Cardiotoxicity after Adjuvant Anthracycline-based Chemotherapy and Radiotherapy for Breast Cancer

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ABSTRACT
There is growing evidence that anthracycline-related cardiotoxicity may occur at a greater frequency and a lower cumulative dose than previously reported. With the increasing use of anthracycline-based adjuvant chemotherapy to treat breast cancers, more clinical research is needed to evaluate the long-term cardiac risk. The addition of postoperative radiotherapy also raises concern about late cardiac risk in patients with left-side breast cancers. This article reviews the current information on the cardiac risk after adjuvant anthracycline-based chemotherapy and radiotherapy.

Key Words: Anthracyclines; Antineoplastic agents/adverse effects; Breast neoplasms; Chemotherapy, adjuvant; Radiotherapy, adjuvant

INTRODUCTION
Anthracycline-based adjuvant chemotherapy is a very popular method of breast cancer management, partly because of its efficacy and partly because of its convenience in administration compared with conventional therapy with cyclophosphamide, methotrexate, and 5-fluorouracil. Although anthracycline is well known to have cardiotoxicity, the cardiac risk is generally considered to be low, because the maximum cumulative doses in anthracycline-based regimens are well below the often-quoted tolerance limit. The cardiac effects of other chemotherapeutic agents, such as 5-fluorouracil and cyclophosphamide, are also minimal at conventional doses. However, in contrast to patients with metastatic breast cancer, many patients with non-metastatic disease would be long-term survivors and subclinical cardiac damage may not manifest until many years afterwards. The use of adjuvant radiotherapy in patients with left-side breast cancers may further increase the cardiac risk.

To review anthracycline-induced cardiotoxicity and to provide an update on the magnitude on the undesirable treatment-related cardiac effects, related articles published in the past 25 years were assessed and summarised.

ANTHRACYCLINE-INDUCED CARDIOTOXICITY

Congestive Heart Failure
Doxorubicin is by far the most studied anthracycline regarding cardiotoxicity. Although acute reversible arrhythmias, subacute toxic myocarditis, and pericarditis have been reported, these complications are rare. The most thoroughly evaluated cardiotoxicity of doxorubicin is cumulative, progressive myocardial damage that leads to clinical events, which range from a slight reduction in left ventricular ejection fraction (LVEF) to irreversible life-threatening congestive heart failure (CHF). Two distinct types of myocyte damage have been reported by researchers who have used endomyocardial biopsy — namely, myofibrillar loss and vacuolar degeneration. The exact mechanism of myocyte damage is unclear but may be related to free-radical formation and local defence reactions to antioxidants.

In the late 1970s, a retrospective analysis by Von Hoff et al identified the total cumulative dose as a major risk factor for doxorubicin-related CHF. The estimated cumulative percentage of patients who developed CHF at a cumulative dose of 400 mg/m² was 3%, increasing to 7% at 550 mg/m² and to 18% at 700 mg/m². Older
age and the use of a schedule of once every 3 weeks (versus every week) were also reported to increase the risk. On the basis of this study, a maximum cumulative tolerance dose of 450 to 500 mg/m² is often recommended. However, the degree of cardiotoxicity may be higher if different definitions or more sensitive detection methods are used, or if the patients are followed up for a longer period. A recent retrospective analysis of 3 clinical trials found that doxorubicin-related CHF actually occurs with a greater frequency and at a lower cumulative dose than previously reported. The reported risk of CHF was 5% at 400 mg/m², 16% at 500 mg/m², and 26% at 550 mg/m². Although widely regarded as the standard assessment, measuring the LVEF by multiple-gated acquisition nuclear scanning was also found to be insensitive in predicting CHF. Of 32 patients who experienced CHF, 21 had a reduction of less than 30% in LVEF values compared with baseline values (the cut-off level for increased risk of CHF). Nevertheless, similar LVEF changes occurred in many other patients who did not develop CHF.

Subclinical Cardiotoxicity

Because the maximum cumulative dose in most doxorubicin-based adjuvant chemotherapy regimens ranges from only 240 to 300 mg/m², patients with breast cancer may seem unaffected. But subclinical cardiotoxicity may still occur at these levels. With a reduction in left ventricular fractional shortening (as detected by echocardiography) as a criterion, subclinical late cardiomyopathy was reported to occur in 39 of 141 patients with lymphoma after a median cumulative dose of 300 mg/m² doxorubicin. The authors also reported male sex, older age, higher cumulative dose (>300 mg/m²), radiotherapy (mediastinal irradiation or total-body irradiation), and overweight as contributing factors. Although this study was based on patients with lymphoma, patients with breast cancer are likely to experience similar subclinical cardiotoxicity after similar doxorubicin doses in adjuvant chemotherapy. So far, however, the long-term clinical impact of these forms of subclinical cardiotoxicity is unclear.

Cardiac assessment for doxorubicin-induced cardiotoxicity has focused on left ventricular systolic dysfunction using multiple-gated acquisition or fractional shortening. But because diastolic dysfunction has been well documented to precede systolic dysfunction in many heart diseases, including ischaemic heart disease and hypertrophic cardiomyopathy, it may be a more sensitive index of cardiotoxicity after doxorubicin-based chemotherapy. In fact, with the use of radionuclide angiography, indices of early diastolic function have been reported to be predictive of the early detection of anthracycline-related cardiotoxicity. These nuclear medicine examinations are, unfortunately, more complicated than others and are thus not commonly used in clinical practice or research.

**MINIMISING CARDIOTOXICITY**

With their excellent clinical efficacy and convenience of administration, anthracyclines are likely to remain in adjuvant chemotherapy regimens for breast cancer until a better alternative is developed. What measures can be taken to minimise the cardiac risk?

Because cardiotoxicity is likely associated with peak plasma drug concentration, giving the drug in weekly low doses or prolonging the infusion time may reduce peak levels. However, the requirement for indwelling catheters and the inconvenience to both patients and medical staff would render this approach unpopular. Liposomal doxorubicin has been shown to have less cardiotoxicity, and dexrazoxane (a cardioprotectant) has been shown to decrease cardiotoxicity when given with doxorubicin. Both liposomal doxorubicin and dexrazoxane, however, are now used only to treat metastatic diseases and have an unclear role as adjuvant therapy. Epirubicin, a more expensive doxorubicin analogue, has been reported to have lower cardiotoxicity than doxorubicin; hence, a cumulative tolerable dose of 900 to 1000 mg/m² has been suggested. Using epirubicin to replace doxorubicin should help to minimise the cardiac risk. Still, because of the superior clinical outcome of high-dose regimens demonstrated in recent studies, the current trend is to give a higher epirubicin dose of up to 100 mg/m². Hence, the overall cardiac risk may be similar. A recently reported study of 85 patients after 6 cycles of 5-fluorouracil 500 mg/m², epirubicin 100 mg/m², and cyclophosphamide 500 mg/m² found 2 cases of CHF and 18 cases of asymptomatic left ventricular dysfunction after more than 8 years of follow-up. Although the 18 patients with asymptomatic left ventricular dysfunction were still asymptomatic after 2 additional years of follow-up, the subsequent clinical impact is not yet clear.

In view of the lack of a reliable clinical tool to predict the cardiac risk and the uncertainty about the long-term clinical impact of subclinical cardiotoxicity, there is so far no need to change clinical practice. More studies are needed to address the long-term cardiac impact and
CHEST WALL RADIOTHERAPY

Given the popularity of breast conservation treatment and the established survival benefit of adjuvant radiotherapy in node-positive patients who have undergone mastectomy, an increasing proportion of patients with early-stage breast cancer are receiving postoperative radiotherapy as well. For left-side chest-wall radiotherapy using conventional techniques, a thin slice of cardiac tissue is irradiated. Long-term results from updated overviews of randomised trials and single, hospital-based reviews have shown a risk of fatal myocardial infarction 10 to 15 years after radiotherapy for cancer of the left breast. Although adjuvant radiotherapy leads to an improved cause-specific survival, the benefit is offset by an increase in ischaemic cardiac mortality.

It should be noted that many patients included in these overviews were treated with orthovoltage (200-300 kV) or cobalt-60 machines before 1975. Moreover, anterior field irradiation to cover the internal mammary chain was also added in some studies, and this would substantially increase the cardiac dose. With smaller fractional doses, careful simulation of radiation ports, better machines, and improved planning, the safety of radiotherapy today is generally believed to have increased.

Owing to the increasing use of computed tomography–based treatment planning and multileaf collimators, cardiac shielding can be added in the tangential fields without significant impairment of the target coverage (Figure 1). The use of the much more complicated and labour-intensive method of intensity-modulated radiotherapy (IMRT) requires further evaluation and study. The evidence for the value of IMRT for breast cancer is mostly limited to descriptive studies, evaluations of technical feasibility, and dosimetric planning studies. There are so far no clinical outcome studies to support its superiority. Moreover, the movements in the thorax from respiration and the beating heart also pose special challenges to the application of IMRT in breast cancer.

Because most of the local cases of recurrence after breast-conserving surgery occur around the tumour bed, partial-breast irradiation is being evaluated to replace whole-breast irradiation. Not only may this development further minimise the cardiac risk, but it may also shorten and increase the convenience of the treatment schedule. Partial-breast irradiation can be performed with intraoperative electron therapy, brachytherapy in either interstitial form or by way of an intracavitary balloon catheter, or 3-dimensional conformal external radiotherapy. The results of ongoing randomised studies (e.g., the National Surgical Adjuvant Breast and Bowel Project B-39) comparing

Figure 1. Beam’s eye view of the tangential fields used for breast cancer at the Pamela Youde Nethersole Eastern Hospital; the method uses computed tomography–based planning, customised cardiac shielding, and multileaf collimators.
partial-breast irradiation with standard whole-breast irradiation would have a great impact on the future standard of radiotherapy.

CONCLUSION
The risk of life-threatening CHF following current anthracycline-based adjuvant chemotherapy for breast cancer is low, but the long-term clinical effect of its more commonly encountered subclinical cardiotoxicity is not yet clear. More clinical studies are needed to define the risk factors and evaluate the true long-term impact. The risk of fatal coronary events after modern radiotherapy should be very low, especially when special techniques for cardiac shielding are used. Development of partial-breast irradiation may further minimise the cardiac risk.

REFERENCES