Advances in early cancer detection and treatment have resulted in patients living longer after diagnosis. According to the Centers for Disease Control and Prevention, about 12 million cancer patients survived in the United States in 2007, two thirds of whom were expected to live at least 5 years after the diagnosis.

With increases in survival time, the long-term adverse effects of various cancer treatments have become a subject of concern. Chemotherapeutic agents and radiation can cause several such effects; the cumulative incidence of chronic health conditions 30 years after cancer diagnosis can be as high as 75%. In particular, the number and severity of adverse cardiovascular effects increase with increasing doses of cardiotoxic chemotherapeutic agents as well as with increasing age, making these effects a large portion of these chronic health conditions.

The onset of the cardiotoxic effects of cancer treatment can be early or late. Late effects usually manifest as dilated cardiomyopathy or arrhythmias. Diastolic dysfunction manifests earlier than any signs or symptoms of clinical heart failure. Given the incidence and timing of these effects, several echocardiographic measures and cardiac biomarkers have been proposed to identify and predict their long-term adverse cardiovascular outcomes.

In this issue of Circulation: Cardiovascular Imaging, Sawaya et al tried to identify predictors of early-onset cardiotoxicity, which are those presenting during the first year after therapy. Among 81 women with newly diagnosed breast cancer related to human epidermal growth factor receptor 2 overexpression (positive) that had been treated with anthracyclines followed by taxanes and trastuzumab, 26 (32%) developed cardiotoxicity, which is a well-known and validated marker of myocardial injury; N-terminal pro-B-type natriuretic peptide; and ST2 protein. N-terminal pro-B-type natriuretic peptide is a validated marker of cardiac wall stress related to pressure and volume overload that is widely used in the diagnosis, risk assessment, treatment, and prognosis in patients with different types of cardiac disease.

The authors also measured concentrations of soluble ST2 protein (also known as interleukin-1 receptor-like 1), a part of a cardioprotective signaling system that interacts with interleukin-33 to prevent myocardial hypertrophy and fibrosis. The ST2 protein is associated with cardiac remodeling; more specifically, with LV ejection fraction and end diastolic volume, and also with aldosterone concentrations, which have a strong profibrotic effect on the heart.

Sawaya et al found that of all the echocardiographic values obtained after anthracycline treatment, only a peak systolic longitudinal myocardial strain <19% predicted late cardiotoxicity, with a sensitivity of 74% (95% CI, 51–90%; P<0.001). Among cardiac biomarkers, only an ultrasensitive cardiac troponin I concentration >30 pg/mL after anthracycline treatment was somewhat associated with subsequent cardiotoxicity, with a sensitivity of 48% (95% CI, 27–69%; P=0.04). The combination of both the above end points had a sensitivity of 35% (95% CI, 16–57%). However, regardless of statistical significance, predictors with a 95% CI containing 50% (ultrasensitive cardiac troponin I concentration or the combined endpoint) are not clinically useful. More compelling were the results of a parallel screening model based on positive results for either predictor. Here, the sensitivity was 87% (95% CI, 66–97%).

The authors also report that the positive predictive value was 53% for a longitudinal strain <19% and 43% for the parallel screening model with both end points. However, in addition to these unremarkable results, the positive predictive value is not a measure of validity because it depends in part on the prevalence of the condition under study (here, the prevalence of cardiotoxicity was 26 of 81, or 32%). Rather, the positive predictive value gives the probability that a positive screening test will correctly identify the outcome of interest in a patient from a specific population in which the incidence of the outcome (in this case, cardiotoxicity) is known.

Mean follow-up in this study was only 15 months from the start of treatment and only 12 months after the completion of anthracycline therapy. Anthracycline-induced cardiotoxicity can present over a variable time during and after treatment and is classified by time of onset. Acute anthracycline cardiotoxicity presents as a reversible episode of myocardial

Screening for Long-Term Cardiac Status During Cancer Treatment

Steven E. Lipshultz, MD; Thomas R. Cochran, BA; James D. Wilkinson, MD, MPH

They also measured concentrations of cardiac troponin I with an ultrasensitive assay (ultrasensitive cardiac troponin I), a well-known and validated marker of myocardial injury; N-terminal pro-B-type natriuretic peptide; and ST2 protein. N-terminal pro-B-type natriuretic peptide is a validated marker of cardiac wall stress related to pressure and volume overload that is widely used in the diagnosis, risk assessment, treatment, and prognosis in patients with different types of cardiac disease.

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dysfunction during therapy in <1% of patients and usually resolves when therapy is discontinued. Early-onset cardio toxicity occurs within 1 year after therapy, and late-onset cardiotoxicity occurs >1 year after anthracycline therapy. Thus, the report by Sawaya et al is limited to predicting early-onset cardiotoxicity. As it may not be long enough for clinically relevant events to develop, the utility for predicting events in this short period is unknown. Because of its design, the report by Sawaya et al cannot address prediction of late-onset anthracycline cardiotoxicity. However, the proportion of patients missed by the study because it is not applicable to late-onset effects would be of interest.

The individual trajectories of changes in LV ejection fraction presented by the authors for patients with cardiotoxicity revealed that many patients with initial LV ejection fraction dysfunction improved between 12 and 15 months after treatment. Understanding whether LV ejection fraction improves and stabilizes over time is necessary to understand the clinical importance of the short-term changes in LV ejection fraction described in this study in which only 5 of 26 patients with cardiotoxicity had cardiac-related symptoms.

Treatment with trastuzumab, paclitaxel, or both, continued throughout the follow-up period and could have confounded predictions specific to anthracycline cardiotoxicity. Finally, as the authors appropriately note, their screening recommendations regarding specific approaches to identifying 12-month cardiotoxicity in this population are based on a small sample size. Because human epidermal growth factor receptor 2 positive breast cancer is relatively common, larger and more definitive studies are needed (and are also feasible) before an appropriate screening approach can be established.

The most important question to be answered for any proposed screening test is, “Is it desirable?” “Is the test valid, cost-effective, socially acceptable, and practical?” According to Wilson and Junger, an effective screening test must meet 4 requirements: (1) it must identify conditions for which an acceptable treatment exists that can change the outcome for patients diagnosed early in the course of the condition; (2) it must be based on an understanding of the condition’s natural history; (3) it must specify the characteristics of people to be treated; and (4) it must be valid and acceptable for screening both affected and unaffected people.

Do the echocardiographic screening and cardiac biomarkers presented in this article by Sawaya et al meet these requirements? Partially.

Most assays for cardiac biomarkers are relatively inexpensive and easy to perform. Echocardiography, although more expensive, would have to be compared with the costs of anthracycline cardiotoxicity, including long-term treatment, potential hospitalizations, and even heart transplantation. Exploratory clinical studies of potential new screening tests are not required to include a sophisticated cost-effectiveness analysis. However, including a back-of-the-envelope estimate of cost-effectiveness would be helpful in evaluating the potential value and feasibility of any proposed new screening procedure. The potential for clinical and psychological effects of false positive or negative results of screening for any disease must also be considered in clinical practice.

Regarding Wilson and Junger’s first requirement, to date, we are unaware of any treatment that can prevent the progression of cardiotoxicity detected at a preclinical stage. In their Introduction, Sawaya et al state that the “decrease in ejection fraction appears to be responding to treatment in a majority of patients,” and they go on to note that “once the LV ejection fraction has decreased in patients treated with anthracyclines, it may be too late to reverse the course of the cardiomyopathy.” We think they accurately report the scientific consensus that no validated intervention can predictably stop, slow, or reverse early cardiotoxicity in anthracycline-treated cancer patients. Even when cardiotoxicity is identified at a clinical stage, treatment with enalapril is at best only temporarily effective because the LV wall continues to thin, leading to progressive deterioration of cardiac function. The authors specifically note that pretreatment with angiotensin-converting enzyme inhibitors or β-blockers was not associated with a decrease in cardiotoxicity after cancer therapy including anthracyclines.

Regarding requirement 2, the short-term natural history of anthracycline cardiotoxicity is understood to a degree, although this understanding is reduced beyond about 5 years after the end of treatment. This natural history of chemotherapy-induced cardiomyopathy tells us that some of the affected patients eventually require heart transplantation. Can early detection and intervention prolong the time to transplant? If we can detect the early signs of cardiotoxicity in cancer survivors, can we alter the ultimate outcome from heart failure in these patients? Are the associated screening tests easy to perform? Sawaya et al do not answer all these questions, but they take us 1 step closer to the answers.

Regarding requirement 3, we do not believe that this study can determine who will be treated, given the variability in the sensitivity of various proposed screening end points and the current lack of a validated early intervention. As for requirement 4, we assume that women with breast cancer would find the relatively noninvasive combination of a blood test and an echocardiogram to be acceptable assuming, of course, that the end points described here were sensitive predictors of eventual cardiotoxicity and that preventive treatment was available.

Cardiotoxicity of chemotherapeutic agents is only 1 cause of adverse cardiovascular effects in cancer survivors, so a global cardiovascular risk assessment is also important in this vulnerable population. Atherosclerosis accelerated by metabolic syndrome, obesity, lack of physical activity, smoking, and drug and alcohol use is common in cancer survivors. That said, the authors should not be expected or required to address these issues in an exploratory clinical study of potential screening tests for cardiotoxicity in women with breast cancer treated with anthracycline chemotherapy.

The more we learn about the long-term cardiovascular effects of cancer treatments, the more we realize the importance of primary prevention. We must tailor therapies to achieve the most favorable long-term outcomes by balancing the tradeoff between cancer control or cure and long-term cardiovascular health. Other chronic conditions that affect these end points must be considered as well. The concomitant use of cardioprotective agents such as dexrazoxane may be promising in this regard. The use of anthracyclines and trastuzumab causes incremental cardiotoxicity that is eliminated in human
epidermal growth factor receptor 2 positive cancer patients by the concomitant use of dextrazoxane.\textsuperscript{30} Similarly, the cumulative dose of chemotherapeutic agents must be controlled to minimize myocardial damage while maximizing therapeutic effectiveness. We must make sure that we are not trading 1 lethal disease (cancer) with another (future cardiovascular disease).

The diagnostic performance of any proposed predictor (whether an echocardiographic measurement or a serum concentration) of a clinical outcome must be assessed against a reference standard and expressed with any number of statistical techniques (eg, likelihood ratios, correlation, receiver operating characteristic curves, and so on). We believe that the analytic approach presented by Sawaya et al\textsuperscript{17} is generally appropriate, but the diagnostic reference standard does need to be identified to ensure that the cardiotoxic effects are measurable.

Although the authors present the receiver operating characteristic curve for peak systolic longitudinal myocardial strain, but the diagnostic reference standard does need to be identified. Comparative receiver operating characteristic curves derived from the full and reduced logistic models. Such a comparison would identify any additional predictive information provided by the proposed predictors above that provided by traditional markers (ie, LV ejection fraction) while directly addressing the issue of redundancy. The same approach would have added to the estimation of attributable sensitivity and specificity.

Sawaya et al\textsuperscript{17} have added to our understanding of the potential value of specific echocardiographic measurements and serum biomarkers in identifying anthracycline-induced cardiotoxicity in women with human epidermal growth factor receptor 2 positive breast cancer. However, the utility of these measures as valid screening tests for early cardiotoxicity raises as many questions as answers. In the end, any screening proposal will be deemed effective only when an intervention will improve patient outcomes if applied early in the course of the disease.

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Disclosures

None.

References


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