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EDITORIAL COMMENT

Trastuzumab Cardiotoxicity After Anthracycline Exposure Constitutes a Complex and Clinically Important Entity*

Michael S. Ewer, MD, JD, PhD,[a] Steven M. Ewer, MD[b]

Our knowledge regarding trastuzumab-related cardiotoxicity has grown considerably since this entity was first recognized more than 20 years ago. We now understand it to be a complex combination of direct effects on cardiac function and synergistic interaction with anthracyclines. Our appreciation of the entity is complicated by suboptimal measurement tools of cardiac function and variable threshold definitions. Notwithstanding considerable progress, questions remain regarding how trastuzumab affects the heart and what are the potential long-term cardiac implications for breast cancer survivors treated with this drug.

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Cardiotoxicity was not anticipated with a monoclonal antibody, but concerns were raised following research by Slamon et al. (1) that demonstrated a 16% incidence of New York Heart Association functional class III or IV heart failure and a 27% incidence of left ventricular systolic dysfunction. This information surfaced at a time when perspectives regarding the cardiotoxicity of anticancer treatment were based on the anthracycline experience of permanent and potentially life-threatening toxicity. The remarkable oncological efficacy demonstrated in patients with *HER2*-positive breast cancer treated with trastuzumab in the metastatic setting led to initiatives to answer 2 fundamental questions: First, in the metastatic setting, could ways be found to continue trastuzumab for ongoing responders? Second, could trastuzumab be administered in the adjuvant setting with sufficient cardiac safety to allow such use?

Efforts to answer these questions ensued, including the initiation of a number of clinical trials that prudently incorporated careful monitoring of the left ventricular ejection fraction (LVEF). As these trastuzumab trials were under way, however, it gradually became evident that not all forms of treatment-related left ventricular dysfunction are equivalent, and an alternative presentation and course to what had been seen with the anthracyclines were recognized. The morphology under electron microscopic scrutiny was markedly different, and the classic cumulative dose relationship of the anthracyclines did not appear to exist. Furthermore, with similar levels of decline in the LVEF, the course, although not always benign, was less malignant compared with the cardiotoxicity seen with anthracyclines. Interestingly, attempts to destroy myocytes in vitro by exposure to trastuzumab have largely failed. These collective differences resulted in the recognition of what is now often referred to as type 2 treatment-related cardiac dysfunction (2). Anecdotally, in the absence of anthracycline use, ongoing trastuzumab administration has been tolerated for many years.

A number of important questions emerged with the understanding that trastuzumab did not directly destroy myocytes as did the anthracyclines: Why do some patients develop serious heart failure after exposure? Why are some patients able to tolerate

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From the [a]University of Texas MD Anderson Cancer Center, Houston, Texas; and the [b]Division of Cardiovascular Medicine, University of Wisconsin School of Medicine & Public Health, Madison, Wisconsin. Dr. M. Ewer is a paid consultant for AstraZeneca, Boehringer-Ingelheim, and Daiichi Sankyo; and has inactive consultancies with Merck and Bayer. Dr. S. Ewer has reported that he has no relationships relevant to the contents of this paper to disclose.

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exposure over many years without experiencing declines in LVEF? Why is late expression of cardiotoxicity sometimes seen after trastuzumab exposure? And why are cardiac biomarkers elevated in some settings and not in others? The accompanying paper by Goel et al. (3) regarding CATS (Cardiotoxicity of Adjuvant Trastuzumab Study) brings us a bit closer to the answers.

Crucial in the explanation is the anthracycline-trastuzumab interaction. All of the patients included in this trial received an anthracycline, either doxorubicin or epirubicin. The cardiotoxic equivalent dose between these 2 anthracycline-containing regimens is not identical. The expected incidence of heart failure for the doxorubicin group was about 1.5% and for the epirubicin group about 0.6% (4). It is therefore no great surprise that cardiotoxicity occurred more often in the doxorubicin group (11%) than the epirubicin group (6.6%) following trastuzumab exposure in CATS.

Three other observations help explain the Goel et al. (3) findings. First, although the adjuvant trials referred to earlier provided hugely important efficacy data, they also hinted at an intriguing and unexpected finding. Together with the data from the Slamon et al. (1) pivotal trial, we note that the shorter the duration of the interval between the anthracycline and trastuzumab, the greater the noted incidence of toxicity: 16% with concomitant use, approximately 3% when the interval between agents was 21 days, 0.6% with an interval of 89 days, and very close to the baseline value of the nonanthracycline arm in the BCIRG (Breast Cancer International Research Group) 006 trial, in which the incidence was 0.4%. The second observation is that when cardiac biopsies were undertaken after anthracycline therapy, the typical electron microscopic changes were no longer present after about 3 months. Cardiac myocytes appeared to have either recovered or undergone apoptosis and were replaced by fibrous tissue. The third observation was that trastuzumab suppresses cell recovery, thereby incrementally increasing the extent of cell injury and death during the recovery phase after anthracycline exposure (5). This explanation in undoubtedly incomplete, as the actions of trastuzumab are complex, as are the possibilities for cardiac effects. The basic picture, however, fits well. Initial anthracycline injury with loss of some myocytes is then followed by a vulnerable period when cell recovery is possible, but repair may be compromised by trastuzumab that then augments the anthracycline injury (6).

What might we expect within this framework as we look at CATS? The post-anthracycline, pre-trastuzumab LVEF was lower in patients who later went on to develop what is defined as treatment-related cardiotoxicity. These patients may have experienced greater pre-treatment compromise in their cardiac reserve or perhaps experienced a greater degree of true anthracycline injury. As intimated, when trastuzumab is administered during the vulnerable recovery period, additional cell loss can be anticipated. It is not surprising that treatment-related cardiotoxicity most often occurs within the first 3 months of trastuzumab treatment or that a lower pre-anthracycline LVEF is a predictor of its occurrence.

Many questions regarding cardiotoxicity might be easier to answer had we a simple test with high predictive value. At the present time, echocardiography still has a false positive rate of about 1% for each determination and an estimated 3.6% for patients undergoing serial observations over time, a number uncomfortably close to what is being reported for some newer agents (7). This brings us to a highly relevant comment in CATS: “it would help define a patient population in whom LVEF monitoring…could be performed less frequently.” The time is right to move in that direction. Reassuringly, we note that clinical heart failure occurred in only 1 patient in this study, an incidence of 0.46%, consistent with what would be expected following anthracycline exposure.

The aim of CATS was, at least in part, to determine if baseline LVEF and change in LVEF after anthracycline are associated with the risk for subsequent treatment-related cardiotoxicity. As would be expected, they clearly are.

ADDRESS FOR CORRESPONDENCE: Dr. Michael S. Ewer, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030. E-mail: mewer@mdanderson.org.

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