Cancer, Chemotherapy, and Cor Pulmonale*

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The development and dissemination of left ventricular assist devices (LVADs) for the treatment of end-stage heart failure have been one of the major developments in heart failure over the past decade, and the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database, funded by the National Heart, Lung, and Blood Institute, has been a critical resource for tracking practice patterns, outcomes, and post-operative complications (1). In this issue of the Journal, the report by Oliveira et al. (2) on outcomes in patients with a history of anthracycline-induced cardiomyopathy after mechanical circulatory support (MCS) from the INTERMACS registry is an example of work that would be impossible to perform from single-center data, as highlighted by the fact that only 2% of 3,812 eligible MCS-implanted patients were reported to have anthracycline-based cardiomyopathy.

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As the number of cancer survivors grows, we can expect to see more patients affected by the late consequences of cardiotoxic medications such as anthracyclines (3). This can be quite a roller coaster for patients who have survived cancer only to find that they now are at risk of major morbidity and mortality from a diagnosis of heart failure! Although newer agents such as trastuzumab and tyrosine kinase inhibitors are well established as a potential cause of heart failure, anthracyclines remain the dominant agent. Despite their use for decades as a cornerstone of the treatment of breast cancer, hematological malignancies, and sarcomas, the mechanism of anthracycline cardiotoxicity remains incompletely understood. Generation of reactive oxygen species has been the dominant theory, but other mechanisms are likely to be critical, as recently reviewed (4). For example, doxorubicin has been demonstrated to induce protein ubiquination and inhibit proteasome activity (5); proteasome inhibition has previously been reported to cause heart failure (6).

Anthracyclines block topoisomerase II (TOP2), a critical enzyme involved in DNA replication. Genetically engineered mice have recently been developed that do not express the isomer TOP2B and appear to avoid acute or chronic cardiotoxicity from exposure to doxorubicin (7), implying a promising option. An anthracycline with specificity for TOP2A, a marker of cell proliferation and thus overexpressed in malignant cells, may offer substantial reductions in cardiotoxicity without compromising antineoplastic effect, a concern that has been raised with dexrazoxane (8).

Along with our improved, but incomplete, understanding of the mechanism of anthracycline cardiotoxicity, it is obvious in retrospect that much less attention has been paid to the impact on the right ventricle. Most studies have reported on the effect on left ventricular (LV) ejection fraction, which is often the dominant, if not sole, parameter used to monitor for myocardial toxicity in clinical practice, although biomarkers appear to improve sensitivity and timeliness of diagnosis (9). A welcome addition to the literature was a recent study from Finland that reported on LV and right ventricular (RV) cardiac structure and function in a series of long-term survivors of childhood cancer using cardiac magnetic resonance imaging. Although this population may not be representative of the larger population receiving anthracyclines, such as older lymphoma and breast cancer patients, it is notable that ~80% of participants had frankly abnormal or subnormal LV and RV ejection fractions, and RV end-diastolic volume was also increased compared with a reference population (10).

The right ventricle is of great interest to clinicians involved in the care of patients being considered for MCS with an LVAD, as post-LVAD RV failure has a poor prognosis. Our understanding of patient selection and peroperative management of RV function has led to a significant decrease in the number of post-LVAD patients in whom RV failure develops, typically defined as the need for inhaled nitric oxide, administration inotrope beyond 14 days, or implantation of an RV assist device. In contrast to earlier reports, contemporary estimates of RV failure requiring an RV assist device after LVAD are typically in the range of 5% or less (11). However, predicting RV failure remains challenging, and the number of published prediction tools is de facto evidence that we do not yet have a simple answer to the question, “Will this patient’s RV function be sufficient to support an LVAD or is another mode of MCS required?”

Oliveira et al. (2) identified 75 patients from the INTERMACS registry who underwent LVAD implantation with a history of chemotherapy-induced cardiomyopathy (CCMP) and compared them with others with ischemic cardiomyopathy (ICMP) and nonischemic cardiomyopathy (NICMP [other than chemotherapy induced]). They noted...
that the CCMP group had fewer comorbidities such as diabetes, history of alcohol abuse, and current smoking and was highly enriched with female patients (72% vs. 13% and 24% for ICMP and NICP, respectively). INTERMACS profiles, a shorthand tool to stratify acuity in patients receiving MCS, were well matched between the 3 groups. It is not surprising that the CCMP group had far more women than previous studies of LVADs, as anthracyclines are a key element of most breast cancer treatment regimens, a disease this is distinctly less common in men. Survival after LVAD was equivalent in the CCMP group, but the risk of postoperative RV failure doubled to ~20%. This finding is important because, on the basis of this study, it may be prudent to add a history of anthracycline exposure as a risk factor for RV failure after LVAD implantation. Pre-implantation hemodynamics, characterized by increased central venous pressure and lower pulmonary artery pressures in the CCMP group, may have provided a clue to the increased risk of RV failure, and particular concern over such marginal hemodynamics in this group is warranted.

The observation that the risk of RV failure after LVAD implantation is higher in patients with anthracycline cardiotoxicity is concordant with what might be expected, given contemporary understanding of the mechanism of anthracycline toxicity and recent evidence highlighting the likelihood of biventricular impairment. One of the important results of the Oliveira et al. (2) study is that it provides additional support of the observation that biventricular failure might be expected after anthracyclines and that it strengthens the case to consider a cardiac monitoring strategy during administration of potentially cardiotoxic chemotherapy that explicitly includes the right ventricle.

Some important caveats bear mention, including the inherent limitations of registry data, as noted by the authors (11%) did not have a history of cancer listed with INTERMACS, and 8% of the NICMP patients had a history of coronary artery bypass grafting, for example). We are also left without information on patients with a history of cardiomyopathy due to other chemotherapy agents that have been implicated in the pathogenesis of heart failure, such as trastuzumab and tyrosine kinase inhibitors.

It is remarkable that only 1 CCMP patient is described as dying of cancer after LVAD implantation, suggesting that the underlying malignancy was thought to be in remission with some confidence in most patients before implantation. As the authors indicate, “because of the stigma associated with the etiology of their heart failure, they may be subjected to stricter requirements for MCS eligibility than their ICMP and NICMP counterparts,” which is corroborated by the lower incidence of alcohol abuse history and increased frequency of implantation intent of destination therapy in the CCMP group. Accordingly, some caution is needed before extrapolating the present data to everyone with a history of CCMP, as the study population had fewer other comorbidities and was likely to have been enriched with patients with lower risk of cancer recurrence. Nevertheless, the key message is one of validation that CCMP patients with end-stage heart failure are likely to have outcomes after LVAD implantation comparable to those without anthracycline-induced cardiomyopathy and should not be excluded from the possibility of benefit solely on the basis of this history.

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REFERENCES


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