Anthracycline-Induced Cardiotoxicity: Risk Assessment and Management

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In the current issue of ONCOLOGY, Hershman and Shao provide a comprehensive review of anthracycline-induced cardiotoxicity (AIC). Risk factors for AIC include age (≤ 18 or ≥ 65 years) at time of treatment, increasing cumulative dose or dose intensity of anthracyclines, mediastinal radiation therapy (RT), and female gender.[1-4]

This article is a review of: Anthracycline Cardiotoxicity After Breast Cancer Treatment

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Classification of Anthracycline-Induced Toxicity

As described by Hershman and Shao, AIC can be categorized as three distinct types: acute, early, and late. Acute AIC, occurring during the anthracycline infusion or within 1 week of therapy, is rare and reversible. It may present as transient arrhythmia, a pericarditis-myocarditis syndrome, or acute failure of the left ventricle.[6-8] Delayed AIC typically presents as a cardiomyopathy and has been reported in approximately 5% of patients.[9,10] It is classified as early subacute cardiotoxicity occurring < 1 year or late cardiotoxicity occurring > 1 year after the cessation of chemotherapy.[11] Late cardiotoxicity may not be apparent until years to decades after the administration of anthracyclines.[11,12] Patients typically have reduced left-ventricular mass, mass index, and ventricular compliance, with increasing susceptibility to cardiac stressors.[13] The majority of patients who develop early subacute cardiotoxicity will manifest late cardiotoxicity.[11,14] While numerous studies have reported late AIC in patients exposed to the drug during childhood, the incidence in the adult population has been difficult to determine, as follow-up time and cardiac monitoring are inadequate in most clinical trials. Our group reported long-term AIC in 32 of 85 patients treated with sequential dose-dense and dose-intense doxorubicin, paclitaxel, and cyclophosphamide (ATC).[15] At a median follow-up of 7 years, the median absolute change in left-ventricular ejection fraction (LVEF), measured by multigated acquisition (MUGA) from baseline was 5.5%, and from the end of chemotherapy was −2.0%. Four patients (12%) had an LVEF < 50%; two of the four patients had an LVEF < 50% at the end of chemotherapy. We concluded from this study that late asymptomatic decline in cardiac function is uncommon, and does not appear to significantly contribute to the morbidity or mortality of the regimen.

Monitoring of Cardiac Function

As Hershman and Shao note, echocardiogram (ECHO) and MUGA scans are standard methods used to monitor AIC. The authors refer to the limited applicability of MUGA scan for frequent monitoring as a result of cumulative radiation exposure; however, when a precisely reproducible measurement is required for patient management decisions or clinical trial monitoring, MUGA may be the method of choice.[16] Serial MUGA assessments of LVEF vary between 2% and 4%, whereas serial ECHO assessments of LVEF vary between 13% and 17%. Several studies have reported a decrease in LVEF > 10 points from baseline or a fall below the institutional lower limit of normal as indicative of AIC.[17-20]
However, such a drop is a late event and would not be detectable until significant cardiac damage has occurred.[21] Therefore, alternative methods of cardiac monitoring are being evaluated. As described by Hershman and Shao, magnetic resonance imaging (MRI) is an alternative method used for assessment of myocardial function, perfusion, and tissue characterization. However, long-term data to support its use in this setting are lacking, especially with the limited availability of this technology.[22] Another modality under investigation is tissue doppler imaging (TDI), which allows the measurement of diastolic and systolic velocities of the ventricular walls and mitral annulus, and appears to be more reliable and less affected by loading conditions than conventional Doppler.[23] In a study by Tassan-Mangina et al, TDI confirmed the occurrence of early diastolic and late systolic impairment of left-ventricular function following moderate-dose anthracycline therapy.[23]

Hershman and Shao refer to troponin T and B-type natriuretic peptide (BNP) as potential biomarkers for earlier detection of cardiotoxicity. BNP levels were monitored for a small number of patients with acute leukemia treated with a daunorubicin-containing regimen; those who had abnormal BNP levels during subsequent stem-cell transplant developed heart failure, whereas those who had normal BNP levels did not.[24] Troponin levels were measured in 211 patients with breast cancer receiving high-dose therapy; abnormal levels predicted the development of future LVEF depression in a 12-month follow-up.[25]

Cardiac Risk Assessment and Management Recommendations

Although anthracyclines have served as the mainstay of effective cytotoxic therapy for breast cancer during the past 30 years, AIC remains a concern. Therefore, better methods for prevention, monitoring, and management of AIC are needed. When making treatment recommendations for breast cancer patients—especially those with early-stage disease—the presence of cardiac risk factors and strong cardiac family history need to be considered. Treatable cardiac risk factors such as hypertension, hyperlipidemia, and diabetes should be closely monitored and managed in an attempt to prevent additional cardiac injury.

In addition, long-term follow-up is needed to identify patients with subclinical late cardiac dysfunction, who may be at a higher risk for subsequent cardiac events. Patients with preexisting cardiac disease and poorly controlled risk factors may consider treatment with alternative non-anthracycline regimens with reported lower risk of cardiotoxicity.

As mentioned by Hershman and Shao, non-anthracycline-containing regimens have been evaluated for treatment of patients with early-stage breast cancer.[26,27] These non-anthracycline regimens appear to be comparable in efficacy and less cardiotoxic than the anthracycline regimens. While relatively short follow-up has been reported for these regimens, at very least they provide an alternative for breast cancer patients with a history of cardiac disease or cardiac risk factors. These nonanthracyline regimens should be discussed with patients as an alternative treatment, with acknowledgment of the relatively short duration of follow-up.

Finally, the potential for delayed cardiotoxicity should continue to be evaluated in adjuvant and neoadjuvant clinical trials, particularly in light of the recent advances with dose-dense therapy as well as with adjuvant trastuzumab (Herceptin).

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