# ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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## Markers of Cardiotoxicity in Breast Cancer Patients

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### H&O How common is cardiotoxicity in cancer patients?

**MS** Cardiotoxicity—defined as any of the side effects of cancer drugs on the heart—is quite common. Cancer patients are susceptible to cardiovascular diseases for a number of reasons. The cancer patient population is older than the general population, and thus at greater risk of cardiovascular disease. In addition, the drugs that are used to treat cancer are often cardiotoxic and can cause a variety of effects, including heart failure; toxicity of the electrical system, resulting in events such as QT prolongation and arrhythmias; and hypertension, to cite a few. The cardiotoxicity of anthracyclines has been the most widely studied. Anthracyclines, which are routinely used in breast cancer and hematologic cancers, in particular are associated with type I cardiotoxicity, which is due to direct damage to cardiomyocytes that is mostly irreversible. Symptomatic heart failure, the most studied event, occurs in 2–5% of cancer patients who have received anthracyclines. There is a much larger occurrence of asymptomatic subclinical dysfunction of the heart, which varies depending on the regimen. Approximately 15–30% of patients who receive regimens containing anthracyclines experience asymptomatic subclinical dysfunction of the heart.

### H&O What are the causes of cardiotoxicity in cancer patients?

**MS** Anthracyclines produce a large quantity of reactive oxidant species, which can be toxic to the cardiomyocytes. They can also cause an overload of calcium, leading to direct damage to the heart. Tyrosine kinase inhibitors have been associated with type II cardiotoxicity, defined by partially reversible damage without apoptosis or necrosis of the cardiomyocytes.

Cardiotoxicity in cancer patients can encompass more than heart failure. For example, vasospasm can be produced by some anticancer drugs and has a different mechanism than the cardiotoxicity I just described. Hypertension has been seen with anti–vascular endothelial growth factor therapies.

### H&O What is the associated morbidity and mortality?

**MS** The existing studies provide incomplete information. We know that in breast cancer patients older than 65, the mortality associated with cardiovascular disease is higher than the mortality associated with cancer. According to retrospective studies of large databases comparing patients who have or have not received anthracyclines, use of these agents is associated with an increased mortality of approximately 10%. These data are based on large registries, which can have their limitations.

### H&O What are the traditional methods of assessing cardiac function in cancer patients?

**MS** The traditional criterion used to assess cardiac function in cancer patients is the ejection fraction, which is a global measure of systolic function. This parameter can be obtained using different techniques, in particular radionuclide angiography (also known as the multigated acqui-

sition [MUGA] scan) and echocardiography. In research, magnetic resonance imaging is sometimes employed. It is well-known that a low ejection fraction seen at baseline before chemotherapy or just after the first phase of treatment with anthracyclines is associated with higher cardiovascular side effects. However, in many cases, the ejection fraction will decrease during treatment, but not enough to discontinue the regimen or consider cardioprotective measures. It is unclear whether measurement of the ejection fraction early in treatment has a real prognostic value long-term, except when the value is very low.

**H&O** What are the data supporting the use of echocardiographic indices and biomarkers in cancer patients?

**MS** There is growing support for the use of echocardiographic indices that are more sensitive than ejection fraction, although the data are still limited to smaller studies and the long-term prognoses are still unknown. In a recent study, our team demonstrated that deformation indices, which are parameters that measure the deformation of the heart using echocardiography, can predict a later decrease in ejection fraction during treatment. Data from our group and from Dr. Daniela Cardinale in Italy show the prognostic value of measuring troponin, which is a biomarker that can reflect myocardial damage. These studies report short-term prognostic value regarding left ventricular dysfunction, but any long-term prognostic value is unknown.

**H&O** What prompted your recent study on assessing echocardiography and biomarkers for the extended prediction of cardiotoxicity?

**MS** There was a need for a predictive index that would have more power than the ejection fraction. The predictive value of the ejection fraction is controversial, and we were looking for more sensitive markers that could be predictive of later left ventricular dysfunction and heart failure.

**H&O** What was the study population, design, and findings?

**MS** We studied 81 women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer who were treated with anthracyclines followed by a taxane and trastuzumab (Herceptin, Genentech), and then by trastuzumab alone. At each of 6 visits, the patients underwent an echocardiogram and a blood draw. The visits took place before initiation of the anthracycline therapy, after the anthracycline regimen ended, after treatment with the taxane and trastuzumab, and then every 3 months during the remainder of the trastuzumab treatment. The last visit occurred 15 months after the start of the study.

The objective was to determine whether later cardiotoxicity could be predicted by measuring a variety of biomarkers, including deformation indices of the myocardium, which is called myocardial strain, and troponin. Cardiotoxicity was defined as a decline of more than 10 points of the ejection fraction to less than 55%—which is still within normal limits—or a decline of more than 5 points of the ejection fraction to less than 55% accompanied by symptoms of heart failure. We found that both the myocardial strain, which is measured at peak systole in the longitudinal dimension, and the troponin levels were predictive of the later occurrence of cardiotoxicity.

**H&O** How might the study findings be applied to clinical care?

**MS** Guidelines are in development from the American Society of Echocardiography and the European Association of Echocardiography in collaboration with the American Society of Clinical Oncology. We are coming to the consensus that patients with a decreased myocardial deformation or an increased troponin should be monitored carefully, even if the ejection fraction is within normal limits. The measurements of these indices can orient the surveillance of patients, even if they still have normal ejection fractions. We cannot, at this point, recommend a change of treatment based only on these indices, but we can recommend more thorough follow-up of these patients. There are several research and grant proposals for studies looking at larger cohorts using both echocardiographic and biomarkers to see if their predictive value exists with other therapies other than the ones in our study.

## Suggested Readings

Sawaya H, Sebag IA, Plana JC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circulation: Cardiovascular Imaging*. 2012;5:596-603.

Cardinale D, Colombo A, Torrisi R, et al. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. *J Clin Oncol*. 2010;28:3910-3916.