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Reviews

Heart Failure Therapies for End-Stage Chemotherapy–Induced Cardiomyopathy

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ABSTRACT

With ongoing advancements in cancer-related treatments, the number of cancer survivors continues to grow globally, with numbers in the United States predicted to reach 18 million by 2020. As a result, it is expected that a greater number of patients will present with chemotherapy-related side effects. One entity in particular, chemotherapy-related cardiomyopathy (CCMP), is a known cardiotoxic manifestation associated with agents such as anthracyclines, trastuzumab, and tyrosine kinase inhibitors. Although such effects have been described in the medical literature for decades, concrete strategies for screening, prevention, and management of CCMP continue to be elusive owing to limited studies. Late recognition of CCMP is associated with a poorer prognosis, including a lack of clinical response to pharmacologic therapy, and end-stage heart failure. A number of advanced cardiac therapies, including cardiac resynchronization therapy, ventricular assist devices, and orthotopic cardiac transplantation, are available to for end-stage heart failure; however, the role of these therapies in CCMP is unclear. In this review, management of end-stage CCMP with the use of advanced therapies and their respective effectiveness are discussed, as well as clinical characteristics of patients undergoing these treatments. The relative paucity of data in this field highlights the importance and need for larger-scale longitudinal studies and long-term registries tracking the outcomes of cancer survivors who have received cardiotoxic cancer therapy to determine the overall incidence of end-stage CCMP, as well as prognostic factors that will ultimately guide such patients toward receiving appropriate end-stage care. (*J Cardiac Fail 2016;*■■:■■–■■)

Key Words: Cardio-oncology, chemotherapy, chemotherapy induced cardiomyopathy, cardiotoxicity, anthracycline, trastuzumab, tyrosine kinase inhibitors, mechanical circulatory support, cardiac resynchronization therapy, heart transplantation.

Advancements in early detection and treatment of cancer contributed to the presence of nearly 14.5 million American cancer survivors in 2014,[1] with numbers projected to reach 18 million by 2020.[2] The advancements in chemotherapy and the rising population of survivors have begun to highlight the importance of the cardiac side-effect profile of many chemotherapeutic agents, especially with increasing administration of these agents in an aging population with traditional cardiovascular risk factors.[3] Chemotherapy-induced cardiomyopathy (CCMP) has become a recognized entity within this spectrum of chemotherapy-associated cardiotoxicity. Among the different chemotherapy regimens associated with CCMP, anthracyclines in particular have been shown to cause end-stage American Heart Association (AHA) Stage C–D heart failure (HF).[4] A paucity of data exists regarding outcomes and response to traditional interventions in patients who develop end-stage CCMP. Analyses of the largest transplant registries of patients with advanced HF have suggested that prevalence of end-stage HF due to chemotherapy is up to 2.5%,[5] but the true incidence of CCMP in the advanced HF population in the United States is unknown owing to the lack of large-scale epidemiologic and outcomes studies

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encompassing CCMP. In a review of patients referred for orthotopic heart transplantation (HT) from 2000 to 2008, Oliveira et al found a significant rise of CCMP as a cause of advanced HF during the time period of 2005–2008, compared with a relatively constant rate of nonischemic cardiomyopathy (NICM) referrals. This finding may reflect the advent of newer targeted chemotherapeutic agents with off-target cardiotoxicities resulting in HF.[5,6] The present review outlines the known evidence to date surrounding the efficacy of advanced cardiac therapies—including pharmacologic therapies, cardiac resynchronization therapy, and end-stage interventions such as mechanical circulatory support and cardiac transplantation—in the CCMP patient population.

Cardiotoxic Agents and Mechanisms

Several chemotherapeutic agents have been known to cause both short and long-term cardiotoxicity. A number of chemotherapeutic agents have been shown to cause cardiotoxic effects without clinically significant HF or cardiomyopathy. The focus in this review is on agents that have been shown to cause CCMP and severe heart failure, particularly anthracyclines, trastuzumab, and tyrosine-kinase inhibitors. Other agents, such as fluoropyridimines, are less commonly associated with CCMP but have been reported in the literature. Because the anticancer mechanisms behind each agents therapeutic effects vary, so too do the purported mechanisms of cardiotoxicity.

There are 2 major classifications of cardiotoxicity—types 1 and 2—that have been implicated in CCMP; although this nomenclature is likely oversimplified and does not adequately address all potential mechanisms of chemotherapy-induced cardiotoxicity, the implications of this classification system may influence management regarding propensity for reversibility and duration of surveillance for cardiotoxicity. Type 1 cardiotoxicity involves characteristic histopathologic changes in the cardiomyocyte ultrastructure, including vacuolization, myofibrillar disarray and dropout, and even myocyte necrosis at higher dosages. These changes are thought to result in potentially irreversible damage and cardiac dysfunction, and may manifest years after therapy. Type 2 cardiotoxicity, on the other hand, does not appear to cause ultrastructural changes to the myocardium. Therefore, there is a higher likelihood of recovery to baseline cardiac function 2–4 months after chemotherapy is stopped.[7] Early detection and prompt initiation of treatment may prevent left ventricular (LV) remodeling and progression to HF from type 1 cardiotoxicity; however, late recognition can result in potentially irreversible LV dysfunction despite treatment.[8,9] Anthracyclines and trastuzumab have been the prototypical class of drugs associated with types 1 and 2 cardiotoxicity, respectively. It should be noted that all chemotherapeutic agents cannot be strictly defined within these 2 entities. For example, with tyrosine kinase inhibitors such as sunitinib, although ultrastructural changes with mild cardiomyocyte hypertrophy and myocyte vacuolization have been observed as a cardiotoxic manifestation, a type 2–like cardiotoxicity with this specific drug class has been postulated as a mechanism, owing to its reversibility.[10]

Pharmacologic Therapies of Chemotherapy-Induced Cardiomyopathy

Prevention

Strategies to prevent CCMP include efforts to identify risk factors, use of imaging and biomarkers to detect early subclinical toxicity, development of less cardiotoxic chemotherapeutic derivatives, use of targeted cardioprotective agents, and use of HF medications, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and beta-blockers, as primary preventative therapies.[11–14]

The true incidence of anthracycline-induced CCMP is unknown. In one study of patients receiving doxorubicin at a cumulative dose of 550 mg/m^2, the incidence of those who would develop doxorubicin-related CHF was estimated to be ~26%, with age being a major risk factor.[15] However, the risk of developing CCMP exists even in patients receiving <400 mg/m^2, with some studies suggesting an incidence of 3–5%.[15–17] Through analyses of the largest registries of patients with advanced HF (such as United Network for Organ Sharing [UNOS], Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS]), Oliveira et al estimated the prevalence of end-stage HF from CCMP to be 0.5%–2.5%, the vast majority of which was suspected to be due to anthracycline exposure.[4]

Primary prevention strategies evaluated to prevent anthracycline-induced cardiotoxicity include reducing cardiotoxic potency by administration via continuous infusion, liposome encapsulation, using less cardiotoxic derivatives (eg, epirubicin or idarubicin), or using cardioprotective agents, such as dexrazoxane, in conjunction with treatment.[11–13] A number of different anthracycline administration schedules were evaluated in early clinical trials, including a single bolus dose every 3 weeks, 3 divided doses every week, or 3 divided doses given 3 consecutive days every 3 weeks. Some studies in adults have suggested that use of divided doses can result in significantly less cardiotoxicity than use of bolus doses.[18] Another theoretic cardioprotective strategy is liposomal encapsulation of anthracyclines, which modifies the pharmacokinetics and restricts the tissue distribution of anthracyclines to inside the vessel wall of organs with tight capillary junctions such as the heart, whereas it can more readily penetrate through tumor vasculature but without compromising antitumor efficacy.[19,20] However it should be noted that there was no difference in cardioprotection between bolus versus continuous administration in a study of a pediatric population.[21] The cardioprotective agent dexrazoxane is currently the only FDA-approved medication to reduce the risk of anthracycline-induced cardiotoxicity in women with metastatic breast cancer who have received a cumulative dose of ≥300 mg/m^2 of doxorubicin or its equivalent.[22–25] A multicenter randomized phase III study of the cardioprotective effect of dexrazoxane in advanced/metastatic breast cancer patients treated with

anthracycline-based chemotherapy showed that patients treated with dexarazoxane experienced significantly fewer cardiac events (39% vs 13%; $P < .001$) and a lower and less severe incidence of congestive HF (11% vs 1%; $P < .05$).[22] Owing to concerns of the potential risk of acute myeloid leukemia and myelodysplastic syndrome in children, its use is not FDA approved in the pediatric population, where higher doses of anthracyclines may be used. More recently, however, dexrazoxane was shown to be cardioprotective without reducing antitumor efficacy and was not associated with a significant increase in second malignancies in pediatric patients receiving doxorubicin treatment for newly diagnosed T-cell acute lymphoblastic leukemia or advanced-stage lymphoblastic non-Hodgkin lymphoma.[26] The mechanism of cardioprotection with dexrazoxane is currently thought to be through its ability to interfere with TOP2β, which conceals DNA double-strand breaks.[27] In addition, though not statistically significant, a Cochrane meta-analysis of 8 trials evaluating the use of dexrazoxane showed a trend toward a decreased clinical response rate with anthraycline therapy (risk ratio 0.89, 95% CI 0.78–1.02).[28] Thus, there is ongoing interest in exploring other pharmacologic therapies with potential cardioprotective properties to patients at risk for cardiotoxicity.

An evolving strategy for primary prevention of CCMP is to use neurohormonal antagonists, including ACE inhibitors, angiotensin receptor antagonists, and beta-blockers for primary prevention. Several small clinical trials of beta-blocker therapy (with the use of carvedilol, metoprolol, and nebivolol), ACE inhibitor therapy (with the use of enalapril), or angiotensin receptor antagonists (with the use of candesartan and telmisartan) prevented declines in LV ejection fraction (LVEF) compared with placebo control groups in patients being treated with the use of anthracyclines or other chemotherapeutic regimens.[29–34] Kalay et al randomized 50 adult patients with predominantly a diagnosis of breast cancer and lymphoma receiving anthracycline therapy to either carvedilol 12.5 mg once daily or placebo. There was no change in the LVEF in the carvedilol group after 6 months whereas there was significant decrease in LVEF by 17% in the placebo group.[31]

The benefits of neurohormonal antagonists in preventing CCMP may be additive, but this has not been a consistent finding. Patients undergoing anthracycline treatments for acute leukemia or other malignant hemopathies appeared to benefit from the combination of carvedilol and enalapril in one randomized prospective trial.[30] More recently, the effects of angiotensin receptor antagonists and beta-blockers were evaluated in the randomized, 2×2 factorial Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy (PRADA) trial of 120 women with early breast cancer. It was reported that those who received a daily 32-mg dose of adjunctive candesartan had a significantly smaller decline in LVEF from baseline to end of cancer treatment compared with those who received matching placebo ($P = .03$). However, there were no significant group differences in LVEF changes between the patients randomly assigned to receive 100 mg daily metoprolol succinate versus placebo.[34]

It is important to note that the studies conducted to date have been relatively small in scale and with relatively short-term follow-ups (~6 mo). Variable results have been demonstrated regarding natriuretic peptides, cardiac troponin levels, or cardiac magnetic resonance imaging findings. None of the trials conducted to date have been adequately powered to address clinical outcomes, and they have mostly used changes in LVEF as primary end points. Although use of neurohormonal antagonists to prevent cardiac toxicity of chemotherapy has not been widely adopted in clinical practice, use of ACE inhibitors, angiotensin receptor antagonists, and/or beta-blockers for primary prevention of cardiotoxicity may be considered, particularly in patients who are at higher risk. Additional adequately powered prospective trials evaluating this approach are needed.

Treatment

Establishing an early diagnosis of CCMP and initiating early medical treatment may be important steps in preventing irreversible cardiac injury and advanced HF. When patients develop evidence of cardiotoxicity with decreased LVEF with or without symptoms of HF, discontinuation of the chemotherapeutic agent, if at all possible, is crucial. In addition, standard guideline-directed medical therapies for HF should be initiated according to current guidelines for HF with reduced ejection fraction,[11] because a number of clinical series have reported clinical response and improvement in LVEF.[9,35–38] Thus, it is possible that initiating cardioprotective therapy may allow for continued cancer therapy with close monitoring if there is improvement in LV function.

An open-label single-center clinical study by Cardinale et al evaluated 114 high-risk adult patients diagnosed with a variety of malignancies, including breast cancer, leukemia, and lymphoma, with elevated troponin I after receiving high-dose anthracyclines. They were randomized to receive either enalapril at a starting dose of 2.5 mg/d with escalation to 20 mg/d if tolerated or placebo for 1 year. Twenty-five patients (43%) in the control group had a decrease in LVEF compared with none in the enalapril group (maximum dose was 16 ± 6 mg/d). Additionally there was a significant reduction in cardiac events in the group receiving enalapril, mainly owing to decreased HF incidence, compared with the placebo group.[29]

Cardinale et al evaluated 201 consecutive patients with a variety of malignancies who presented with anthracycline-induced cardiomyopathy—defined as LVEF ≤45%—and serially evaluated LVEF while initiating treatment with carvedilol and enalapril with the intention to titrate to goal-directed doses. However, 36% of patients were only able to tolerate enalapril alone, owing to adverse effects with the use of carvedilol. The majority of patients (74%) exhibited New York Heart Association (NYHA) functional class I–II symptoms and 26% exhibited NYHA III–IV symptoms. Of the patients undergoing HF therapy, 42% were classified as responders (demonstrated recovery of LVEF to ≥50%), 13% were partial responders (LVEF increased ≥10% but did not

exceed 50%), and the rest were nonresponders (LVEF increased <10% and did not exceed 50%). No patients who started HF therapy >6 months after the end of chemotherapy showed improvement in LVEF. Finally, patients who were responders had a lower cumulative cardiac event rate than partial responders and nonresponders (5%, 31%, and 29% respectively; $P < .001$).[9]

Cardinale et al later conducted a single institutional prospective study of 2625 patients being treated for various malignancies with the use of anthracycline with a median follow-up of 5.2 years with serial LVEF measurements. The overall incidence of cardiotoxicity—defined as an LVEF decrease of >10% to <50%—in this study was 9%: 9.7% of the patients with breast cancer and 6.2% of the patients with non-Hodgkin lymphoma. The median time between the end of chemotherapy and cardiotoxicity development was ~3.5 months. In this study, HF therapy was initiated on all patients with cardiotoxicity around the time of diagnosis; however, only 8% and 1.3% of patients were able to tolerate monotherapy with enalapril and beta-blockers, respectively. Ninety-eight percent of cardiotoxicity cases occurred within the 1st year, with 11% of patients demonstrating full recovery (recovery of LVEF to baseline) with a mean time to recovery of 8 months; 71% of patients had partial recovery (LVEF increase >5% to >50%), with the rest not demonstrating any recovery. These studies appear to demonstrate the concept that timely diagnosis and immediate pharmacotherapy on diagnosis of anthracycline-induced cardiomyopathy may be crucial in allowing for the best chances of LVEF recovery.[39]

The value of treatment with ACE inhibitors was also demonstrated in a prospective series of women who were monitored for evidence of LV dysfunction while they received epirubicin for metastatic breast cancer; 7 of 8 women treated with an ACE inhibitor had a sustained increase in LVEF of ≥15%. In contrast, there was only 1 such response among 33 cases treated with a digitalis preparation plus a diuretic.[35] Although data are limited, these results support the use of ACE inhibitors as 1st-line therapy for both asymptomatic LV dysfunction and overt HF with reduced ejection fraction.

Nevertheless, it is important to note that multicenter randomized clinical trials have not been performed and that the large-scale randomized clinical trials evaluating efficacy of different medications for HF with reduced ejection fraction overall have, with few exceptions, not reported outcomes among the different nonischemic etiologies for HF. Use of newer medications, including the neprilysin–angiotensin receptor antagonist sacubitril-valsartan, which has been shown to be superior to the ACE inhibitor enalapril, and the I_f channel inhibitor ivabradine for patients in sinus rhythm with elevated resting heart rate despite maximally tolerated beta-blocker doses, may also be considered.[40,41] Additional clinical data are needed to assess whether patients with CCMP benefit to the same degree as patients with other etiologies for HF that have greater representation in large-scale clinical trials.

Among patients who have subclinical evidence of cardiotoxicity detected by cardiac biomarkers such as troponins or natriuretic peptides, or detected by imaging such as strain echocardiography, initiation of treatment with the use of HF medications has also been evaluated. Prevention of worsening LVEF appeared to be more pronounced if there was early initiation of ACE inhibitor and beta-blocker therapy. If LVEF improves on subsequent reassessments, consideration may be given to restarting chemotherapy after multidisciplinary assessment taking the risk of recurrent cardiac injury into consideration.

Cardiac Resynchronization Therapy

An important therapeutic option for patients with CCMP is cardiac resynchronization therapy (CRT).[42,43] In patients with LVEF <35%, and QRS duration >120 ms, CRT is a class I indication according to American College of Cardiology (ACC)/AHA guidelines for the management of cardiomyopathy.[44] In patients with CCMP meeting standard criteria for CRT, there appears to be a favorable response following CRT implantation. Jones et al[45] wrote the first published case of CRT use in a patient with CCMP following treatment with the use of anthracycline for acute myeloid leukemia. Another report involving a 46-year-old woman treated for breast cancer highlighted the role of CRT in CCMP in a patient with narrow QRS duration, albeit with documented echocardiographic evidence of dyssynchrony.[46] Ajijola et al[47] reported a series of 4 consecutive patients with anthracycline-induced CCMP, all of who had prolonged QRS duration (>120 ms). In this population, mean LVEF improved from 21 ± 4.7% to 34 ± 5% at 1 month and increased further to 46 ± 7.5% at 6 months. Also improved were LV end-diastolic volume and dimension, and NYHA functional class. Of particular interest is that the response was favorable regardless of the duration of cardiomyopathy (0.9–8 y), suggesting that there is no temporal limitation to CRT efficacy in CCMP. In a larger study by Rickard et al,[48] 18 patients with CCMP from anthracycline use who underwent CRT implantation were compared with 189 patients with other forms of NICM. The authors demonstrated that these patients showed significant improvements in LVEF, LV dimensions, mitral regurgitation, and NYHA functional class in response to CRT. Compared with other NICM patients, the magnitude of improvement in cardiac indices was similar in the CCMP cohort.

Although there are a limited number of studies examining CRT in CCMP patients, it is important to note that the pathophysiology of CCMP is such that in the presence of echocardiographic or electrocardiographic evidence of dyssynchrony, CRT can have a significant impact. Knowing that there is likely a therapeutic benefit to CRT in CCMP, a number of important questions remain. It is unclear whether the benefit of CRT in CCMP can be extended to cardiomyopathy from nonanthracycline chemotherapeutic agents or to all forms of cardiomyopathy in cancer patients. Furthermore, the arrhythmia burden and appropriate versus inappropriate defibrillator therapies in this population are poorly understood. It also remains unclear whether

dyssynchrony needs to be demonstrated for CRT to be effective. Some of these questions may be answered by a large randomized control trial, the Multicenter Automated Defibrillator Implantation Trial—Chemotherapy-Induced Cardiomyopathy (MADIT-CHIC; Clinical Trial Registration No. NCT02154721).[49] The primary end point of the trial is improvement in LVEF, as determined by means of echocardiography at 6 months. The secondary end points are all-cause mortality, LV volumes/dimension, and NYHA functional class. Finally, regarding sudden death prophylaxis, there may be a significant number of CCMP patients who do not receive an implantable cardioverter defibrillator (ICD). A review by Oliveira et al of the INTERMACS registry showed that only 66% of patients with CCMP had ICDs compared with 77% of other patients, emphasizing the need for active echocardiographic screening in cancer survivors who have a history of cardiotoxic chemotherapy.[4] CRT holds promise for patients with CCMP, but much remains to be understood before wide application of this therapy to patients with cardiomyopathy and narrow QRS.

Mechanical Circulatory Support

Mechanical circulatory support (MCS) is well accepted for patients with advanced HF both as a bridge to heart transplantation (BTT) as well as destination therapy (DT), for patients currently ineligible for transplantation. Implants as DT have continued to increase, representing almost one-half of patients since 2012.[50] MCS therapy has been used as both BTT and DT in patients with end-stage HF due to CCMP.

Extracorporeal Membrane Oxygenation

Extracorporeal membrane oxygenation (ECMO) is a modality for short-term cardiopulmonary support of patients unable to achieve adequate physiologic support owing to heart/lung failure, such as severe biventricular failure or cardiogenic shock with impaired oxygenation.[51] Several studies have evaluated the morbidity and mortality of ECMO in adult patients with HF, with one study showing a 5-year survival rate of 24%.[52] Although most of these patients received ECMO in the setting of postcardiotomy, acute myocardial infarction, and decompensated HF, to our knowledge no studies have identified the use of ECMO in adults with end-stage HF due to CCMP. ECMO use as BTT was <1% in CCMP in a study by Oliveira et al.[5] Overall outcomes with ECMO use are poor and marked by early mortality after HT[53] or MCS.[54] Caution is advised in the setting where patients may not be a candidate for either transplantation or MCS.

Clinical Demographics and Outcomes of CCMP Patients With MCS

The INTERMACS registry, a national registry in the United States, was used to better assess the CCMP population undergoing MCS implantation. From June 2006 to March 2011, 75 patients (2%) with CCMP out of of 3812 patients had undergone LV assist device (LVAD) implantation. This population was significantly more likely to be female (72% vs 24% and 13%; both $P < .0001$), with lower body mass index (26.0 vs 28.9 vs 28.0 kg/m^2; both $P < .0001$), and less likely receiving implants as DT (33% vs 14% vs 23%; $P < .0001$ compared with other NICM patients; $P = .03$ compared with ischemic cardiomyopathy patients). There was no difference in NYHA functional class or INTERMACS profiles nor in pre-implantation use of inotropes, ventilatory support, or intra-aortic balloon pump. Overall, survival of patients with CCMP was similar to that of ischemic and other NICM patients with 1-, 2-, and 3-year survivals of 73%, 63%, and 47%. In addition, there was no difference between the BTT and DT groups in this population.[55]

LVAD use was similar between patients undergoing HT owing to dilated cardiomyopathy secondary to chemotherapy and other NICMs ($P = .935$) in an analysis of the UNOS registry. However, there was greater use of right ventricular (RV) assist devices (5.6 vs 2.3%; $P = .002$). In a separate analysis of the UNOS registry (1987–2010), restrictive cardiomyopathy (RCM) due to radiation/chemotherapy represented a smaller proportion of patients undergoing HT (n = 35 of 544), with lower MCS use in those with RCM compared with other cardiomyopathies (10% vs 16%; $P < .0001$) and 11% of the radiation/chemotherapy cohort undergoing implantation. As such, data are limited and further study is warranted to further understand the implications of MCS implantation in RCM secondary to radiation/chemotherapy.[56]

Right Ventricular Dysfunction

Right ventricular function is critical to successful LVAD placement, mitigating the need for biventricular assist devices. RV involvement has been demonstrated in CCMP,[57,58] and this has inherent implications for MCS implantation. In the INTERMACS registry (2006–2011), surrogates for RV dysfunction were more frequent among CCMP patients preoperatively compared with other NICM and ischemic cardiomyopathy patients, including elevated right atrial pressure (16.5 vs 13.5 vs 12.5; $P = .01$ vs other NICM; $P = .0001$ vs ischemic), lower pulmonary artery systolic pressure (43.9 vs 49.4 vs 51.2; $P = .0015$ vs other NICM; $P < .0001$ vs ischemic), and more commonly moderate to severe tricuspid regurgitation (62% vs 43% vs 49%; $P = .0037$ vs other NICM; $P < .04$ s ischemic). The CCMP group undergoing LVAD implantation had RV failure more frequently, occurring in almost 20%, compared with the other groups (other NICM and ischemic cardiomyopathy), with a significantly increased need for subsequent or concomitant RVAD support (19% vs 11% [other NICM] vs 6% [ischemic]; $P = .006$). Post-LVAD RV failure was associated with significantly mortality: 33% of deaths occurred in the biventricular assist patients.[55]

Evidence of increased frequency of RV failure was also reported in the International Society of Heart and Lung Transplantation registry (2002–2008). During the study period, 19.6% of CCMP patients underwent LVAD as BTT with 5.6% requiring RVAD support. The rate of LVAD use was similar

to that of other NICM patients (19.4%; $P = .935$). However, RVAD utilization rates were more than twice in CCMP patients compared with other NICM patients (2.3%; $P = .002$).[5]

Careful assessment of the RV before LVAD placement is warranted in this population, given the increased propensity for RV failure in patients with CCMP. At present, options for durable RVAD support are limited. Use of the Total Artificial Heart (TAH), currently approved only as a BTT device with a DT trial underway,[59] has been reported in isolated cases.[60] Alternate support, though not currently approved by the Food and Drug Administration, is biventricular support with currently available devices such as the Thoratec PVAD or Heartware HVAD.[61]

Recovery

LVADs as bridge to recovery (BTR) in patients developing acute decompensated HF after anthracycline-induced cardiomyopathy has been reported in case reports.[62–64] This successful intervention with LVAD for BTR was performed early in the decompensated HF disease course and was coupled with aggressive neurohormonal blockade with beta-blockers, ACE inhibitors, and aldosterone antagonists. Early intervention before any irreversible damage (ie, myocardial apoptosis, significant scarring) may decrease the chance of adverse remodeling and is likely key to ensure successful BTR. Therefore, frequent assessment of LV function coupled with early intervention with the use of LVADs may be instrumental to BTR success, although larger systematic studies are warranted for confirmation and to better elucidate the mechanism of acute ventricular dysfunction and reverse remodeling in CCMP. In a recent study of a small number of patients receiving LVAD therapy with a history of anthracycline exposure, no significant correlation was found between the severity of histopathologic changes and the onset or duration of HF symptoms, however, there was a trend toward more severe histopathologic changes (more extensive fibrosis) in patients who continued to require LVAD support than in patients whose LVAD was explanted owing to recovery.[65] Whether recovery can be assessed histopathologically remains unknown.

Total Artificial Heart

Another option for MCS in patients with end stage HF due to CCMP may be the TAH. The Cardiowest TAH is a biventricular, pneumatic, pulsatile blood pump that completely replaces the patient's native ventricles and all 4 cardiac valves orthotopically. It may be useful in patients for whom LVADs and BiVADs are contraindicated, such as those with cardiac arrhythmias or irreversible biventricular failure (which is common in CCMP) requiring high pump outputs. In patients eligible for transplantation, it has been shown to improve the rates of survival to cardiac transplantation and survival after transplantation in those with irreversible biventricular failure compared with those who do not receive MCS.[66] TAH support with full replacement of the native heart has been used in a small fraction of patients with need for durable biventricular support,[50] mostly as BTT. The use of TAH in CCMP patients with biventricular failure as BTT has been described in case reports for either very rare primary cardiac malignancies[67] or CCMP patients[60,68] as BTT. The ability to provide biventricular support in patients with severe biventricular failure or to explant the heart in rare primary cardiac tumors may be served with TAH support in these infrequent cases as BTT or as DT therapy[59] for patients who are ineligible for transplantation. Although needed in only rare instances, this offers another MCS option for CCMP patients.

Cardiac Transplantation

Orthotropic heart transplantation is an effective therapy for patients with end-stage HF, with survival rates of ~50% at 11 years after transplantation.[69] HT for patients with CCMP runs the potential risk of relapse of the primary neoplasm, resulting in lower long-term survival. This is especially important in patients undergoing HT compared with renal transplantation, as HT requires a greater level of immunosuppression to prevent rejection owing to greater HLA mismatch.[70] Previous listing criteria for HT considered active or recent solid organ or blood malignancy within 5 years to be an absolute contraindication to HT.[71] A 5-year period of having to be cancer free may potentially prevent patients with CCMP for transplant eligibility, especially those with breast cancer and hematologic malignancies, for whom the prognosis and likelihood of recurrence can be established with reasonable certainty at presentation depending on cancer staging.[72] The cumulative incidence of malignancies in post-HT CCMP patients has been shown to be similar to that in post-HT NICM patients.[5] A recent update in HT listing criteria was more liberal in its exclusionary criteria, accepting the diverse nature of preexisting neoplasms, the need for collaboration with oncology specialists to stratify each cancer patient's individual risk of disease reoccurrence after transplantation, and to consider MCS/HT when tumor reoccurrence is low and response to therapy is good with negative metastatic work-up.[73] Thus, no arbitrary cancer-free interval is recommended before listing for HT.

The exact contribution of CCMP to the estimated 150,000–250,000 patients with advanced HF in the United States in 2013 is not known. As previously mentioned, analyses of the largest registries of patients with advanced HF, those of UNOS and INTERMACS, found that patients with CCMP accounted for 0.8%–2.5% of all HT recipients. More than 50% of patients with CCMP who received transplants were women.

In INTERMACS, 0.5% of those implanted with mechanical circulatory support devices had CCMP. Almost one-fifth of patients with CCMP required biventricular support, which was significantly higher than both ischemic and other nonischemic patients (19% vs 6% vs 11%; $P = .006$). Another interesting aspect of LVAD use in this population is that about one-third received implants as DT, significantly more than other NICM and ischemic cardiomyopathy patients (14% and 23%, respectively; $P < .0001$).[4]

Outcomes of 232 CCMP HT patients in the UNOS registry from 2000 to 2008 were similar to those of other nonischemic patients, with similar 1-, 2-, and 5-year survivals (86% vs 87%, 79% vs 81%, and 71% vs 74%; $P = .19$). The patients with CCMP undergoing HT were more likely to be younger, female (reflecting greater prevalence of breast cancer), and to have required MCS before HT. Interestingly, the risk of cardiac allograft rejection in the 1st year after transplantation was lower in patients with CCMP than in other nonischemic patients (28% vs 38%; $P = .03$), likely reflecting lingering immunologic downregulation due to chemotherapy exposure. Consistent with this hypothesis, post-transplantation infection rates were higher in the CCMP group (22% vs 14%; $P = .04$).[5] Also, skin cancer, but not malignancy recurrence or death from cancer, was more frequent among CCMP recipients. In line with younger age[74] and fewer comorbidities, CCMP recipients had lower incidence of post-transplantation renal dysfunction (24% vs 29%; $P = .02$), and unlike other patients, none required renal replacement therapy or renal transplantation. Regarding the risk of cancer reactivation due to immunosuppressive therapy, it should be noted that in 232 transplant patients with CCMP, only 1 death occurred because of recurrence of the primary malignancy.[5] These findings were confirmed in a larger UNOS analysis of 435 CCMP HT recipients from 1987 to 2011. In that study, the 10-year survival of CCMP recipients was not only similar but also superior when adjusted for age, sex, and history of malignancy (hazard ratio 1.28, 95% confidence interval 1.03–1.59; $P = .026$). Finally, it showed a >3-fold increase in the proportion of CCMP among nonischemic patients from 1987 to 2011 (0.5% to >1.5%; $P < .001$), suggesting a rising prevalence of CCMP among transplant recipients.[75]

Not all patients with end-stage HF exposed to chemotherapy have similar outcomes with the use of HT, however. Thirty-five transplant recipients identified in United Network of Organ Sharing (1987–2010) with restrictive cardiomyopathy due to chemotherapy and radiation had worse survival (1, 5, and 10 year survivalss of 71%, 47% and 32%, respectively) compared with those with other types of restrictive cardiomyopathy.[56] A smaller Mayo Clinic series (1992–2010) of 12 patients representing 4% of a total transplant cohort (297 patients) undergoing HT for radiation-induced end-stage HF showed survival at 1, 5, and 10 years of 91.7%, 75%, and 46.7%, respectively, findings that were not significantly different than the overall transplant cohort.[76]

Discussion

One of the major limitations of CCMP is the difficulty in estimating the true incidence of AHA class III–IV cardiomyopathy in the general population. It is likely that many patients, because of distant history of cancer treatment, may not have been recognized as potentially having chemotherapy/radiation as a risk factor in developing HF, so it is possible that the true incidence of this disease is underestimated. As for the MCS/HT population, underrecognition may also underestimate the true incidence of those requiring advanced support and/or transplantation, particularly in older patients who may have developed other confounding comorbidities (eg, coronary artery disease, hypertension, diabetes) that may make it difficult to elucidate the true mechanism of their cardiomyopathy. This may also be difficult to ascertain given the range of HF severity observed with the use of different chemotherapeutic agents, which by themselves have an unclear incidence. In addition, clinical, imaging, and histopathologic criteria for CCMP requires further study.

Identifying those patients who develop HF as the result of a chemotherapeutic agent are more likely to be accurately assessed when the onset of symptoms is acute to within a few years of exposure. As such, determining the true incidence of advanced HF and CCMP in cancer survivors is difficult and complicates identifying the population that would most benefit from closer HF surveillance, prophylactic treatment (eg, beta-blockers, ACE inhibitors, etc.), and/or determining the population that will respond to therapy. Although Oliveira et al reported that the characteristics of HF needing MCS were mostly younger healthier woman (with significantly lower rates of diabetes mellitus, hypertension, and tobacco, alcohol, and illicit drug use),[4] there could potentially be an underestimation of the actual number of patients with CCMP as well as its associated mortality, particularly if childhood survivors are also included.

The number of studies evaluating the impact of MCS are small, as there are several methodological obstacles in achieving a population of statistical significance to properly study the historical time course of end stage CCMP and available interventions. This is due to the overall low incidence of patients developing advanced HF from chemo- and/or radiotherapy, as well as limited availability of advanced therapies to CCMP patients. Studies will likely be observational in nature for quite some time; however, randomized controlled trials looking at the efficacy of such therapies are warranted and necessary. A more national and international multidisciplinary collaboration between cardiologists, oncologists (both adult and pediatric), and epidemiologists is needed to track, longitudinally, the outcomes of cancer survivors.

In summary, as anticancer therapies continue to evolve and prolong the lives of cancer patients, both inherent cardiotoxic properties of certain chemotherapeutic agents as well as baseline cardiovascular risk factors may put more cancer patients at short- and long-term risk of CCMP. Although small studies have shown potential benefit with pharmacologic agents during cancer treatment, there is evidence to suggest that the likelihood of poor response to cardiomyopathy treatments can be increased if detection of CCMP is significantly delayed. In a minority of such patients, significant clinical worsening can result, leading to consideration of advanced cardiac therapies. In evaluating the spectrum of advanced cardiac therapies, although some interventions have performed favorably in the CCMP population—eg, CRT and HT—others have not,

Table 1. Additional Considerations for Advanced Heart Failure Therapies in Chemotherapy-Related Cardiomyopathy

	Candidacy Considerations	Post-procedural Considerations
ICD	• LVEF ≤35% • Life expectancy >12 mo (if recurrence or other major comorbid illness)	• Routine post-procedure follow-up
CRT	• LVEF ≤35% • QRS duration ≥120 ms (preferably LBBB pattern) • NYHA functional class ≥I • For CRT-D, life expectancy >12 mo (if recurrence or other major comorbid illness) • For CRT-P, life expectancy >6 mo (if recurrence or other major comorbid illness)	• Routine post-procedure follow-up, including device optimization for CRT response
Heart transplantation	• Malignancy-free period before transplantation in consultation with oncology	• Secondary malignancy (ie, skin cancer) • Malignancy recurrence in setting of long-term immunosuppression
Mechanical circulatory support	• History of recently treated or active cancer with life-expectancy >2 y may be considered with evaluation in conjunction with oncology • Generally not recommended as a bridge to transplant or destination therapy in patients with active malignancy with life expectancy <2 y • Right ventricular failure • Hematologic risk (eg, hypercoaguability risk, cytopenias)	• Bleeding • Right ventricular failure • Thrombosis • Stroke • Device-related infection

CRT-D, cardiac resynchronization therapy–defibrillator; CRT-P, cardiac resynchronization therapy–pacemaker; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction.

such as the utility of VAD being associated with a greater need for RV support and a higher subsequent mortality (Table 1). Although these therapies can give insight into the pathophysiology of CCMP in its advanced stages, their efficacy is limited by significant selection bias without an accurate bearing on the overall incidence of CCMP in the HF population. Long-term registries tracking the outcomes of cancer survivors who have been exposed to specific agents, such as anthracyclines, are crucial to accurately quantifying the overall incidence of long-term cardiotoxic sequelae. Although end-stage CCMP patients now have many pharmacologic and invasive options, collaborative research efforts are needed between the cardiology and oncology disciplines to track survivors in the long term—the Childhood Cancer Survivor Study is one such example—and to implement appropriate surveillance measures to effectively detect and treat subclinical and early-onset cardiac dysfunction to potentially reduce the progression to later HF stages and lessen the need to resort to significant measures of MCS and/or HT. However, for those that do end up developing end-stage CCMP, such studies will allow for a more accurate view of the historical progression of this disease process, and will provide more evidence-based treatment strategies as to when advanced cardiac therapies are indicated.

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