Carvedilol: A Promising Tool in the Meager Armamentarium of the Cardio-Oncologist!

Sarina Sachdev, M.D.[a, b], Bassam Omar, M.D., Ph.D.[a], Christopher Malozzi, D.O.[a]

Abstract

The CECCY Trial (Carvedilol for Prevention of Chemotherapy-Related Cardiotoxicity) is a recently published prospective, randomized, double-blind, placebo-controlled study which examined the role of carvedilol in the prevention of chemotherapy-related cardiotoxicity (1). This was specifically defined in this study as a decline in left ventricular ejection fraction (LVEF) of ≥ 10% at 6 months after start of chemotherapy. Other end-points examined were carvedilol's effect on cardiac troponin, B-type natriuretic peptide, and diastolic dysfunction, among other measurable echocardiographic parameters.

Patients were eligible if they were receiving anthracycline (ANT) chemotherapy for HER2-negative breast cancer and had a normal LVEF prior to chemotherapy. The study investigators identified and randomized 200 such patients to receive carvedilol or placebo throughout the duration of chemotherapy (which included cyclophosphamide, doxorubicin at a total cumulative dose of 240 mg/m^2, and paclitaxel).

The CECCY Trial is one of a few randomized, prospective trials studying the effects of beta blockers, specifically carvedilol, on chemotherapy induced cardiotoxicity. Previous studies evaluating beta blockers for the prevention of chemotherapy-related cardiotoxicity have been somewhat controversial because of design limitations (2 – 4).

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a Division of Cardiology, University of South Alabama, Mobile, AL, USA

b Corresponding Author: Sarina Sachdev, Division of Cardiology, University of South Alabama, 2451 USA Medical Center Dr., Mobile, AL 36617, USA.

Email: ssachdev@health.southalabama.edu

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The more recent PRADA trial (5), however, was well designed to address the primary prevention hypothesis. It was a double-blind, placebo controlled trial with a 2 x 2 factorial randomized design. Breast cancer patients enrolled also received ANT but may also have received trastuzumab and/or radiation. Patients receiving the latter were excluded in the CECCY trial. Subjects were assigned metoprolol succinate, candesartan, or placebo. There was no effect on LVEF in the metoprolol group. However, data favored the use of candesartan. The CECCY investigators were able to compile a larger patient population and focus on one chemotherapeutic agent and one therapeutic intervention. They hypothesized that the use of a different beta blocker with different pharmacologic properties than metoprolol succinate could succeed in primary prevention of chemotherapy related cardiomyopathy (CrCM).

Results

A drop in LVEF of ≥ 10% occurred in 14 patients receiving carvedilol and 13 patients receiving placebo (p = 1.0). For the majority of patients with a decrease in LVEF in each group, their LVEF did not fall outside the normal range. There was one patient in each group with an LVEF drop of more than 10%, to a level of < 55%. No significant differences in change of LVEF were noted. There was, however, a significant difference between groups in troponin I (TnI) levels over time (p = 0.003). The carvedilol group had lower TnI levels compared to placebo. Also, a lower incidence of diastolic dysfunction was noted in the carvedilol group (p = 0.039). Although nonsignificant, there was a trend toward a less pronounced increase in left ventricular end-diastolic diameter in the

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carvedilol group (44.1 ± 3.6 mm to 45.2 ± 3.2 mm; 2.5% increase) compared with the placebo group (44.9 ± 3.6 mm to 46.4 ± 4.0 mm; 3.3% increase; $p = 0.057$).

Therefore, although after 6-month therapy with carvedilol alongside chemotherapy, the addition of carvedilol did not significantly impact the LVEF, more importantly, there was a statistical significance of the use of carvedilol leading to lower troponin levels and less diastolic dysfunction as compared to placebo.

Conclusion

common among female patients undergoing treatment for breast cancer. ANTs are associated with early and late dose-related cardiotoxicity, primarily HF (7 – 9). This study examined the effects of carvedilol on prevention of CrCM. Cardiologists who are referred a patient with HFrEF secondary to CrCM will likely reach for routine guideline directed therapy for HF. Likely, they will start with an angiotensin converting enzyme inhibitor (ACE-I), beta blocker (BB), or both in attempt to prevent worsening of cardiac function and HF, and hopefully improve LVEF. Unfortunately, with many CrCMs, the myocardial damage is often not appreciably reversible. This is often the case with ANT exposure. Identifying ways to prevent cardiotoxicity has been the focus of much research including pharmacotherapy and imaging techniques. Despite the significant insights gained from many recent studies, there remains a major gap in our understanding of the mechanisms and ability to alter this debilitating consequence of chemotherapy.

Clinical Implications

Survival rates in cancer patients have increased steadily over the last few decades (6). This is primarily due to rapid advancements in cancer therapies. However, many chemotherapeutic agents are invariably cardiotoxic. Cardiovascular complications of cancer treatment portend significantly poorer outcomes with worsened morbidity and mortality in these patients. One of the more commonly recognized cardiotoxicities is the development of CrCM and heart failure (HF). ANT use is very common among female patients undergoing treatment for breast cancer. ANTs are associated with early and late dose-related cardiotoxicity, primarily HF (7 – 9). This study examined the effects of carvedilol on prevention of CrCM. Cardiologists who are referred a patient with HFrEF secondary to CrCM will likely reach for routine guideline directed therapy for HF. Likely, they will start with an angiotensin converting enzyme inhibitor (ACE-I), beta blocker (BB), or both in attempt to prevent worsening of cardiac function and HF, and hopefully improve LVEF. Unfortunately, with many CrCMs, the myocardial damage is often not appreciably reversible. This is often the case with ANT exposure. Identifying ways to prevent cardiotoxicity has been the focus of much research including pharmacotherapy and imaging techniques. Despite the significant insights gained from many recent studies, there remains a major gap in our understanding of the mechanisms and ability to alter this debilitating consequence of chemotherapy.

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