

## Advanced Heart Failure in the Cancer Patient

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### Introduction

Innovations in anti-neoplastic treatments have amplified the number of long-term survivors. Even with novel malignancy therapies, anthracyclines are the foundation of cancer treatment, especially in hematologic malignancies, sarcomas, and breast cancer.<sup>1</sup>

Heart failure (HF) has been described in up to 10% of tumor survivors, and the progression to end-stage HF in 2% to 3%. According to estimations grounded on retrospective registry data, such as United Network for Organ Sharing (UNOS) or Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registries, 0.5-2.5% of patients undergoing advanced HF therapies such as left ventricular assist devices (LVAD) and orthotopic heart transplantation have had previous cancer treatment.<sup>1</sup>

These studies also revealed exceptional individualities of these patients with advanced HF. They are usually younger (44–53 years) and mostly women (62%–72%), and with less comorbidities. Despite the concern with the history of previous cancer and the sequelae of cancer treatment, many studies have suggested that these patients do not have worse outcomes than other cases of HF. Therefore, discussing advanced HF and its management in this population has become imperative.

### Mechanical circulatory support in chemotherapy-induced cardiomyopathy

Patients with chemotherapy-induced cardiomyopathy (CCMP) and advanced HF are often precluded from heart transplantation because of the history of recently treated or current cancer. In these cases, mechanical circulatory support (MCS) may work as bridge to candidacy, destination therapy or even bridge to recovery of the patients.<sup>1</sup> Data are limited regarding MCS in CCMP.

Analysis of the INTERMACS including 3812 patients between June 2006 and March 2011 compared 75 patients

(2% of total) with chemotherapy-induced CCMP in MCS with 1345 ischemic cardiomyopathy (ICMP) patients and 2392 non-ischemic cardiomyopathy patients (NICMP).<sup>2</sup> Patients with CCMP were younger, mostly women (72%) and with less comorbidities, and destination therapy was more common as an implantation strategy compared to the other two groups (33% versus 14% in non-ischemic and 22% in ischemic cardiomyopathy). There was no difference in INTERMACS profile or functional class, and left ventricular ejection fraction was similar between groups. Concomitant surgery (usually valve procedure) was more common in CCMP. Overall survival was similar between groups, and heart transplantation was possible for 29% of CCMP group, 32% of ICMP group and 36% of NICP group.

However, biventricular involvement is common in CCMP<sup>3</sup> and in this publication,<sup>2</sup> surrogate markers of right ventricular dysfunction were more frequent in CCMP patients compared to the other two groups: CCMP patients had higher atrial pressure, lower pulmonary systolic pressure, and higher central venous pressure/pulmonary wedge pressure ratio. These findings were translated in a 19% rate of need for right ventricular mechanical support in CCMP, compared to 11% in NICMP and 6% in ICMP ( $p=0.006$ ). The need for right ventricular mechanical support was associated with worse survival, while CCMP patients on LVAD had similar survival compared to the other two groups.<sup>2</sup>

In the analysis of INTERMACS registry, left ventricular recovery was present in only one patient in the group of CCMP. There are few case reports in literature of patients on LVAD or biventricular support in which MCS weaning was successful. A case report and literature review published in 2018<sup>4</sup> presents a case of biventricular support in a female patient with anthracycline-induced cardiomyopathy who was on a LVAD and had right ventricular assistance with a centrifugal pump and a membrane oxygenator. After 64 days, she was submitted to a mitral annuloplasty and was weaned from biventricular support eight days after the procedure. Other eight cases of LVAD support in CCMP patients were reviewed<sup>4</sup> and the time on support before weaning MCS varied from two to 17 months, suggesting recovery do not happen in the short term and long term MCS may be needed to enable recovery in this group of patients.

Myocarditis leading to cardiogenic shock may also be a consequence of cancer therapy.<sup>5</sup> The use of the antimetabolite 5-fluoracil or high doses of cyclophosphamide may rarely lead to myocarditis, but more recently the use of immune checkpoint inhibitors (ICI) has been associated with fulminant myocarditis in up to 1% of cases, with high fatality rate of 50%.<sup>6</sup> In

### Keywords

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## Review Article

ICI-related myocarditis, myocardium is infiltrated by T-lymphocytes and macrophages leading to myocyte death and acute cardiac dysfunction. Short-term MCS may be necessary in acute HF patients presenting cardiogenic shock, while immunosuppressive therapy with intravenous methylprednisolone is warranted. There are only case reports about MCS in this scenario,<sup>7</sup> and usual acute HF management is recommended by current guidelines in these cases.<sup>8</sup>

### Heart transplant

Heart transplant (HTx) is an effective treatment for patients with advanced HF and may be considered in patients with cancer therapeutics-related cardiac dysfunction.<sup>9</sup> Due to the potential risk of relapse of primary neoplasia, resulting in lower long-term survival, malignancy within five years was previously considered a contraindication to HTx. However, data from large registries did not confirm this hypothesis.

In an analysis of the International Society for Heart and Lung Transplantation (ISHLT) registry of patients submitted to HTx between 2000 and 2008, 232 patients with chemotherapy-related cardiomyopathy were identified.<sup>10</sup> The most common malignancies were leukemia or lymphoma (33%) and breast cancer (31%). Short-term and long-term survival rates were similar to those with other cardiomyopathies. Allograft rejection in the first year after transplant was significantly lower and hospitalizations for post-transplant infections were higher in patients with chemotherapy-related cardiomyopathy. Those findings may be explained by persistent immunosuppression from previous cancer therapies. Skin cancer, but not malignancy recurrence or death from cancer, was more frequent. Only one case of cancer recurrence was seen, suggesting that this is not a big concern in selected patients with CCMP.

Similar results were found in an analysis of the UNOS registry comparing 453 HTx recipients with CCMP to 51,312 recipients with other causes of cardiomyopathy, between 1987 and 2011. Patients with CCMP were younger and more likely female. There was no significant difference in unadjusted 10-year survival or death due to malignancy rates between the groups. Actually, after adjusting for age, gender, and history of malignancy, the 10-year survival was even higher in the chemotherapy-related cardiomyopathy group.<sup>11</sup>

A more recent analysis of the UNOS registry was performed including patients listed for HTx from 2008 to 2018. This cohort included 18,270 patients (357 with CCMP, 10,662 with dilated cardiomyopathy and 7,251 with ischemic cardiomyopathy). Patients with chemotherapy-related cardiomyopathy were younger, predominantly women, less likely to be diabetic or to have an LVAD at the time of HTx. Breast cancer and hematologic malignancies were the most common type of neoplasia (44% and 25%, respectively). Short-term and long-term survival post-HTx were similar between the groups.<sup>12</sup>

Nevertheless, patients with restrictive CCMP and specially radiation seem to have worse prognosis. In another study using data collected between 2000 and 2015 from the UNOS

registry, 87 patients with radiation-induced restrictive CMP were compared with patients with restrictive CMPs of other etiologies (n=1,049) and all the others (n=44,805). Patients with radiation-induced restrictive CMP were younger and more likely to have previous cardiac surgeries. They had longer lengths of stay after transplant and higher early and long-term mortality.<sup>13</sup>

Current guidelines suggest collaboration with oncology specialists to stratify patients according to their risk of tumor recurrence and no arbitrary observation time is recommended.<sup>14</sup> HTx should be considered when tumor recurrence is low based on tumor type, response to therapy, and negative metastatic workup.

### Conclusion

The management of patients with advanced HF due to CCMP is highly controversial, both because there are few studies in this population and because of issues about the underlying disease and sequelae of its treatment. This concern is justified, since, as we discussed, this population has some peculiarities that affect treatment response. Although the overall outcome of patients with CCMP is not inferior to that of other etiologies, these patients may have worse prognostic factors, such as biventricular dysfunction, pulmonary hypertension, among others. In addition, concerns about cancer and its treatment often impact the decision for heart transplantation, although more recent studies have shown a similar progression to other cardiomyopathies. Therefore, better understanding the peculiarities of this population is important and justifies the advances in cardio-oncology in recent years, especially in the field of advanced HF.

### Author Contributions

Conception and design of the research: Ferreira SMA, Belfort DSP; Writing of the manuscript: Ferreira SMA, Belfort DSP, Freitas AKE; Critical revision of the manuscript for important intellectual content: Ferreira SMA, Seguro LFBC, Bacal F, Moura LZ.

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### Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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