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EDITORIAL COMMENT

Trastuzumab Cures Cancer and Disrupts the Practice of Cardiology*

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It is fitting that the inaugural issue of *JACC: CardioOncology* presents a manuscript dealing with how to best use the anti-HER2 drug trastuzumab (1). The explosive growth of the field of cardio-oncology was likely catalyzed by the approval of trastuzumab in 2006 as adjuvant therapy for HER2-positive breast cancer. A common and more often than not fatal form of breast cancer became a curable disease, if the potentially dire cardiac side effects of trastuzumab could be deftly navigated.

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In 2002, a team led by cardiologists and oncologists from Memorial Sloan Kettering Cancer Center in New York described the unexpected syndrome of cardiac dysfunction associated with the administration of trastuzumab (2). This toxicity was recognized only late in trastuzumab development when the agent was systematically paired with anthracyclines for the treatment of metastatic breast cancer. Cardiac dysfunction was particularly common when trastuzumab and anthracyclines were given at the same time (27%), still present but less often when trastuzumab was given after anthracyclines (13%), and estimated to be rare when trastuzumab was used without anthracyclines (2). Because oncologists realized how effective trastuzumab was as a breast cancer agent, urgent plans were made to limit the potential for cardiac toxicity when trastuzumab would be used as adjuvant therapy. With adjuvant therapy for breast cancer, large numbers of women were now likely to survive their HER2-positive breast cancer and should not be subject to disability or death from heart failure. During planning of pivotal studies of trastuzumab in the adjuvant setting, it was judged that there would be at least an 8% absolute survival benefit from trastuzumab at 10 years (70% vs. 62%) (3). Given this level of expected benefit, study planners somewhat arbitrarily agreed that an absolute increase of 4% in the incidence of cardiac events with trastuzumab, defined as confirmed New York Heart Association (NYHA) functional class III or IV heart failure or possible or probable cardiac death attributable to trastuzumab would be acceptable, and patient accrual could be continued to study conclusion. If at any interim analysis the difference in cardiac events with versus without trastuzumab was statistically >4% (1-sided $p < 0.05$), accrual was to be suspended (3). Accordingly, strict monitoring of left ventricular ejection fraction (LVEF) and trastuzumab stopping criteria were used in the pivotal trastuzumab adjuvant trials to identify at-risk patients. The investigators reasoned that if trastuzumab was stopped for a fall in LVEF, these women would not experience advanced heart failure or cardiac death during the study period, and the trial could continue to completion. The trials were in fact successfully completed and demonstrated a highly significant improvement in survival with trastuzumab. On the basis of those results, trastuzumab was approved in 2006 for use as adjuvant therapy in HER2-positive breast cancer.

When this agent was introduced as adjuvant therapy, the trastuzumab (Herceptin) prescribing information (package insert) closely followed the recommendations for suspension of trastuzumab used in these pivotal clinical trials (4). The package insert recommends assessing the LVEF before

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initiation of Herceptin and at regular intervals during treatment. Moreover, it is recommended that Herceptin is withheld for at least 4 weeks for any of the following: ≥16% absolute decrease in LVEF from pre-treatment values, LVEF below institutional limits of normal, and ≥10% absolute decrease in LVEF from pre-treatment values. Herceptin may be resumed if, within 4 to 8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%. Permanently discontinue Herceptin for a persistent (>8 weeks) LVEF decline or for suspension of Herceptin dosing on >3 occasions for cardiomyopathy.

These recommendations to suspend or discontinue trastuzumab remain in effect today. These safety recommendations persist even though we now understand that patients with an asymptomatic decline in EF to above a level of 40% may never develop heart failure despite continuing trastuzumab (5–7). Further, a full year of trastuzumab prolongs disease-free and overall survival in patients with HER2-positive breast cancer (8), and premature and permanent discontinuation of trastuzumab because of cardiac toxicity has been associated with adverse cardiac and cancer outcomes (9,10). Finally, the anticipated disease-free survival benefit from trastuzumab that somewhat arbitrarily shaped the original safety guidelines actually underestimated the anticancer efficacy of trastuzumab (11,12). Thus, there is a strong rationale to revisit the initial trastuzumab safety guidance in an attempt to capitalize more fully on the therapeutic potential of trastuzumab therapy.

Leong et al. (1) present an elegant, small, single-arm and thus necessarily limited trial that adds to the understanding of the risks of trastuzumab breast cancer therapy. In SCHOLAR (Safety of Continuing CHemotherapy in Overt Left Ventricular Dysfunction using Antibodies to Human Epidermal Growth Factor Receptor-2), patients treated with anthracyclines followed by trastuzumab were enrolled if they had an LVEF between 40% and 54% or a fall in LVEF ≥15% from baseline without symptoms of NYHA functional class III or IV heart failure. All 20 eligible participants referred by oncologists for study agreed to participate and were enrolled. All were treated with angiotensin-converting enzyme inhibitors and/or beta-blockers during continued trastuzumab therapy and were followed carefully with clinical assessments and echocardiograms in a cardiology clinic. The primary outcome was dose-limiting cardiac toxicity defined as cardiovascular death, LVEF <40% with any heart failure symptoms, or any LVEF <35%. Eighteen patients (90%) received all planned trastuzumab doses, and in 2 (10%), heart failure with LVEF <40% developed. In these 2 patients the trough LVEFs were 28% and 26% but improved to 56% and 47%, respectively, after permanent discontinuation of trastuzumab therapy. Importantly, both patients' symptoms improved to NYHA functional class I with medical therapy.

SAFE-HEaRt (Prospective evaluation of the cardiac safety of HER2-targeted therapies in patients with HER2-positive breast cancer and compromised heart function) is the other trial that prospectively evaluated the safety of continuing trastuzumab despite evidence for mild cardiotoxicity (5). SAFE-HEaRt results were quite similar to those of SCHOLAR; 29 of 31 trastuzumab-treated patients were able to complete their planned course, whereas 2 had a clinical event or the EF fell to <35%. In practice and clinical trials, the rate of discontinuation of trastuzumab, largely because of cardiac toxicity, varies between 8% and 31% (10,13). Therefore, strategies to enable continued trastuzumab dosing despite relatively mild forms of cardiac toxicity have the potential to allow significantly more women to be fully and thus more effectively treated for their breast cancer. With their limited size and single-arm design, SCHOLAR and SAFE-HEaRt do not provide the information required to accurately assess whether the added cardiac risk offsets the expected gains in breast cancer outcomes from a full course of trastuzumab therapy.

It is reassuring that using the existing stopping rules for trastuzumab, the rates of heart failure remain low for as long as 11 years of follow-up (12). In other words, in long-term follow-up trials, trastuzumab-related modest falls in LVEF below the lower limit of normal in women without NYHA functional class III or IV heart failure have not been associated with a measurably increased rate of heart failure in the long term if trastuzumab is stopped. One can speculate that if guideline-directed medical therapy with angiotensin-converting enzyme inhibitors or beta-blockers stabilizes patients after a fall in LVEF and prevents further LVEF decline, late heart failure will continue to be relatively less common and will not diminish the expected improvement in breast cancer survival when more women receive a complete course of trastuzumab.

But this is just speculation. SCHOLAR is limited to a 1-year follow-up, so late changes in LVEF or cardiac symptoms are not known. Several patients in this study had only modest impairment of left ventricular systolic function with an LVEF >50% at the time of enrollment. They were motivated participants very carefully followed with echocardiograms and clinical assessments in a dedicated cardio-oncology clinic. Guideline-directed medical therapy was aggressively

pursued, although dosing was submaximal in many patients.

Despite hundreds of thousands of women being treated with trastuzumab since its introduction as an adjuvant therapy for breast cancer, the information available to date is much too limited to fully inform the risks and benefits of continuing trastuzumab in the presence of mild cardiomyopathy. Specifically, longer follow-up data in more patients will be needed to determine whether the expected improvement in breast cancer outcomes driven by more complete courses of trastuzumab outweigh the potential risk of heart failure associated with a SCHOLAR-like strategy of patient monitoring and treatment. Larger studies are also needed to identify predictors of favorable cardiac outcomes in patients with mild cardiotoxicity who continue trastuzumab treatment. This first issue of *JACC: CardioOncology* is emblematic of the enthusiasm and newly found power of the field of cardio-oncology. We should channel this energy into larger-scale, cooperative studies that address this pivotal question.

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