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EDITORIAL COMMENT

Progression of Heart Failure From AHA/ACC Stage A to Stage B or Even C

Can We All Agree We Should Try to Prevent This From Happening?*

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Over the past decade, cardiology in general has dramatically improved and enhanced the distribution of guidelines. The scope of data and opinion that is summarized in these various guidelines is nothing short of astounding. The diagnosis and treatment of heart failure (HF) is one disease area that has undergone extensive review, revision, and updating with the end product being a definitive anthology of what is known, and in part, what is not known, about the contemporary management of HF. Beginning in 2001, a new classification of HF was introduced by the American College of Cardiology and the American Heart Association that included stage A (patients at high risk for the development of HF) and stage B (patients with structural abnormalities who are asymptomatic). Stage C patients had current or past symptoms of HF, and then stage D had evidence of refractory HF in need of specialized management. This staging system was an expansion of the New York Heart Association classification, and the stated purpose was to "help healthcare providers identify patients early who are at risk for the development of HF" (1). This more inclusive staging system certainly achieves the goal of improved identification, if one truly considers high-risk conditions carefully. The next goal resulting from improved identification would be to halt progression of HF to a higher stage of disease.

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In this issue of the *Journal*, Chen et al. (2) report on the incidence of HF or cardiomyopathy (CM) that develops in older women (>67 years of age) with breast cancer who received trastuzumab, anthracyclines, or both over a 3-year period. Using the Surveillance, Epidemiology, and End Results database for oncology, these researchers found a significantly higher incidence of HF (treatment emergent) in patients treated with trastuzumab or trastuzumab and anthracyclines and lower incidence with anthracyclines alone. These rates were compared with those of age-matched and comorbidity-matched cancer patients not being treated with chemotherapy as well as those of cancer-free Medicare patients.

The strengths of these data include the fact that the dataset is inclusive, taking advantage of a national database that collects diagnoses and treatment of a very broad representation of cancer patients and that the authors focused on a more elderly population that may not be fully represented in a typical oncology treatment trial. There are some inherent weaknesses as well that include the fact that International Classification of Disease-9th Revision-Clinical Modification coding was the method to confirm a diagnosis of HF, not a careful prospective assessment that used objective clinical criteria. Additionally, there were no careful medication administration data that suggested which treatments may be cardioprotective, such as angiotensin-converting enzyme inhibitors or β-blockers. If a patient was taking these medications, this might have influenced the treatment-emergent incidence of HF. Furthermore, mortality data were not provided that compared those in whom HF developed with those who did not have HF, which would have provided a window into the substantial impact that HF has on overall outcome. Finally, it is somewhat surprising that the vast majority of all the patients were not treated with chemotherapy, which may suggest a reluctance to provide aggressive treatment in older patients.

These issues notwithstanding, there are some very important lessons that can be learned from this report. First, HF or CM are quite common in typical Medicare-age breast cancer patients, occurring nearly 20% of the time over a 3-year period. Second, trastuzumab and anthracycline administration (alone or in combination) seriously raises the risk and incidence of HF developing. Third, traditional cardiovascular risk factors occur frequently in this population and are important for the development of HF. For instance, more than 50% of these patients had hypertension and hyperlipidemia as well as other cardiovascular risks, such as diabetes and atrial fibrillation, which occurred at a lower, but not inconsequential, rate.

It is interesting that the initial unadjusted analysis suggested that anthracyclines may be protective even for the incidence of HF or CM, but after adjustments, a modest increase risk for HF or CM was identified. One might question the fact that, if no left ventricular function assessment or other testing were performed, then an International Classification of Disease-9th Revision-Clinical Modification, diagnosis of HF or CM never would be recorded. It

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seems likely that this observation is the case largely because past anthracycline use is not commonly considered a major risk for the development of HF in a typical cardiology or oncology practice, and an assessment of left ventricular function is not routinely performed. As a result, no diagnosis of HF or CM would be made in that case. Furthermore, as soon as left ventricular dysfunction is identified, patients do not seem to be treated optimally with cardiac medications, as frequently as we might expect (3). However, trastuzumab initially was believed to greatly increase the risk of HF or CM, and serial testing during treatment is widely recommended and practiced, especially in research trials. This may explain why trastuzumab had such a higher treatment-emergent HF rate than anthracyclines, but generally this therapy is not considered to be as damaging as an anthracycline. Another fascinating observation from these data includes the fact that hyperlipidemia was protective for the development of HF or CM. It could be theorized that because hyperlipidemia was identified and presumably treated, these patients likely were taking statin medications that are protective against the progression of HF (4). Further analysis of this concept is needed.

Overall, this analysis is very important, particularly in understanding how common HF and CM are in cancer patients and how substantially increased the incidence is over 3 years in patients treated with chemotherapy. No doubt trastuzumab, anthracyclines, and the combination have to be considered as major risk factors for the development of HF or CM, thus identifying a clear stage A HF patient. Engaging providers, particularly cardiologists, in the active management of cancer patients to prevent their progression from stage A HF to stage B or even stage C is a calling we all must respond to because it may be occurring in up to 20% of these cancer patients being treated with certain chemotherapies (5). After all is said and done, identification of HF or CM is only the first step. Prevention and optimal management to delay progression of HF is the real goal.

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