Editorial

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Detection of anthracycline-induced cardiotoxicity: is there light at the end of the tunnel?

Cardiac contractile dysfunction is the most serious cardiotoxic effect of anthracycline therapy and a major limitation for the use of this effective antineoplastic treatment. The reported incidence of doxorubicin-induced cardiac dysfunction varies from 4%, at a cumulative dose of 500–550 mg/m^2, to >36% in patients receiving 600 mg/m^2 or more [1]. Interestingly, there is a non-linear correlation between the incidence of contractile dysfunction and the cumulative dose of anthracyclines, and toxicity varies significantly among different anthracyclines.

The prognosis of anthracycline-induced cardiotoxicity is poor, and possibly even worse than those of ischemic or idiopathic dilated cardiomyopathies [2]. In untreated patients, mortality from anthracycline-induced cardiomyopathy is as high as 40% over 5 years. However, recent data suggest that medical therapy may improve the prognosis of patients dramatically. Furthermore, the onset of anthracycline-induced heart failure can occur years after the treatment and recent data from pivotal trials with an antibody against the tyrosine kinase receptor HER2 (trastuzumab) suggest that anthracycline-induced cardiotoxicity can be latent for years. Not only patients treated concomitantly with anthracyclines and trastuzumab, but also patients with prior anthracycline treatment, were at a higher risk of trastuzumab-associated cardiac dysfunction and heart failure [3]. These observations suggest a 'cardiac memory' for prior anthracycline treatment and early detection of chemotherapy-induced cardiac damage, even if subclinical, is warranted.

Patients treated with anthracyclines or trastuzumab therefore need careful cardiac monitoring. This monitoring should ideally be highly sensitive and specific, non-invasive, and available at reasonable cost. Clinical monitoring of patients based on symptoms and findings of heart failure is not sufficient since time of cardiac contractile dysfunction relative to anthracycline exposure is highly variable and treatable cardiac dysfunction frequently precedes the onset of symptoms. So, what is the best method of monitoring patients for anthracycline-induced cardiac dysfunction?

Right ventricular myocardial biopsy, resting and exercise echocardiography, and radionuclide ventriculography have been used to detect early signs of anthracycline-induced cardiotoxicity. Most of these methods, however, have not been prospectively evaluated. In this issue of *Annals of Oncology*, Jensen et al. [4] report a prospective examination of the left ventricular function in breast cancer patients treated with epirubicin. They found that cardiotoxicity was closely correlated with the cumulative dose of epirubicin. However, there was a great variability of cardiotoxicity among patients and a dramatic increase in susceptibility in older patients. Using radionuclide ventriculography they detected a progressive decrease in cardiac contractile function starting 3 months after initiation of chemotherapy and 20% of their patients treated with high-dose epirubicin developed severe dilated cardiomyopathy within 5 years. The authors conclude that assessment of left ventricular function during or immediately after chemotherapy is unlikely to predict anthracycline-induced cardiotoxicity and that serial assessment of left ventricular function months to years after anthracycline administration is needed to detect cardiotoxicity.

The results of Jensen et al. [4] are not surprising since it is known that cardiac dysfunction, irrespective of its etiology, is a progressive disease. In the past decade, it became clear that this progression is largely mediated by the activation of neurohormones such as the renin–angiotensin–aldosterone or the β-adrenergic systems. Therefore, it also comes as no surprise that treatment with drugs such as ACE-inhibitors or β-receptor blockers, which inhibit or attenuate the activation of neurohormones, is beneficial in patients with anthracycline-induced cardiotoxicity. However, the detection of, the frequently asymptomatic, contractile dysfunction is a prerequisite to prevent the deleterious natural course of anthracycline-induced cardiotoxicity.

Serial assessment of cardiac function with radionuclide ventriculography after anthracycline therapy is elaborate, expensive and not widely available. Furthermore, radionuclide ventriculography only detects systolic dysfunction and by that time myocardial damage might have already significantly progressed. It would therefore be advantageous to have markers of early anthracycline-induced myocardial damage. Again in this issue of the *Annals of Oncology*, Cardinale et al [5] report their findings on the use of troponin I for the detection of chemotherapy-induced cardiotoxicity. These investigators measured plasma troponin I concentration during and shortly after administration of chemotherapy and assessed left ventricular contractile function by serial echocardiographic measurement 1–12 months after the end of treatment. Approximately 50% of their patients were treated with a chemotherapeutic regimen containing anthracyclines whereas the rest of the patients had been treated previously with anthracyclines. Cardinale et al. [5] found a rise in circulating troponin I in 33% of their patients, almost 80% of whom were treated with

epirubicin (200 mg/m^2). Furthermore, the investigators detected a close correlation between maximally elevated plasma levels of troponin I and the decrease of echocardiographically determined left ventricular ejection fraction.

The troponins, a protein located in the contractile apparatus of myocytes, have been extensively studied over the past decade and are sensitive and specific markers for myocardial injury. In patients with acute coronary syndromes the plasma levels of troponin correlate well with short-term, as well as long-term, mortality. However, troponins are only released into the plasma when myocardial myocytes undergo necrosis. Therefore, a rise in troponin during and shortly after chemotherapy reflects the acute cardiotoxicity of chemotherapeutic treatment. Whether this rise in troponin levels is correlated with chronic anthracycline-induced cardiotoxicity, which typically becomes manifest months to years after chemotherapy, remains to be seen. Pathophysiological mechanisms other than cell necrosis, such as oxidative stress induced changes in contractile protein turnover and mitochondrial function, leading to myofibrillar disarray and apoptosis might play a major role in chronic anthracycline-induced cardiotoxicity. These changes are not likely to be detectable by the release of tropinin I. Furthermore, the negative predictive value of troponin for anthracycline-induced chronic cardiotoxicity has not yet been determined.

In the search for other markers of chemotherapy-induced cardiac toxicity it is important to understand the pathophysiology of anthracycline-induced cardiotoxicity. Anthracycline-induced heart failure is a progressive clinical syndrome characterized by abnormalities of left ventricular function and neurohormonal activation, which are frequently accompanied by fluid retention. The most commonly recognized form of anthracycline-induced heart failure is systolic dysfunction caused by contractile failure of the myocardium leading to reduced left ventricular ejection fraction. The ejection fraction is the proportion of blood that is expelled from the ventricle with each heart beat, with a normal ejection fraction being ≥50%. If the ejection fraction falls below 50%, the left ventricular pressure at the end of diastole rises, leading to elevated pressures in the pulmonary vessels and causing pulmonary congestion. A similar elevation of the left ventricular end diastolic pressure is the consequence of diastolic dysfunction, which in anthracycline-induced cardiac dysfunction possibly precedes systolic dysfunction [6]. Diastolic dysfunction is characterized by normal systolic function but impaired relaxation properties of the ventricle, leading again to an elevated end diastolic pressure and pulmonary congestion. Therefore, measuring the end diastolic pressure would be a reliable marker for the early detection of anthracycline-induced cardiac dysfunction but presently the only reliable method for the assessment of this pressure is cardiac catheterization.

A new tool for the diagnosis and assessment of heart failure is the 32-amino acid polypeptide B-type natriuretic peptide (BNP). The synthesis of BNP occurs in the ventricles of the heart and the serum level correlates with the severity of heart failure and with left (as well as right) ventricular pressures. Elevated BNP is found both in patients with diastolic dysfunction and those with systolic dysfunction, and the plasma level correlates with left ventricular end diastolic pressure [7]. Since the negative predictive value of BNP is as high as 98%, low BNP plasma levels make ventricular dysfunction highly unlikely and BNP might therefore be the long awaited tool to screen for anthracycline-induced cardiotoxicity. Since diastolic dysfunction in anthracycline-induced cardiotoxicity likely precedes systolic dysfunction, elevated BNP levels might also be a more sensitive marker for monitoring cardiac function after chemotherapy than any other currently used screening tools. So far, two small studies have evaluated the usefulness of BNP as a predictor of anthracycline-induced cardiotoxicity [8, 9]. Both have shown promising results and the findings suggest that BNP might not only be able to detect overt anthracycline-induced cardiotoxicity but also subclinical left ventricular diastolic dysfunction [9]. These preliminary results need to be confirmed in large-scale prospective trials, some of which are about to start. It would be a great relief for oncologists as well as cardiologists if BNP would be the light at the end of the tunnel in the detection of anthracycline-induced cardiotoxicity.

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