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Point of View

Mixing Anthracyclines and Radiotherapy in Early Breast Cancer: How Safe is it?

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ANTHRACYCLINE-CONTAINING schedules are challenging classical CMF (cyclophosphamide, methotrexate, 5-fluorouracil) for the treatment of women with early breast cancer, especially in young or high risk individuals. Is this the result of careful testing or just good marketing? The question is important because anthracyclines and radiotherapy are a potentially dangerous mix.

Everyone agrees that anthracyclines are effective in women with early breast cancer [1], but their superiority to classical CMF is neither certain nor quantified. Some randomised trials report statistically significant survival advantages for anthracycline-containing regimens compared with CMF, but in each case other confounding factors may have contributed to the benefits [2–4]. Other randomised trials report no survival advantages for anthracycline regimens [2, 5, 6]. Until lingering doubts are removed, uncertain benefits need to be weighed against the real dangers of prescribing anthracyclines and radiotherapy, especially for women with left-sided cancers.

Whereas there is no doubt regarding the efficacy of adjuvant radiotherapy in reducing local recurrence, its long-term effect in terms of overall survival remain controversial, with no significant benefit demonstrated so far [7–11]. Postmastectomy radiotherapy is associated with a reduced risk of breast cancer deaths (a few less deaths per 100 women irradiated), but is undermined by fatal radiation-induced heart disease (relative risk of 1.6 in trials started before 1975, representing 1–2 excess cardiac deaths per 100 women irradiated) [7, 12]. The latency period for ischaemic heart disease is 5 years and the risk is greatly influenced by technique and the volume of heart irradiated [13]. Radiotherapy practices have improved over the years. Direct photon fields to the chest wall or mediastinum, which point directly at the heart, are no longer used unless there is a special indication to treat the internal mammary chain. Tangential fields to the breast or chest wall are much safer, and accurate field localisation ensures the minimum exposure of cardiac tissue [14]. Even so, tangential megavoltage beams to the left chest wall/breast omitting the internal mammary chain still include portions of the anterior left ventricular wall and left anterior descending coronary artery [15, 16]. We cannot expect the problem of radiotherapy-induced heart disease to have disappeared altogether.

Whereas the pathology of radiation damage to the heart chiefly reflects damage to the vasa vasorum of the coronary arteries leading to atherosclerosis [17], the commonest cardiac problem associated with anthracyclines is dose-related cardiomyopathy leading to congestive cardiac failure. The pathological features include profound degeneration of muscle cells, vacuolisation of myocytes with dilated mitochondria, interstitial oedema and fibrosis [18, 19]. These features of cardiac injury are not commonly seen below total cumulative doses of 450–550 mg/m^2 of doxorubicin and 900 mg/m^2 of epirubicin [20, 21]. In the conventional anthracycline regimens used in the adjuvant treatment of women with breast cancer, there is a $\leqslant$2–36% lethality [19, 22–25]. A higher proportion will have asymptomatic cardiomyopathy [26]. Long-term cardiac follow-up data of adult patients with doxorubicin-induced asymptomatic cardiomyopathy are scarce. One report by Dresdale and coworkers suggests [27] that long-term deterioration in cardiac function may occur in patients over 40 years. Asymptomatic, all-cause, dilated cardiomyopathy in adults carries a 50% mortality at 7 years [28]. Symptomatic, all-cause, dilated cardiomyopathy patients have a 50% 2-year mortality [29].

It is reasonable to expect the risks of cardiac toxicity from radiotherapy and anthracyclines in combination to be additive, and although animal studies are consistent with this model, clinical data are scarce. Valagussa and coworkers [30] reported on 825 women with operable breast cancer treated in randomised trials of adjuvant chemotherapy with or without doxorubicin and followed for a median of 80 months. All patients received chemotherapy with CMF with 501 of 825 (61%) patients also receiving four cycles of doxorubicin (75 mg/m^2) at 3-weekly intervals before, after or alternating with CMF. The mean total dose of doxorubicin received was 285 mg/m^2 (range 72–312). Postoperative

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radiotherapy using cobalt^{60} or 6 MV photons was given to 360 of 825 (44%) women to a dose of 50 Gy in 25 fractions over 5 weeks by tangential fields to the chest wall or breast. Patients treated by breast conserving surgery had a boost to the affected quadrant of 10 Gy in five fractions using a direct field. The dose received by the internal mammary chain from the tangential fields was estimated to be 25–30 Gy. The radiotherapy commenced 4–6 weeks after surgery and was concomitant with chemotherapy. Cardiac assessment was based on clinical examination and annual electrocardiograms, with echocardiography and radionucleide ventriculography according to specific indications.

Cardiac abnormalities of some kind were recorded in 88 of 825 (10.7%) patients at a median of 8 months (range 0–128) from the end of treatment, including 2 fatalities. CMF on its own, or combined with irradiation, was not associated with cardiotoxicity, in keeping with the data of Coombes and Bonadonna and their coworkers [3, 4]. The only data relating to the added toxicity of combining radiotherapy and doxorubicin relate to congestive cardiac failure (4 patients), disturbances of rate and rhythm and/or conduction (16 patients) and ventricular repolarisation problems (28 patients). Congestive cardiac failure developed in 3 of 114 (2.6%) women receiving doxorubicin plus radiotherapy compared with 1 of 387 (0.26%) women receiving doxorubicin without radiotherapy, and none in irradiated patients without doxorubicin. 2 of 4 women with congestive cardiac failure died. The rates for disturbance of rate and rhythm and/or conduction were 4.4% for doxorubicin and left breast irradiation, 2.1% for doxorubicin without left breast irradiation and 1.4% for left breast irradiation without doxorubicin. 5 of 16 patients needed supportive treatment. With regard to ventricular repolarisation problems, there was a 4.2% incidence for left breast irradiation without doxorubicin, and a 13.2% incidence for left breast radiotherapy with doxorubicin. The doxorubicin group in total (with or without left breast irradiation) had a 3.8% incidence of ventricular repolarisation problems. 7 of 28 patients needed supportive treatment. Cytotoxics did not increase the risks of radiation-induced ischaemic heart disease; these were 5.4% for left breast radiotherapy and 0.6% for the right breast regardless of concurrent chemotherapy. 9 of 16 patients needed treatment. The small number of events limits interpretation, but are consistent with additive toxicity (except in the case if ischaemic heart disease) when both forms of treatment are used. The paper has been criticised [31] on the basis of the relatively young age of women in the study group (median 47 years), the relatively poor prognosis of the group receiving anthracyclines, the relatively short follow-up period (6.7 years) and electrocardiographic follow-up, which taken together may underestimate the cardiac risk to the general population with early breast cancer. Patients were also censored at first sign of disease recurrence rather than followed up for cardiac toxicity to death [30].

The report from Valagussa and colleagues [30] is the only review examining cardiac toxicity in the context of a randomisation to anthracyclines in a subgroup receiving CMF chemotherapy and radiotherapy. Other literature sources provide very little additional information on the cardiac toxicities of combined anthracyclines and radiotherapy compared with one or other treatment on its own. Reports of follow-up on patients after both forms of treatment record high and low rates of cardiac complications. For example, Loprinzi and colleagues [32] identified symptomatic cardiac toxicity in 8 of 32 (25%) patients with advanced local-regional breast cancer treated by primary surgery, local-regional radiotherapy and chemotherapy. Chemotherapy comprised two cycles of CMF $\pm$ prednisone $\pm$ tamoxifen starting after surgery, followed by 50 Gy in 25 fractions to the chest wall and regional lymph nodes, including internal mammary chain, followed by maintenance chemotherapy with eight cycles of CMF $\pm$ prednisone alternating with eight cycles of AV (doxorubicin 60 mg/m^2 and vincristine 1.2 mg/m^2) at 3 weekly intervals. The report does not specify if the internal mammary chain was encompassed by an anterior photon field, irradiating a large portion of myocardium, or incorporated in the tangential fields. 7 of 8 affected patients had been treated for left-sided tumours to a cumulative dose of doxorubicin between 105 and 420 mg/m^2.

In an abstract, Harrigan and coworkers [33] reported on cardiac toxicity in 296 patients with $\geq$4 axillary node-positive patients treated with doxorubicin 45 mg/m^2 and cylophosphamide 500 mg/m^2 to a total dose of 225 or 450 mg of doxorubicin. 100 patients received adjuvant radiotherapy (no further details are given). At a median follow-up of 3.3 years, doxorubicin on its own induced 0.8–1.1% cardiac events per patient year. The addition of left breast irradiation at the higher dose level (450 mg total dose) increased the rate to 3.7% ($P = 0.030$). By contrast, no clinical cardiac toxicity was noted in the follow-up of 774 patients receiving anthracycline-containing chemotherapy schedules combined with adjuvant radiotherapy after primary surgery for early breast cancer [34]. No radiotherapy details were stated in this abstract, except that it was concomitant with, or sequential to, polychemotherapy including cumulative doses of doxorubicin and epirubicin of 320 mg/m^2 and 360 mg/m^2, respectively.

In the paediatric setting, Steinhertz and coworkers [35] reported the outcome of 201 children treated at a median age of 10 years (range 2–23) followed for a median of 7 years (range 4–20) after polychemotherapy for leukaemia or solid tumours. The patients received a median total cumulative dose of doxorubicin or daunorubicin of 450 mg/m^2 (range 200–1275) over a period of 1–3 years. 51 children received mediastinal radiotherapy to a median incidence of abnormal cardiac status was 47 of 201 (23%), and higher at each anthracycline dose level in those patients receiving mediastinal radiotherapy ($P < 0.01$).

The optimum integration of chemotherapy and radiotherapy is another controversial issue. Delay in administration of chemotherapy results in decreased distant disease-free and overall survival. There are conflicting reports as to whether delay in radiotherapy whilst chemotherapy is given results in reduced local control [36]. Concurrent chemo-irradiation has been practised for breast cancer patients, but is associated with worse cosmetic results and higher sub-acute and chronic complication rates when CMF is used e.g. 1% pneumonitis after sequential chemo-irradiation versus 9% after concomitant chemo-irradiation [37–39]. From animal experiments, maximal enhancement of toxicity occurs when chemotherapy is given concurrently or a few days post radiotherapy [40]. In a retrospective study of testicular teratoma patients, Yarnold and colleagues [41]

showed that the toxicity was much greater when combination chemotherapy was administered concurrently or up to 4 months after radiotherapy compared with when chemotherapy was given first.

In conclusion, it is reasonable to assume that the risks of cardiac toxicity (excluding ischaemic heart disease) are additive when anthracyclines and local-regional radiotherapy for breast cancer are combined, although the quantitative relationships are poorly understood. The avoidance of anthracyclines in patients with left-side tumours requiring radiotherapy might be considered unless the patient is part of a research protocol, or until the survival advantages of anthracyclines are estimated reliably by systematic overview. Where radiotherapy and anthracyclines are combined, sequential treatment is probably safer than concomitant therapy, although randomised studies are needed to clarify these relationships. Other measures to minimise the risk of long-term damage to the heart include exclusion of the internal mammary chain from the target volume, unless in the context of a randomised trial, and maximum care in the planning and delivery of tangential fields. Finally, better radiotherapy techniques are needed to exclude the heart altogether from the high-dose zone. These are feasible nowadays with the applications of computer technology to three-dimensional imaging, planning and delivery.

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