therapies are recognized: CCMP and radiotherapy-induced cardiomyopathy (RT-CMP), collectively known as cancer therapeutics–related cardiac dysfunction (CTRCD).[8] Comorbid cardiovascular diseases in cancer survivors confer poorer survival, and patients with HF from chemotherapy have one of the worst prognoses of all forms of HF.[9]

Recently, oncocardiology has emerged as a multidisciplinary practice to mitigate the risk of cardiovascular disease in cancer patients through prevention and early interventions.[10,11] Given the complexity of antineoplastic therapies and extent of comorbid conditions in these patients, advanced HF treatment in this population requires special considerations. This article reviews the epidemiology, pathophysiology, and available treatment modalities for cancer survivors who develop advanced HF in the era of device therapies and heart transplantation.

EPIDEMIOLOGY OF ADVANCED HEART FAILURE IN CANCER SURVIVORS

The exact number of patients with advanced HF among cancer survivors is not known. Data extrapolated from large registries for advanced HF (eg, Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] and United Network for Organ Sharing [UNOS]) can, however, reveal the approximate contribution of CTRCD to the overall advanced HF population. For example, in INTERMACS, CCMP was the primary diagnosis in 75 (2%) of 3812 patients implanted between 2006 and 2011 in the United States.[12] In UNOS, CCMP accounted for 453 (0.8%) of 51,765 patients who underwent primary heart transplantation between 1987 and 2011.[13] RT-CMP, on the other hand, is much rarer. For example, in UNOS, RT-CMP was diagnosed in 87 (0.2%) of 45,041 adults who underwent transplantation (2000–2015).[14] Similarly, of 297 patients who underwent heart transplant at Mayo Clinic from 1992 to 2010, only 12 (4%) had history of radiation therapy.[15] These numbers most likely represent an underestimation of the general pool of patients with CTRCD with end-stage HF, because only a small fraction of these patients are eligible for or have access to durable mechanical support or transplant.

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Large registries have revealed certain unique characteristics of patients with advanced CTRCD. These patients are younger (mean age 44–53 years) and overwhelmingly women (62%–72%), contrary to nonischemic cardiomyopathy (NICM) and ischemic cardiomyopathy (ICM), which are more prevalent in older and male patients.

For example, in a review of the INTERMACS registry for MCS, the CCMP cohort was predominantly female (CCMP 72% vs NICM 24% vs ICM 13%; $P<.0001$). The CCMP patients were significantly younger than those receiving MCS for ICM (mean age 53 vs 60 years old; $P<.001$) but of similar age to other forms of NICM (53 vs 51 years old; $P = .41$). Lower body mass index was noted in the CCMP group (CCMP 26.0 vs NICM 28.9; $P<.0001$ vs ICM 28.0; $P = .0019$). Comorbid conditions were favorable in the CCMP group with less frequent prevalence of diabetes (CCMP 25% vs NICM 31%; $P = .29$ vs ICM 46%; $P = .0004$), coronary disease (CCMP 0% vs NICM 16%; $P = .0002$ vs ICM 100%; $P<.0001$), previous alcohol abuse (CCMP 5% vs NICM 16%; $P = .01$ vs ICM 18%; $P = .01$), or smoking history (CCMP 1% vs NICM 12%; $P = .01$ vs ICM 15%; $P = .0016$). Therapies prior to MCS implantation were variable in that CCMP patients were more likely to be receiving angiotensin-converting enzyme inhibitors (CCMP 68% vs NICM 53%; $P = .02$ vs ICM 51%; $P = .01$), yet they were less likely to be implanted with an ICD (CCMP 66% vs NICM 77%; $P = .03$ vs ICM 77%; $P = .03$).

Corroborated by data from the transplantation registries, it is clear that patients with CTRCD with advanced HF have lower prevalence of comorbidities, such as hypertension, diabetes, obesity, and ischemic heart disease. There also seems to be lower utilization of implantable defibrillators (ICDs), probably due to acuity and severity of HF presentation, not allowing time for optimal medical therapy and defibrillator implantation, but this remains speculative. A majority of patients in these registries are breast and hematologic cancers survivors, for whom anthracyclines are most commonly given. **Table 1** summarizes the demographics and clinical characteristics of these patients.

HEART FAILURE PATHOPHYSIOLOGY AND RIGHT VENTRICULAR INVOLVEMENT

HF caused by cardiotoxicity of drugs is believed to be a global myocardial process. Therefore, it is intuitive to imagine that both the left and right ventricles are equally affected. Because the RV contains less muscle mass and consequently less contractile reserve, it stands to reason that the toxic effects of chemotherapy should be felt in