

ADVANCES IN ONCOLOGY

Current Developments in the Management of Solid Tumor Malignancies

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IN FOCUS: Breast Cancer

Cardiovascular Complications of Breast Cancer Therapy

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H&O What is the historic evidence of cardiac complications associated with cancer chemotherapy?

SS The main complications discovered many years ago by Dr. Daniel Von Hoff and coworkers resulting from cancer chemotherapy were associated with anthracyclines (eg, doxorubicin). Von Hoff's findings showed that cardiac toxicity increased with the amount of anthracyclines given over time. The cumulative drug dose was found to be correlated with toxicity. The research that led to this discovery was based on the retrospective review of thousands of patients who experienced significant heart failure, many of whom died. Today, based on the recognition of this anthracycline-based toxicity, the cumulative amount of anthracyclines administered to a given patient with breast cancer is limited. Several years ago, my colleagues and I published prospective data showing that cardiotoxicity occurred at a lower cumulative dose (ie, 300 mg/m²) than had been reported by Von Hoff. In this prospective research, cardiotoxicity was detected earlier, and, as a result, most patients did not die. Anthracycline-induced cardiotoxicity—myocardial damage and necrosis—therefore was characterized several years ago.

A 2007 article in the *Journal of Clinical Oncology* by Pinder and colleagues from The University of Texas M. D. Anderson Cancer Center assessed the Medicare database and showed that patients who received adjuvant anthracyclines had a much higher rate of hospitalization for heart failure than patients who had not received adjuvant chemotherapy or patients who had received nonanthracycline-based adjuvant chemotherapy. Thus,

we must ask what happens to a patient who receives anthracyclines after 20 years. Are these patients at increased risk? This study would suggest that the risk is in fact increased. However, this study used the Medicare database, which could include patients incorrectly characterized as having experienced heart failure due to anthracycline therapy. Still, despite data flaws that require continuing research, this large retrospective study does suggest that the risk of heart failure is related to the use of anthracyclines.

More recently, with the widespread use of trastuzumab (Herceptin, Genentech) in the treatment of women with HER2-positive disease, after or with anthracyclines, it was observed that cardiotoxicity increased. This cardiotoxicity, however, does seem to be reversible in a large percentage of patients, although further research is needed. Trastuzumab-related cardiotoxicity seen in the adjuvant trials was reversed in most cases when patients discontinued trastuzumab therapy. It should be noted that with trastuzumab, the cardiotoxicity is most likely related to prior damage from anthracyclines; in other words, cardiotoxicity is most commonly seen in trastuzumab-receiving patients who previously received anthracyclines. In a trial that did not include anthracyclines, very little cardiotoxicity was seen among patients who received trastuzumab.

H&O What is the best strategy to avoid cardiotoxicity while maintaining positive outcomes?

SS The strategy to avoid cardiotoxicity by not administering anthracyclines has been assessed in two trials. The docetaxel, carboplatin, trastuzumab (TCH) regimen used in the Breast Cancer International Research Group (BCIRG) 006 trial was a study arm that did not include anthracyclines in order to assess this strategy. At the sec-

ond interim analysis, it appeared that TCH is effective in increasing disease-free survival in patients who have HER2-positive early breast cancer. Another strategy recently assessed was described by Dr. Stephen Jones in a second update at the San Antonio Breast Cancer Symposium; the trial by Jones and associates compared docetaxel (Taxotere, Sanofi-Aventis) plus cyclophosphamide (TC) to doxorubicin plus cyclophosphamide (AC). A survival benefit was found for TC over AC. As a result, many clinicians in the United States are shifting their treatment strategies away from the use of anthracyclines in patients with HER2-positive disease.

There are preclinical data suggesting that topoisomerase II overexpression is associated with the response to anthracyclines. Most patients who have HER2-negative disease do not have topoisomerase II amplification. Therefore, it has been hypothesized that anthracyclines are not needed in patients with HER2-negative disease.

H&O As a result of these preclinical findings on HER2-negative disease along with the clinical findings on HER2-positive disease, in what percentage of the breast cancer patient population can use of anthracyclines be eliminated?

SS In my opinion, 100% of breast cancer patients can be treated successfully without anthracyclines, but this issue remains somewhat controversial because the data come from a single trial each in HER2-positive and -negative disease. Approximately 80% of patients have HER2-negative disease and the other 20% have HER2-positive disease, but the notion that anthracyclines should not be given to any patients has not yet been completely adopted. Further trials are being performed in each of these settings with nonanthracycline-containing regimens.

H&O What risk factors exist for cardiotoxicity in this setting?

SS Age over 65 years is an important risk factor that appears to be associated with an increase in cardiac toxicity. The risk associated with older age has been demonstrated by several studies. In the trastuzumab era, two studies showed that age over 65 years was associated with a higher risk of cardiotoxicity. In these studies, hypertension and baseline ejection fraction below normal contributed to a higher incidence of cardiotoxicity.

H&O What remains to be elucidated about cardiotoxicity in the setting of breast cancer?

SS First, researchers should try to clarify whether trastuzumab-associated cardiotoxicity is, in fact, reversible.

Many clinicians are interested to know more about this because cardiotoxicity does seem to be reversible in some patients who had received anthracyclines but not others. If anthracyclines have not been used, is cardiotoxicity truly reversible? Second, many patients experience an asymptomatic drop in ejection fraction—do these patients eventually develop heart failure? Do these patients require treatment with cardiac medications even though they are asymptomatic? Third, is it possible to use an angiotensin-converting enzyme (ACE) inhibitor to prevent heart failure when giving cardiotoxic chemotherapy? One small study did administer an ACE inhibitor in conjunction with chemotherapy and showed that the troponin change, which is associated with heart failure, was less in patients who received the ACE inhibitor. Can the administration of an agent such as an ACE inhibitor prior to or simultaneously with chemotherapy prevent cardiotoxicity?

H&O What studies are ongoing to evaluate cardiotoxicity associated with anticancer therapy in patients with breast cancer?

SS There are two relevant adjuvant trials ongoing in patients with HER2-positive disease, the BETH trial (Treatment of HER2 Positive Breast Cancer With Chemotherapy Plus Trastuzumab vs Chemotherapy Plus Trastuzumab Plus Bevacizumab) and the ALTTO trial (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation). In the BETH trial, patients are carefully monitored from the outset for changes in heart function; the addition of bevacizumab (Avastin, Genentech), which is associated with hypertension, could potentially increase the risk of heart failure. ALTTO is investigating lapatinib (Tykerb, GlaxoSmithKline), which is a small-molecule tyrosine kinase inhibitor of HER2, to assess prospectively whether there is a difference in the decrease in ejection fraction or rate of heart failure between lapatinib and trastuzumab.

H&O How can a clinician help a patient understand her risk of cardiac toxicity in terms of the overall anticancer benefits of therapy?

SS A clinician can present the data from the adjuvant trials that show the benefit trastuzumab confers in this setting, particularly the decrease in mortality. There is a cardiac risk model presented by the National Surgical Adjuvant Breast and Bowel Project (NSABP) at the 2007 annual meeting of the American Society of Clinical Oncology, which takes into consideration age, ejection fraction, and hypertensive medications. This model was based on data from the NSABP B31 trial and can be

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used to quantify the risk of cardiotoxicity. However, this model requires prospective validation. Still, a clinician could use this model to help a patient understand the risk she faces.

Suggested Readings

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