First, Do no Harm

Filipa Lynce Sandra M. Swain

Washington Cancer Institute, Washington Hospital Center, Washington, D.C., USA

The progress made over the last years has turned cancer into a potentially curable, or at least, chronic disease [1]. Thus, our concern moves towards toxicity. While some years ago cardiotoxicity was an issue mainly in children with leukemia treated with anthracyclines, today it has become a significant problem for many others. Moreover, a prolonged survival allows more time for the use of different potentially cardiotoxic agents as well as radiotherapy.

The agents most commonly associated with cardiac toxicity are anthracyclines and trastuzumab. Anthracycline-induced cardiotoxicity is progressive and dose-dependent. It can range from asymptomatic cardiac dysfunction to overt congestive heart failure (CHF). Asymptomatic systolic dysfunction, evaluated by decrease of left ventricular ejection fraction (LVEF), was 6% higher in patients treated with adjuvant doxorubicin compared to CMF [2]. A retrospective analysis showed that 5–48% of patients who had received anthracyclines presented with symptomatic CHF, depending on the cumulative dose [3]. Trastuzumab-associated cardiotoxicity has a different mechanism and has been classified as type II chemotherapy-related cardiac dysfunction [4]. It is not dose-related and is mostly reversible. However, the short period of follow up in trastuzumab adjuvant trials offers us a limited picture of the potential risks [5]. Furthermore, direct comparison of toxicity between trials is difficult due to different definitions of cardiac endpoints, eligibility criteria and treatments regimens.

Since we do not routinely screen asymptomatic people in the general population for subclinical cardiac disease why, many may think, worry about cancer survivors? Cardiac dysfunction is a progressive condition that can lead to CHF. The 5-year survival of women with CHF (38%) is higher than that of women with metastatic breast cancer (26.1%), but much lower than of women with regional (81.3%) or localized breast cancer (98%) [6, 7]. It is important to balance the risk/benefit ratio. Recent data seem to confirm our concerns. In an obser-

vatational study, Pinder et al. report a 26% increased risk of CHF in older women treated with adjuvant anthracyclines for breast cancer, compared with non-anthracycline regimens [8]. Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin. The troponin complex consists of 3 subunits: troponin C (TnC), troponin I (TnI) and troponin T (TnT), each performing specific functions. TnC is a calcium-binding protein. TnI binds to actin and inhibits actin-myosin interactions. TnT provides proper fixation of TnC and TnI on the actin-tropomyosin filament. Although both TnT and TnI are present in cardiac and skeletal muscle, their amino acid sequences encode tissue-specific isoforms detected by monoclonal antibody-based assays. TnC is not used clinically because both cardiac and skeletal muscles share the same isoforms [9]. The notion that troponin is increased only after irreversible myocardial necrosis has already been challenged [10]. Cardiac troponin elevation is common in many diseases and does not necessarily indicate the presence of a thrombotic acute coronary syndrome.

In this issue of ONKOLOGIE, Horacek et al. [11] report a study of the cardiac function of 23 patients with acute leukemia treated with anthracycline-containing chemotherapy. Patients had cardiac function evaluated during chemotherapy and 6 months after treatment with conventional imaging (echocardiography with systolic and diastolic left ventricular parameters) and cardiac troponin I (cTnI) and T (cTnT) measurements. The authors report that monitoring cTnI during anthracycline treatment, but not cTnT, identifies patients at risk of developing drug-related cardiotoxicity. Previous studies have shown the benefit of cTnI [12] and cTnT [13] in the early identification of patients at risk of cardiac events. In a study with more than 700 patients treated with different antineoplastic agents, it was demonstrated that cTnI elevation predicted late cardiac dysfunction and major adverse cardiac events in the subsequent 3 years [14]. Both cTnI and cTnT have been con-

sidered to have comparable diagnostic utilities [15]. However, a direct comparison between cTnI and cTnT results was not done in the studies previously mentioned. It is intriguing in the present report that there is no relationship between the elevation of cardiac troponins or LV dysfunction and the cumulative dose of anthracyclines. This contradicts previously published data showing that the risk of anthracycline cardiotoxicity is associated with increasing dose [3].

Currently, the most common noninvasive method of monitoring myocardial toxicity is the evaluation of systolic function parameters (LVEF and fractional shortening, FS), either by echocardiography or radionuclide angiography. Several studies suggest that diastolic dysfunction is an early sign of anthracycline-induced cardiac dysfunction, evaluated by E/A inversion and E-wave deceleration [16]. Dobutamine stress echocardiography also seems to be a sensitive indicator of cardiac dysfunction [17].

On the other hand there are studies that have shown that high levels of another biomarker, probrain natriuretic peptide (pro-

BNP), correlates with impairment of LV function while using anthracycline [18] and trastuzumab-containing treatments [19].

With a sensitive and specific biomarker that predicts future cardiac disease, we can identify which patients need closer follow up and strategies to prevent further cardiac damage. Even though effective prophylaxis has always been a challenge, some interventions have been suggested such as blocking the renin-angiotensin system with either angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) [20,21]. Also, dexrazoxane for metastatic breast cancer patients who have received a cumulative dose of ≥ 300 mg/m² of doxorubicin has been shown to be effective [22].

In the future, trials should focus on identifying reliable markers with long-term prognostic significance that can help us to decide how to better treat patients without affording them significant toxicity. Back to Hippocrates, 'first, do no harm'. [23].

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