Continual advances in antineoplastic therapies have produced better cancer outcomes with 13.7 million cancer survivors in the United States in 2013. However, a significant number of survivors may develop cardiac disease as a result of cancer treatment, whether chemotherapy, radiation, or a combination of both. Although radiation can cause significant heart disease, both alone and with chemotherapy, this review will only address cardiomyopathy induced by chemotherapy agents, especially anthracyclines, commonly used to treat pediatric and adult cancers. Whereas anthracyclines remain the most common cause of chemotherapy-induced cardiomyopathy (CCMP), recently developed targeted therapies can also cause cardiac dysfunction. Newer drugs that target survival pathways in cancer cells, such as the HER-2 (human epidermal growth factor 2) and vascular endothelial growth factor inhibitors, have been directly implicated in left ventricular (LV) systolic dysfunction through off-target effects. Because cancer and heart cells share many of the same survival pathways, it is likely that newer targeted therapies will continue to cause off-target impairment of cardiomyocyte survival and heart failure (HF). However, whereas LV dysfunction associated with targeted therapies seems reversible, anthracyclines remain the only agents that seem capable to cause end-stage HF.

In this review, we critically appraise the data available to support the use of advanced HF therapies in this patients with CCMP and end-stage HF. Specifically, we review treatments indicated for American College of Cardiology/American Heart Association stages C-D HF, including implantable cardiac defibrillators, cardiac resynchronization therapy (CRT), mechanical circulatory support devices, and orthotopic heart transplantation (OHT).

**Epidemiology**

Herein defined as cardiomyopathy caused by anthracycline damage with or without exposure to other cardiotoxic agents, CCMP has been described in 1% to 5% of cancer survivors and arguably portends the worst survival among cardiomyopathies. Unlike any other cause of HF, CCMP is completely iatrogenic and predictably caused by escalating doses of anthracyclines. At cumulative doses of <400 mg/m², the incidence of HF is 0.14% but increases to 5%, 26%, and 48% at 400, 550, and 700 mg/m², respectively. Factors that potentiate CCMP are age extremes (<4 years or >65 years), radiation, female sex, pre-existing cardiac diseases, hypertension, liver disease, exposure to cyclophosphamide, and whole-body hyperthermia.

Consequently, the 2 groups of survivors most susceptible to CCMP are those with cancers commonly treated with anthracyclines: children and adults with hematologic malignancies and women with breast cancer. For example, among 607 children treated with doxorubicin, 2.8% to 5% developed HF after 6 to 15 years, and 3% of patients treated for Hodgkin lymphoma developed HF after 11 years of follow-up. Furthermore, a sibling-controlled study from the childhood cancer survivor registry showed that childhood survivors of hematologic malignancies were at 6× likelier to develop HF than their siblings and that the cumulative risk persisted >30 years after diagnosis. Similarly, among 4000 women followed up >18 years after breast cancer treatment with chemotherapy and radiation, 382 (8.7%) developed HF. Finally, in a retrospective analysis of the pivotal trastuzumab trials, HF developed in 40 (28%) of 143 patients who received combination chemotherapy (trastuzumab, anthracycline, and cyclophosphamide), 27 (67%) of whom had New York Heart Association (NYHA) class III or IV HF.

However, the exact contribution of CCMP to the estimated 150,000 to 250,000 patients with advanced HF in the United States in 2013 is not known. Analyses of the largest registries of patients with advanced HF, the United Network of Organ Sharing, and the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS), found that patients with CCMP accounted for 0.8% to 2.5% of all OHT recipients and 0.5% of those implanted with mechanical circulatory support devices. Therefore, extrapolating from large databases of highly selected patients, the prevalence of end-stage HF from CCMP is between 0.5% and 2.5%. These numbers likely represent a gross underestimation because many patients with CCMP neither have access nor are eligible for advanced therapies.

**Demographics**

Large databases have unveiled unique characteristics of patients with CCMP treated with advanced therapies. They...
are often younger and consistently healthier, with significantly less prevalence of diabetes mellitus, hypertension, tobacco, alcohol, or illicit drug use.\textsuperscript{25,27} Also, women seem to be significantly more susceptible than men. Of all 75 patients with CCMP identified in the INTERMACS registry, 54 (72\%) were women, in contradistinction to ischemic and nonischemic cardiomyopathy where men predominate at 87\% and 76\%, respectively.\textsuperscript{27} Similarly, $\leq66\%$ of patients with CCMP transplanted were women.\textsuperscript{25,26} The reason for this sex disparity is not entirely clear although predominance of breast cancer in women has been implicated. However, factors intrinsic to female sex may play a role as is suggested by similar findings\textsuperscript{25} among patients with hematologic malignancies that typically lack sex predilection.

**LV Function Recovery**

Although we have reported myocardial recovery in $\leq55\%$ of patients with LV systolic dysfunction or HF during cancer therapy,\textsuperscript{28} we think that true anthracycline-induced CCMP represents a different entity, which is ultimately irreversible.\textsuperscript{29} Indeed, whereas cancer therapy–related LV dysfunction may occur from insults known to be reversible,\textsuperscript{30} such as sepsis,\textsuperscript{31} catecholamine release,\textsuperscript{32,33} arrhythmias,\textsuperscript{34} and drug-induced myocarditis,\textsuperscript{35,36} it is often mistakenly attributed to chemotherapy (guilty by association). In reversible cardiomyopathies, apoptosis is scarce and cardiomyocytes retain normal mitochondrial density undergoing adaptive changes through autophagy.\textsuperscript{37} In contradistinction, CCMP caused by anthracycline damage is characterized histologically by myofibroblast dropout with sarcoplasmic vacuolization and decreased cardiomyocyte density. This is thought to occur because anthracyclines generate reactive oxygen species that disrupt cardiac topoisomerase 2β activity causing DNA double-strand breaks, irreversible mitochondrial dysfunction, and apoptosis.\textsuperscript{38,39} Finally, irreversibility of advanced CCMP is further supported by recent reports that doxorubicin depletes progenitor stem cells responsible for restoring myocardial cells and promoting LV recovery.\textsuperscript{40,41} Therefore, in light of dubious biological plausibility, the scattered cases reporting device explantation and myocardial recovery in CCMP-labeled patients\textsuperscript{42–46} likely illustrate patients with reversible cancer therapy–associated LV dysfunction and not end-stage anthracycline-induced CCMP.

**Right Ventricular Involvement**

Pathology studies have long established right ventricular (RV) injury by anthracyclines.\textsuperscript{47} In fact, whereas diagnostic yield of LV biopsies is superior for most cardiomyopathies,\textsuperscript{48} RV biopsies have reliably diagnosed, tracked, and predicted LV dysfunction in CCMP.\textsuperscript{17,49}

Indeed, in CCMP systolic dysfunction occurs earlier in the RV and carries important clinical consequences. For example, patients with breast cancer followed up by echocardiography had significant decreases in tricuspid annular plane systolic excursion and RV fractional area after only 2 cycles of doxorubicin.\textsuperscript{50} Similarly, 29 of 36 (81\%) patients with breast cancer receiving doxorubicin and trastuzumab developed greater RV than LV impairment at 12 months by cardiac MRI.\textsuperscript{51}

The clinical relevance of RV impairment was only recognized after it was associated with higher risk of postimplant RV failure and death in patients with LV assist devices (LVADs).\textsuperscript{52} Analyses of advanced therapies in CCMP have confirmed the prevailing clinical suspicion that these patients have increased incidence of RV failure. Patients with CCMP were twice as likely to have biventricular assist devices at time of transplantation as other nonischemic patients (5.6 versus 2.3; $P=0.002$).\textsuperscript{37} In INTERMACS, almost a fifth of patients with CCMP required biventricular support, significantly higher than both ischemic and other nonischemic patients (19\% versus 6\% versus 11\%; $P=0.006$; Figure 1). Surrogate markers of RV function were also more abnormal in patients with CCMP, with higher mean right atrial pressures, lower mean pulmonary artery pressure, higher central venous pressure:pulmonary capillary wedge pressure ratio, and higher incidence of severe tricuspid regurgitation.

**Table 1. Comparison of Right Ventricular Function Parameters Before Mechanical Circulatory Support Devices Implantation Between Chemotherapy-Induced Cardiomyopathy, Nonischemic Cardiomyopathy, and Ischemic Cardiomyopathy**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CCMP (n=75)</th>
<th>NICMP (n=2392)</th>
<th>ICMP (n=1345)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP, mm Hg</td>
<td>16.5</td>
<td>13.5</td>
<td>12.5</td>
</tr>
<tr>
<td>Systolic PAP, mm Hg</td>
<td>44</td>
<td>49</td>
<td>53</td>
</tr>
<tr>
<td>Diastolic PAP, mm Hg</td>
<td>25</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Mean PCWP, mm Hg</td>
<td>24.1</td>
<td>25</td>
<td>24.4</td>
</tr>
<tr>
<td>RAP/PCWP</td>
<td>0.68</td>
<td>0.54</td>
<td>0.51</td>
</tr>
<tr>
<td>PVR (wood units)</td>
<td>2.4</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>TR (Moderate to severe)</td>
<td>62%</td>
<td>43%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Reprinted from Oliveira et al\textsuperscript{27} with permission of the publisher. Copyright © 2014, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. CCMP indicates chemotherapy-induced cardiomyopathy; ICMP, ischemic cardiomyopathy; NICMP, nonischemic cardiomyopathy; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; and TR, tricuspid regurgitation.
Table 2. Summary of Outcomes of Cardiac Resynchronization Therapy in Chemotherapy-Induced Cardiomyopathy

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Patient</th>
<th>Follow-Up (Mean)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al55 2007</td>
<td>1</td>
<td>12 mo</td>
<td>Weaned off ventilator and inotropic supports, EF improved from 22% to 35% at 1 mo and 55% at 1 y</td>
</tr>
<tr>
<td>Ajjila et al57 2008</td>
<td>4</td>
<td>18.5 mo</td>
<td>EF improved from 21% to 46%, LVEDD from 54.5 to 47 mm and NYHA class from IV and III to II to I</td>
</tr>
<tr>
<td>Ahlehoff et al56 2010</td>
<td>1</td>
<td>6 mo</td>
<td>EF from 25% to normal, improvement in ventricular dyssynchrony and NYHA class from III to I</td>
</tr>
<tr>
<td>Rickard et al58 2010</td>
<td>18</td>
<td>9.1 mo</td>
<td>EF improved from 19% to 27%, LVEDD from 60 to 55 mm, and NYHA class</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; LVEDD, left ventricular end-diastolic dimension; and NYHA, New York Heart Association.

(Table 1). These data corroborate the importance of RV impairment in CCMP and underscore the need for fastidious assessment of RV function before LVAD.

Table 3. Summary of Outcomes of Ventricular Assist Devices in Chemotherapy-Induced Cardiomyopathy

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Patient</th>
<th>Device</th>
<th>Strategy</th>
<th>Treatment Period</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musci et al62 1997</td>
<td>2</td>
<td>BiVAD (Berlin)</td>
<td>BTT</td>
<td>4–7 wk</td>
<td>Transplant</td>
</tr>
<tr>
<td>Casarotto et al63 2003</td>
<td>1</td>
<td>BioMedicus and Novacor LVAD</td>
<td>BTT</td>
<td>50 mo</td>
<td>Transplant</td>
</tr>
<tr>
<td>Simsir et al64 2005</td>
<td>1</td>
<td>HM LVAD</td>
<td>DT</td>
<td>≥6 mo</td>
<td>Improvement of symptoms</td>
</tr>
<tr>
<td>Potapov et al65 2005</td>
<td>1</td>
<td>Extracorporeal BiVAD (Berlin)</td>
<td>BTT</td>
<td>420 d</td>
<td>Transplant</td>
</tr>
<tr>
<td>Castells et al63 2009</td>
<td>1</td>
<td>LV axial pump (incor; continuous flow)</td>
<td>BTR</td>
<td>135 d</td>
<td>LV recovery; device explantation</td>
</tr>
<tr>
<td>Freilich et al64 2009</td>
<td>1</td>
<td>LVAD (continuous flow)</td>
<td>BTT</td>
<td>12 mo</td>
<td>LV recovery; device explantation</td>
</tr>
<tr>
<td>Pak et al62 2010</td>
<td>13</td>
<td>LVAD (continuous flow)</td>
<td>BTT (7); DT (6)</td>
<td>3 died within 2 mo 5 patients with DT switched to BTT. 7 patients received OHT</td>
<td></td>
</tr>
<tr>
<td>Kurihara et al66 2011</td>
<td>1</td>
<td>LVAD</td>
<td>BTR</td>
<td>239 d</td>
<td>LV recovery; device explantation</td>
</tr>
<tr>
<td>Khan et al65 2012</td>
<td>1</td>
<td>HM II LVAD (continuous flow)</td>
<td>BTT</td>
<td>15 mo</td>
<td>Improvement in EF and removal of device</td>
</tr>
<tr>
<td>Oliveira et al67 2013</td>
<td>75</td>
<td>Variety of devices (84% continuous flow)</td>
<td>BTT (64%); DT (33%)</td>
<td>Not reported</td>
<td>Death (25%); transplant (29%); and recovery (1%)</td>
</tr>
</tbody>
</table>

BiVAD indicates biventricular assisted device; BTR, bridge to recovery; BTT, bridge to transplant; DT, distention therapy; EF, ejection fraction; HM, HeartMate; LVAD, left ventricular assisted device; and OHT, orthotopic heart transplantation.
sarcoma, and most of them received radiation. After a mean follow-up of 9.1 months, patients with CCMP benefited from resynchronization as much as others, with improvement in all echocardiographic parameters, including EF (from mean of 18.6±7.6% to 27.2±13.5%), LVEDD (from mean of 6.04±0.63 to 5.56±0.95 cm), mitral regurgitation severity (from mean of 4.3±2 to 3.1±1.9), and NYHA class (from mean of 2.9±0.3 to 2.4±0.3; Table 2).

Although promising, the role of CRT in treatment of CCMP remains undefined. However, post hoc analyses of the MADIT-CRT (Multicenter Autonomic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) cohort, such as the one suggesting more pronounced clinical benefits in patients with nonischemic cardiomyopathy when compared with ischemic cardiomyopathy (hazard ratio, 0.30; *P*<0.001),59 could provide further insight. Finally, the upcoming initiation of the MADIT-CHIC study, designed to evaluate the role of resynchronization therapy in patients with CCMP prospectively who meet current guidelines, will likely determine the value of CRT in this population.

Whereas there are no data specifically addressing the use of implantable cardioverter defibrillator in CCMP, we found that only 66% of patients with CCMP in the INTERMACS registry had implantable cardiac defibrillators when compared with 77% of others (*P*<0.05).27 This observation may suggest that a third of patients with CCMP remain undiagnosed until presenting acutely and progressing too quickly for implantable cardiac defibrillators placement. Whatever the reason, it is concerning that a high percentage of patients with CCMP do not receive appropriate sudden death prophylaxis. These findings emphasize the need for active echocardiographic screening in cancer survivors with a history of cardiotoxic chemotherapy to unveil asymptomatic CCMP in a timely fashion.

### LV Assist Devices

Durable LVADs have been approved as bridge to transplant and destination therapy for patients with advanced HF refractory to medical therapy.60 Whereas their use has increased survival of patients with HF61, their benefits in patients with CCMP had been, until recently, anecdotal.

The first use of LVADs in patients with CCMP was described in 1997 when Musci et al62 reported a series of 5 patients bridged to transplant, of whom 2 required biventricular support. Subsequently, other cases were published with

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**Figure 2.** Survival of patients with chemotherapy-induced cardiomyopathy (CCMP) implanted with mechanical circulatory support devices. **A.** Patients with CCMP only; **B.** CCMP vs (ischemic cardiomyopathy [ICMP] and nonischemic cardiomyopathy [NICMP]) adult primary implants; **C.** CCMP vs ICMP vs NICMP adult primary implants; **D.** patients with CCMP by device strategy; **E.** CCMP by patient profile; **F.** CCMP patients by device side. BIVAD indicates biventricular assist device; BTT, bridge to transplantation; LVAD, left ventricular assist device. Reprinted from Oliveira et al27 with permission of the publisher. Copyright © 2014, Elsevier. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
both Novacor and HeartMate I, illustrating the feasibility of these pulsatile-flow pumps in patients with CCMP. More recently, Pak et al. reported the first series of 13 patients with CCMP implanted with continuous flow LVADs as bridge-to-transplant or destination therapy. Of these, 3 died within 2 months, 7 were transplanted, and 3 were still listed (Table 3).

The safety and efficacy of LVADs in this group was recently established by an INTERMACS analysis of 75 patients with CCMP. Despite having increased bleeding and requiring more biventricular support, patients with CCMP had similar outcomes to other patients in the registry (Figure 2, survival curves). Because the curves separate within the first 3 months, when most patients with biventricular support die (Figure 2B), it is possible that postimplant RV failure contributed significantly to mortality in that group.

It also was evident that patients with CCMP presented sicker and more acutely than other groups, with a trend toward higher inotrope use, higher B-type natriuretic peptide, and less use of defibrillators. Another interesting aspect of LVAD use in this population is that about a third were implanted as destination therapy, significantly higher than nonischemic cardiomyopathy (14% and 23%; P<0.0001). Because this occurs despite their younger age and better health, the most logical inference is that about one third were implanted as destination therapy.

In conclusion, LVADs are effective and safe for patients with CCMP and end-stage HF. Despite increased need for biventricular support and higher frequency of bleeding, patients with CCMP selected for LVADs have survival comparable with other similarly treated patients. Because the population in our study was unusually young and otherwise healthy, it remains unclear whether this form of treatment would yield similar survival in older patients.

Orthotopic Heart Transplantation

Heart transplantation remains the definitive therapy for end-stage HF with an adjusted median survival of 11 years. However, patients with CCMP are often ineligible for transplant because of current or previous history of malignancy, and their eligibility has been often tempered by concerns for malignancy recurrence in the setting of immunosuppressive therapy. Nevertheless, there is appropriate evidence supporting the safety of transplant in CCMP. In addition to anecdotal cases and small series, there are 2 recent large-scale reports analyzing the outcomes of patients with CCMP treated with OHT.

Outcomes of 232 CCMP transplanted patients in the United Network of Organ Sharing registry between 2000 and 2008 were comparable with other nonischemic patients, with similar 1-, 2-, and 5-year survival (86% versus 87%, 79% versus 81%, and 71% versus 74%; P=0.19; Figure 3). Interestingly, the risk of cardiac allograft rejection in the first year post-transplant was lower in patients with CCMP than in nonischemic patients (28% versus 38%; P=0.03), likely reflecting of lingering immunologic downregulation from chemotherapy exposure. Consistent with this hypothesis, post-transplant infection rates were higher in the CCMP group (22% versus 14%; P=0.04). Also, skin cancer but not malignancy recurrence or death from cancer was more frequent among CCMP recipients. In line with younger age and less comorbidities, CCMP recipients had lower incidence of post-transplant renal dysfunction (24% versus 29%; P=0.02), and unlike other patients, none required renal replacement therapy or renal transplantation.

More recently, Lenneman et al. confirmed our findings in a larger United Network of Organ Sharing analysis of 435 CCMP heart transplant recipients from 1987 to 2011. In their 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=0.026). Finally, they showed more than a 3-fold increase in the proportion of CCMP among nonischemic patients from 1987 to 2011 (0.5% to >1.5%; P<0.001), suggesting a rising prevalence of CCMP among transplant recipients.

Not all patients with end-stage HF exposed to chemotherapy have similar outcomes with OHT; however. Thirty-five transplant recipients identified in United Network of Organ Sharing (1987–2010) with restrictive cardiomyopathy from chemotherapy and radiation had worse survival when compared with those with other types of restrictive cardiomyopathy. A possible explanation for this is the presence of coexisting radiation-induced restrictive lung disease in such patients.

In conclusion, OHT is appropriate, safe, and may yield better survival in CCMP recipients than in those transplanted for other cardiomyopathies. About the risk of cancer reactivation by immunosuppressive therapy, it should be noted that of 232 transplanted patients with CCMP only one death occurred because of recurrence of the primary malignancy. This implies that the arbitrary 5-year period of cancer-freedom commonly imposed before granting transplant eligibility for patients with CCMP is probably too stringent, especially in patients with breast cancer and hematologic malignancies, for whom the prognosis and likelihood of recurrence can be established with reasonable certainty at presentation depending

![Figure 3. Post-transplant survival of chemotherapy-induced cardiomyopathy (CCMP) compared to other patients with nonischemic cardiomyopathy (NICMP): Kaplan–Meier survival curves are shown for numbers of patients alive at baseline and 1, 2, 3, 4, and 5 years. Patients with CCMP are indicated by bold dotted lines, with the associated confident intervals as small dotted lines, and patients with NICMP are indicated by the black line, with 95% confidence intervals as faint black lines. Reprinted from Oliveira et al with permission of the publisher.](https://circ.ahajournals.org/content/1054/25/1054/suppl/DC1)

1054 Circ Heart Fail November 2014
Finally, because patients with CCMP are younger, healthier, and may not be as easily supported with currently approved devices, we propose that the blanket 5-year moratorium before transplant be abandoned altogether and that time to OHT eligibility be decided in consultation with an oncologist, on an individual basis, and as short as possible. Table 4 summarizes the literature on OHT in CCMP.

### The Future

The future of any iatrogenic form of cardiomyopathy should be that of a forgotten oddity in medical history books. However, until safer and more efficacious cancer therapies are developed, emphasis should be placed on preventive strategies that allow cancer treatment while minimizing risk of cardiotoxicity. In patients undergoing cancer therapy, preemptive strategies to mitigate cardiotoxicity and fastidious echocardiographic monitoring to detect preclinical LV dysfunction may avert the development of CCMP altogether. In cancer survivors with previous cardiotoxic treatment, echocardiographic screening may unveil subclinical structural heart disease and allow initiation of treatment at earlier HF stages, thereby preventing or slowing progression to end-stage HF.

For those in whom prevention is no longer an option, future approval of biventricular support devices offers hope of safer bridging to transplant. Furthermore, development of devices that dispense external power sources may offer more permanent alternatives to OHT in younger patients. Indeed, the future advent and the use of total cardiac support devices will likely allow for better outcomes and more options for patients with CCMP.
substitution devices may allow patients to continue cardiotoxic but life-saving cancer treatment even after development of end-stage heart disease. Finally, other forms of therapy currently under investigation for HF in general, such as the use of pluripotent stem cells, and some interventional-based therapies, may ultimately have some role to play in CCMP.

**Conclusions**

CCMP causes end-stage biventricular HF, affects predominantly younger women, and has no definitive prevention other than withholding its iatrogenic cause: the life-saving drug family of anthracyclines. In comparison with other refractory therapies currently under investigation for HF in general, such as sunitinib for renal cancer.

**Disclosures**

None.

**References**


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Key Words: anthracyclines ■ cardiac resynchronization therapy ■ heart failure ■ heart transplantation
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