volume in patients receiving aromatase inhibitors is due to the discontinuation of tamoxifen treatment and not a direct effect of aromatase inhibitors. As we mentioned in our article [1], future clinical trials looking at the endometrial safety of endocrine treatments, particularly those trials involving sequential treatments with selective estrogen receptor modulators and aromatase inhibitors, should also take into account the potential effect on the uterus of a wash-out period after tamoxifen treatment. Only then can we determine whether tamoxifen-induced changes would eventually resolve over time or whether aromatase inhibitors can offer a protective effect on the endometrium of patients treated with tamoxifen. While there are data on how endometrial thickness decreases over time following discontinuation of tamoxifen treatment [2], a direct comparison with the decrease achieved in patients receiving aromatase inhibitors is not available. Likewise, whether a difference in uterine effects between steroidal and non-steroidal aromatase inhibitors exists or whether there is a difference between the three agents is not known. Furthermore, the potential of aromatase inhibitors to reverse tamoxifen-induced uterine changes should be confirmed through randomized clinical trials. Recently, the Intergroup Exemestane Study presented data similar to ours, showing the decrease in endometrial thickness and uterine volume in women receiving exemestane compared with tamoxifen [3].

The second issue raised by Cohen is whether the polyps visualized by transvaginal sonography in the present study were real endometrial polyps and not subendometrial fibroids. In our institution, color Doppler imaging is routinely performed to confirm the presence of a polyp. In a prospective observational study on 3099 consecutive patients referred for the assessment of the endometrium and myometrium, 182 polyps were detected and 139 of them had a clear feeding vessel. A distinct vascular pedicle from the myometrium reaching at least the middle of the endometrium (called the ‘pedicle artery sign’) was related to the presence of a polyp in 81% of the patients, or to any focal lesion in 94.2% of cases [4]. We also reported that this sign was observed in 32 of 687 patients without an endometrial polyp. However, 22 of the 32 patients with false-positive results had other intracavitary pathology: submucous fibroids (7%), hyperplasia (2.9%), endometrial cancer (1.8%) and persistent trophoblastic tissue (1.2%). Only in 5.8% of the patients with a positive test was the cavity normal. These findings were very similar for 310 tamoxifen-treated patients, where the ‘pedicle artery test’ had a sensitivity for detecting polyps of 89%, specificity of 86%, positive predictive value of 85% and negative predictive value of 89%. Overall accuracy was 87% [5]. In addition to the presence of a feeding vessel, the characteristic appearance of a Swiss-cheese pattern and the ‘bright edge of the polyp’ were all considered to confirm the presence of a polyp versus a uterine fibroid. Therefore, we might safely assume that the vast majority of the presumed polyps in the present study were real polyps, and that only a small proportion may have been fibroids rather than polyps.

References


doi:10.1093/annonc/mdi237
Published online 3 May 2005

Is cardiac troponin T serum level an accurate surrogate for acute doxorubicin-related myocardial injury?

Since anthracyclines are still among the most frequently used antineoplastic drugs, early detection and/or prediction of anthracycline-induced cardiotoxicity is urgently needed. Serum levels of cardiac troponin T (cTnT) are increasingly becoming recognized as potential biochemical markers of even subclinical myocardial injury. In a recent paper, Lipshultz et al. [1] affirmed that ‘the serum level of cardiac troponin T is an accurate surrogate for acute myocardial injury in children, specifically that related to doxorubicin’. The same authors previously showed that low-level elevations of cardiac troponin T induced by doxorubicin were associated with histological evidence of myocardial injury [2], and that dexrazoxane-treated rats had less frequent elevations in cardiac troponin T and less severe cardiac injury on histological analysis and were in better health than rats that did not receive dexrazoxane [3].
Despite these findings, there is still little information about the exact mechanisms responsible for the cTnT release, especially with regard to the gradual development of myocardial injury, and the role of cTnT in diagnosis and monitoring of cardiac damage remains controversial. Moreover, the lack of evaluation of diastolic heart function represents a negative point of design of the study by Lipshultz and colleagues. Therefore the question immediately arises as to whether the diastolic heart function may have a non-negligible power for prediction of chronic/late cardiotoxicity of anthracyclines. As a consequence, the identification of a reliable serum indicator of early diastolic dysfunction in cardiomyocytes after doxorubicin treatment could be advisable.

Doxorubicin cardiomyopathy is typically associated with myofibrillar deterioration and intracellular calcium overload, which may trigger indiscriminate activation of calcium-dependent proteases resulting in degradation of key myofibrillar proteins. In animal models, oxidative damage to the sarcoplasmic reticulum (SR) and activation of the sarcosomal L-type calcium channels or the SR ryanodine receptors would result in calcium accumulation in the cytosol, which alone may be sufficient for activation of calpains. In adult rat ventricular myocytes, calpain-mediated proteolysis of the elastic domain of titin, whose extensible segment underlies the passive and restoring forces of the cardiomyocyte and helps to maximize myocardial efficiency, can predictably lead to impaired diastolic or systolic function, both of which can occur acutely after doxorubicin treatment [4].

Because dexrazoxane reduces free-radical injury, the findings by Lipshultz et al. [1] suggest that doxorubicin-associated myocardial injury may be related, at least in part, to oxidative damage. The attenuating effect of dexrazoxane on doxorubicin-induced cardiotoxicity may be attributable to intracellular conversion of its active form (ADR-925), which binds free iron or removes it from the doxorubicin–iron complex, thus preventing the formation of oxygen radicals. However, chronic cardiomyopathy develops after summation and mutual feedback of multifactorial processes. Whether, and how, these processes contribute to inducing cardiotoxicity in patients is controversial, and it is not clear how precisely iron and reactive species of the oxygen intervene in these multiple settings [5].

Thus, the exclusive use of cTnT as an indicator of subclinical doxorubicin-related myocardial injury in children with cancer cannot completely reflect the acute contractile dysfunction caused by doxorubicin. On the contrary, since the stretch-sensitization response is essential to the regulation of heart contractility, calpain-mediated proteolysis of the elastic domain of titin may have acute physiological consequences, predisposing cardiomyocytes to diastolic dysfunction, myofila ment instability and necrosis [4]. Unfortunately, this finding has been demonstrated only in a rat myocyte model. Reliable serum markers capable of early detection of the disassembly of the myofilament complex during the normal sarcomere turnover are urgently needed, and may offer a novel diagnostic tool for the acute contractile dysfunction associated with doxorubicin-induced myocardial calcium overload and oxidative stress.

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References


doi:10.1093/annonc/mdi203
Published online 27 April 2005