Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 57, No. 22, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2010.11.064

EDITORIAL COMMENT

Can Modern Echocardiographic Techniques Predict Drug-Induced Cardiotoxicity?*

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Trastuzumab is a humanized monoclonal antibody and is approved for the treatment of patients with human epidermal growth factor receptor II (HER-2) positive breast cancer, in the adjuvant and metastatic settings. It was approved by the U.S. Food and Drug Administration in 1998, but the first studies were not designed to detect any cardiac side effects. Trastuzumab has substantial therapeutic benefits in the treatment of primary breast cancer and was considered to be a revolutionary adjuvant drug to anthracyclines when 2 separate studies about its effects and side effects were published in 2005 (1–3).

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However, the antibody has been associated with risk of development of cardiotoxicity. This risk is further increased when combined with anthracycline chemotherapy, which itself is strongly associated with cardiac toxicity. Up to one-fourth of all patients receiving trastuzumab have been reported to develop ventricular dysfunction. Most of the reported cardiac effects have been regarded as mild-to-moderate, asymptomatic, reversible, and manageable by medications (4,5).

In their paper in this issue of the *Journal*, Fallah-Rad et al. (6) use tissue Doppler and strain echocardiographic methods to reveal early signs of decreased ventricular function in patients receiving trastuzumab.

They showed that an early decline in tissue velocity and strain parameters was followed by a later and clinically significant decline in left ventricular (LV) function assessed by ejection fraction. Serum levels of troponin-T, C-reactive protein, and brain natriuretic peptide failed to demonstrate LV failure. Only 42 patients were studied, and 10 of these developed trastuzumab-mediated cardiomyopathy. A specified reduction in peak systolic myocardial velocity and peak global strain measurements at 3 months could detect the development of trastuzumab-mediated cardiomyopathy in all 10 patients. Their study is important. The development of cardiomyopathy due to a treatment regime is concerning and might also be devastating for some patients. Therefore, an easily available tool that can detect such development at an early and reversible state is needed, and the present study is reporting important results in this matter.

We should also notice that despite a discontinuation of the antibody treatment after 6 months, LV parameters did not recover completely in a new echocardiographic study approximately 6 months after termination of trastuzumab. The continuing reduction in LV function is further supported by the myocardial scar found by contrast-enhanced magnetic resonance imaging in the present study. Until now, all trastuzumab-mediated cardiomyopathy has been regarded as reversible, but the present results might indicate that this assumption is not correct (4). Therefore, further studies of the long-term effect on LV function are needed to provide a more complete picture of trastuzumab-induced cardiotoxicity.

Improved echocardiographic tools for accurate assessment of ventricular function have been launched during the last 2 decades. Even subtle wall motion abnormalities can be demonstrated by tissue Doppler and strain techniques (7,8). There is no doubt that the introduction of these modern echocardiographic techniques has made it possible to accurately perform quantitative and objective measures of regional ventricular function. Essential clinical decisions should only be done after careful consideration. One must acknowledge that a decrease in systolic myocardial velocities of <1 cm/s from start of treatment to the next echocardiographic study might be due to changes in the hemodynamic state of each patient and might have other explanations as well. Therefore, other echocardiographic measurements supporting a decline in LV function should be obtained in each patient. Generally, a combination of parameters that demonstrates similar findings will make it easier to make a correct decision. One of the strengths of echocardiography is that many parameters that can accurately characterize LV function are easily available. A decision based on only 1 measurement of myocardial velocities of the lateral LV wall should only be done with great caution.

There are many pitfalls related to all use of echocardiography. One obvious risk in these patients would be that low image quality would give false low myocardial velocities, which again can lead to wrong interpretations and wrong decisions. Much experience with these novel techniques is therefore needed before we jump to possible erroneous conclusions for patients.

All echocardiographic laboratories should use these techniques on a regular basis to acquire sufficient knowledge on how they work and their strengths and weaknesses. It is not

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recommended to restrict their use to selected patient groups. Until other studies confirm the findings of Fallah-Rad et al. (6), each laboratory should earn experience in patients receiving trastuzumab and learn how these echocardiographic parameters can predict cardiotoxicity in these particular patients.

A termination of a potential life-saving treatment should only be done after careful consideration. Therefore, cardiologists and oncologists should balance the risk of recurrent cancer against the risk of cardiovascular morbidity and mortality when trastuzumab is given to these patients.

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Key Words: breast cancer ■ cardiomyopathy ■ doxorubicin ■ tissue velocity imaging ■ trastuzumab.