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EDITORIAL COMMENT

One Small Step . . .*

Ileana L. Piña, MD, MPH

Heart failure (HF) cardiologists have long been caring for patients who, after having triumphed over a malignancy, now face a difficult challenge due to the HF symptoms of anthracycline-induced cardiomyopathy (AIC). HF is often called the "cancer of the heart" due to its overall mortality. As aggressively as HF specialists practice using medical and device therapies, some patients with AIC may stabilize and/or improve. However, many continue to deteriorate and become candidates for advanced therapies such as heart transplantation or mechanical assistance (1). Even more tragic is the younger age of the AIC population, many of them women who have survived a breast cancer diagnosis already. Heart failure due to AIC is not an ordinary nonischemic cardiomyopathy and is comparable in survival to HIV or to infiltrative myocardial disease, with a 3-times-higher mortality than idiopathic cardiomyopathy (2). Through the past 10 years, much time has been spent describing the pathological changes of AIC, including recent basic science reports of early loss of cardiac mass leading to myocardial atrophy, which may be a very early marker of AIC (3). Furthermore, efforts toward early identification of AIC have included the recognition of risk factors, such as hypertension, and tracking damage and response with biomarkers, such as troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (4,5). Pre-symptom detection strategies have been extended into echocardiography with measurement of global longitudinal strain incorporated into the imaging guidelines (6). On the therapeutic side, there have been a multitude of studies reporting on pharmacologic therapy with the same medications that the American College of Cardiology/American Heart Association guidelines for HF call "guideline-directed medical therapy" (GDMT) (7). The results have been variable, with agents such as angiotensin-converting enzyme inhibitors (8,9), beta blockers, and mineralocorticoid receptor antagonists (10). For example, a meta-analysis of carvedilol reported lower rates of left ventricular dysfunction and less deterioration of ejection fraction as primary prevention (11). Overall, however, these agents, especially angiotensin-converting enzyme inhibitors, seem to be protective post-chemotherapy, with the ongoing discussions agreeing on their usefulness early in the course of AIC (4). Unfortunately, many patients may reach the HF specialists long after the AIC has evolved and symptoms have called attention to its presence.

In the midst of this truly unmet need is the promise of cell therapy, with encouraging results in preclinical and early clinical trials of bone marrow-derived mesenchymal stromal cells (allo-MSCs) with low immunogenicity. The potential for cell therapy to be beneficial in AIC would address some of the pathological changes, including the replacement of myocytes and fibrosis, among others. Enter Bolli et al. (12) in this issue of *JACC: CardioOncology*, who boldly present the SENECA (Stem Cell Injection in Cancer Survivors) trial from the Cardiovascular Cell Therapy Research Network of the National Institutes of Health (12). The primary purpose of this first-in-human phase 1 study was judiciously chosen to test the safety and feasibility of allo-MSCs injected transendocardially. The results of this study would inform

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From Wayne State University, Detroit, Michigan; and Central Michigan University, Midland, Michigan, USA.

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phase 2 and 3 trials. The study design was elegant, using an open lead-in phase followed by a randomized controlled design, and for this step, the investigators should be congratulated. Although not powered for outcomes and measures of cardiac function, Bolli et al. nonetheless wisely collected a group of parameters that will be informative for future studies and serve as hypotheses generating, such as magnetic resonance imaging (MRI) measures, NT-proBNP, a functional measure with the 6-minute walk, and the ever-important health-related quality of life (HRQoL) representing patient-reported outcomes using a standardized instrument. If there were positive signals, these could be amplified in a follow-up trial. The ability to collect MRI data would be challenging, given the prospect that a large number of patients with AIC would have qualified for an implantable cardioverter-defibrillator. However, using an imaging protocol developed by the MRI Core Lab at Johns Hopkins and training sites for safety, the study was able to image 94% of participants at the 12-month visit, although 59% had MRI-noncompatible devices. Other safety-based processes included only patients with >2 years of cancer-free survival to minimize chances of recurrence, the exclusion of New York Heart Association functional class I and IV and more recently diagnosed individuals.

As expected, more than one-half of the patients were women at ages younger than that of the average patient with HF in the United States. With an ejection fraction of approximately 33%, this group was indeed in the HF with reduced ejection fraction category and eligible for GDMT. The patients were well medicated by percentage on therapy, although doses were not reported, and a large percentage had implantable cardioverter-defibrillators. Future trials should include GDMTs to test whether allo-MSCs will succeed with concomitant current quality care. The injections were successfully deployed in 97% of the patients with no new tumors detected and without evidence of immune reaction to the injections. Serious adverse events were evenly balanced between treatment and control with more 20% being cardiac. There was 1 death in the treated group due to progressive HF and 7 hospitalizations for 5 patients with worsening HF. Clinical outcomes were not unexpected and were similar between groups, with the exception of a borderline 6-minute walk finding and HRQoL results favoring the allo-MSC group. Thus, the trial was successful and met the feasibility and safety primary objective.

Beyond the results, and as in most clinical trials, there are observations worthy of note and that are highly informative:

1. The diverse racial and ethnic patient recruitment is worthy of praise, with 23% Black and 13% Hispanic participants. It is hoped that this diverse patient group is equally represented in phase 2 studies and beyond.
2. More than 40% of patients had hypertension, a risk factor for the development of AIC. The length of time between the original chemotherapy and the current study is impressive and gives credence to the need for heightened screening and follow-up many years beyond when chemotherapy ends.
3. Although primarily a New York Heart Association functional class II population, nearly 50% had been previously hospitalized for HF, and 23% had an emergency department visit for HF, with 38% reporting ventricular arrhythmia. Furthermore, the ventricular volumes were abnormal (13) and the NT-proBNP levels were elevated, indicative of the appropriate population to be studied.
4. The 6-minute walk results were also abnormal and had wide variability. Future trials will need a large number of participants recruited to capture meaningful differences.
5. The improvement in HRQoL is certainly intriguing if patients in fact feel better before changes seen in MRI measurements. It will be important to explore which portions of the instrument improved, for example, function, symptoms, or quality of life. This finding will need to be confirmed in a larger future trial, but its collection is in keeping with the current emphasis on patient-reported outcomes.

In summary, this is an important step to the resolution of an undesired effect of chemotherapy that has been deeply concerning to both oncologists and cardiologists, as well as patients and their loved ones. Although it had a small number of participants, this study can be considered a landmark with hope. A small step in the field, it may become a large step for many more in the future.

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AUTHOR DISCLOSURES

Dr. Piña has reported that she has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Ileana L. Piña, Wayne State University, 2627 Fairmount Boulevard, Cleveland Heights, Ohio 44106. E-mail: ilppina@aol.com. Twitter: @ilppina.

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