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Short communication

Toxicity of intra-arterial doxorubicin in locally advanced breast cancer

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Summary. Four patients with inoperable, locally advanced breast cancer were treated i.a. with 25–35 mg/m^2 doxorubicin given as a 6-h infusion on 2 successive days. In each patient, the catheter was introduced percutaneously via the femoral or brachial artery using local anaesthetic and positioned in the internal mammary artery without complications. However, within 48 h of starting treatment all four patients developed extensive erythema over the chest wall, which progressed to superficial ulceration in one case. Two patients also developed a raised hemidiaphragm and phrenic nerve paralysis that was associated with a pleural effusion in one case. This study closed prematurely because of unacceptable local toxicity; thus, we cannot assess the activity of doxorubicin given in this way. If this approach to local control is to be tested further in locally advanced breast cancer, lower doxorubicin doses should be used, or different drugs selected.

Introduction

Patients presenting with inoperable, locally advanced breast cancer have a poor prognosis if treated by radiotherapy alone [14]. Initial treatment with i.v. chemotherapy achieves an objective response in 60%–70% of patients [15] and may decrease tumour burden sufficiently to make mastectomy possible. A recent EORTC study [16] showed that treatment with a combination of cyclophosphamide, methotrexate and 5-fluorouracil given after initial radiotherapy significantly decreased but did not eliminate local recurrence. Chemotherapy given i.a. could enable increased drug delivery to the tumour, resulting in enhanced cell kill without increasing systemic toxicity. Such a reduction in tumour load may make subsequent local treatment more effective.

Doxorubicin given i.v. is more effective at high (70 mg/m^2) than at low (35 mg/m^2) doses in patients with advanced breast cancer [4]. Pharmacokinetic models predict that in patients with locally advanced disease, the efficacy of doxorubicin may be further increased by i.a. administration. It has been estimated that if doxorubicin is given into a vessel such as the internal mammary artery, with its blood flow of 75 ml/min (P. B. Deverall, personal communication), drug delivery to the region it perfuses is more than 10 times greater than that achieved with the same dose given i.v. [5]. However, systemic drug delivery is the same for both routes of administration, as doxorubicin is not metabolised by the tumour. Therefore, the potential improvement in local tumour response to i.a. chemotherapy would not occur at the expense of treating systemic micrometastases.

Intra-arterial doxorubicin has been used in patients with head and neck cancer [6], limb sarcoma [1, 8, 10] and breast cancer [11, 19]. The aims of this study were to assess the efficacy and toxicity of doxorubicin given i.a. as a 35 mg/m^2 infusion on 2 successive days in patients with locally advanced breast cancer.

Patients and methods

We evaluated i.a. doxorubicin in patients with inoperable, locally advanced breast cancer [15]. These patients had no evidence of distant metastases after clinical examination, chest radiograph, biochemical screen and isotope bone scan. They had not received prior chemotherapy, radiotherapy or endocrine treatment. All patients gave informed consent.

A 5-F endhole arterial catheter was introduced under local anaesthetic, and the tip was placed securely in the internal mammary artery on the side of the affected breast. The procedure was carried out via the percutaneous femoral route, except in one patient in whom this was not possible and a percutaneous, high brachial approach was used. The position of the catheter tip was confirmed by arteriography and the capillary bed to be perfused was imaged by a radionuclide scan using technetium 99 m-labelled microspheres injected through the catheter. After the imaging studies were completed, doxorubicin was given by i.a. infusion in two divided doses of 25 or 35 mg/m^2, each prepared in 60 ml saline. The doxorubicin infusions were given over approximately 6 h on 2 successive days. The position of the catheter was checked by chest radiograph before the second infusion, after which it was removed.

We had planned to give a second course of i.a. doxorubicin 3 weeks later. In patients who responded to i.a. chemotherapy, this was to be followed by two cycles of 70 mg/m^2 doxorubicin given i.v. at 3-week intervals. After a total of four cycles of doxorubicin, patients were to be assessed and their tumours, classified as operable or in-

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Table 1. Clinical course of patients treated with i. a. doxorubicin

Patient	Doxorubicin i. a.	Cutaneous toxicity	Other toxicity	Operability after i. a. and i. v. chemotherapy	Subsequent treatment	Comment
JB	35 mg/m^2 days 1, 2	Grade 1 erythema and persisting area of pigmentation	Ipsilateral pleuritic chest pain, pleural effusion and raised hemidiaphragm	Operable	Radiotherapy (5,000 cGy in 25 fractions with 1,200 cGy in 4 fractions to breast mass)	Refused surgery; marked skin reaction following radiotherapy
SD	35 mg/m^2 days 1, 2	Grade 3 ulceration	–	Inoperable	Radiotherapy (4,600 cGy in 23 fractions)	Skin started to heal during i. v. chemotherapy and continued to head during radiotherapy
DL	35 mg/m^2 days 1, 2	Grade 1 erythema	–	Operable	Modified radical mastectomy	
DW	25 mg/m^2 days 1, 2	Grade 1 erythema	Paralysis of ipsilateral hemidiaphragm	Inoperable	Radiotherapy	Doxorubicin dose reduced because of previous gold treatment for rheumatoid arthritis

operable. Patients with operable tumours were to be offered a total mastectomy with axillary clearance; those whose tumours remained inoperable were to receive radiotherapy to the breast and gland fields. Treatment toxicity was assessed by WHO criteria [12].

Results

The outcome for the four patients studied is shown in Table 1. In each patient the catheter was successfully positioned in the internal mammary artery. No complications arose from the cannulation procedure, and the radionuclide scan demonstrated perfusion of the tumour and axillary node metastases. After a single cycle of i. a. doxorubicin, three patients showed signs of an early response to chemotherapy. However, all four patients experienced local toxicity following this first cycle; consequently, none received a second i. a. treatment. Instead, each patient received three cycles of i. v. doxorubicin. The first i. v. cycle was given 3 week after i. a. doxorubicin, and subsequent i. v. doxorubicin was given at 3-week intervals.

After completing chemotherapy, two of the patients were assessed as having operable tumours; one underwent a modified radical mastectomy, whereas the other refused surgery and was treated with radiotherapy. The two patients whose tumours remained inoperable after chemotherapy also received radiotherapy to the breast and gland fields.

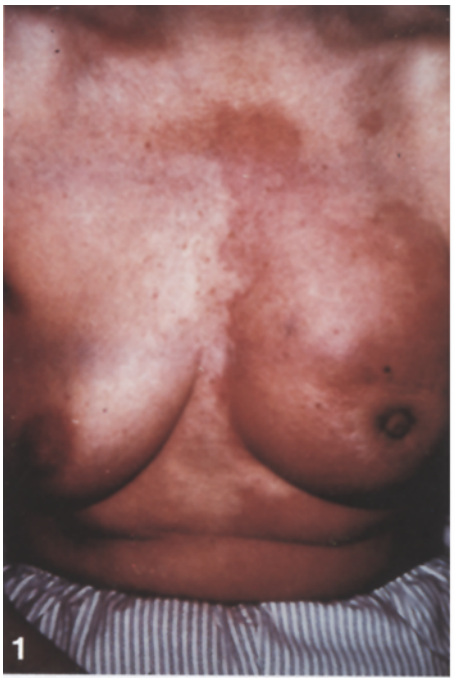
All four patients developed erythema over the ipsilateral breast and chest wall within 48 h of starting i. a. doxorubicin (Fig. 1). The affected area extended from the clavicle to the hypochondrium, closely corresponding to the area supplied by the internal mammary artery on a radionuclide perfusion scan (Fig. 2). In one patient the erythema progressed to superficial ulceration and pigmentation (Fig. 3). In the remaining patients it resolved over 1 – 2 weeks, but one had a persistent area of cutaneous pigmentation adjacent to the biopsy scar (Fig. 4) and experienced a marked skin reaction to subsequent radiotherapy.

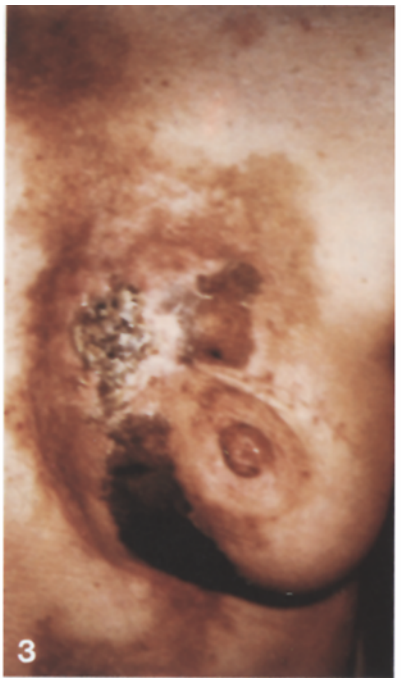
One patient became febrile and developed ipsilateral pleuritic chest pain 12 h after completing i. a. treatment. A pleural effusion was detected and confirmed on chest radiograph, which also showed a raised ipsilateral hemidiaphragm. The effusion contained only mesenchymal cells and resolved after aspiration, but the hemidiaphragm was still elevated 10 months later. A raised ipsilateral hemidiaphragm was also noted in a second patient 2 months after i. a. doxorubicin. In both patients, screening of the diaphragm suggested that this was secondary to phrenic nerve paralysis. The incidence of systemic side effects after i. a. doxorubicin was similar to that expected after i. v. administration.

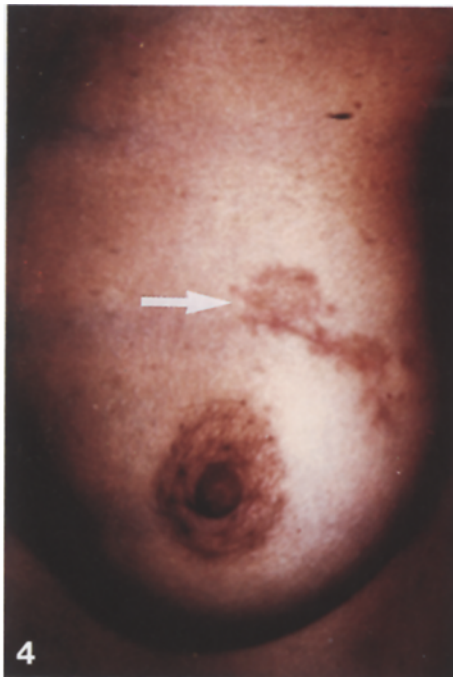
Discussion

Although death due to distant metastasis remains the major problem in patients with locally advanced breast cancer [14], this study was primarily concerned with improving control of loco-regional disease. We chose to give doxorubicin because it is the most active single agent in patients with advanced breast cancer [18]. Intra-arterial doxorubicin has been used in patients with a variety of tumours [1, 8, 10], including breast cancer [11, 19], although widely differing regimens, doses and schedules have been used. We gave doxorubicin on 2 successive days as a 6-h infusion at a total dose of 70 mg/m^2. This dose was chosen due to our extensive previous experience with 70 mg/m^2 doxorubicin given i. v. to patients with locally advanced breast cancer [15] and metastatic breast cancer [18]. A similar schedule of i. a. doxorubicin was tolerated well by patients with limb sarcoma.

This study demonstrates that in patients with locally advanced breast cancer, doxorubicin can be delivered into the internal mammary artery through a catheter introduced percutaneously into the femoral artery under local anaesthetic. This technique has the advantage of avoiding the surgery used in other studies [3, 9, 11]. Our most important observations concerned the toxicity of







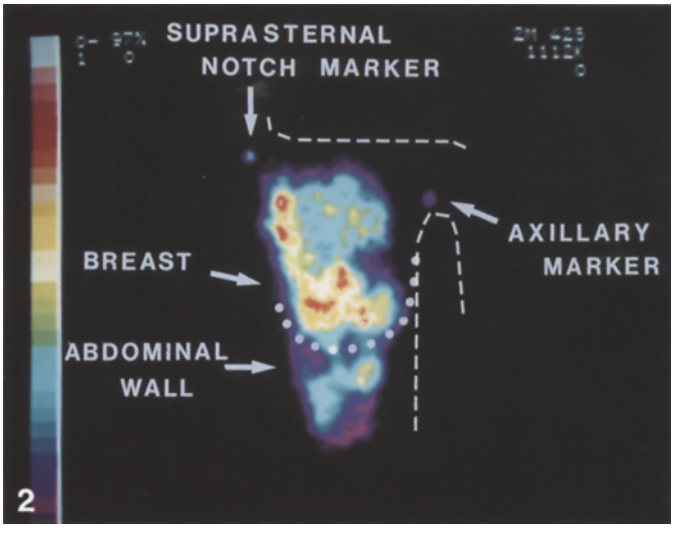


Fig. 1. Patient SD, 24 h after the first cycle of i. a. doxorubicin
Fig. 2. Technetium microsphere radionuclide scan before treatment
Fig. 3. Patient SD, 8 weeks after treatment
Fig. 4. Patient JB, 8 weeks after treatment (*arrow*, pigmented area)

doxorubicin using this schedule. All four patients experienced cutaneous toxicity. Similar cutaneous reactions have been reported by others [2, 8, 19], which appear to be more common when high doses of doxorubicin are given i. a. [17, 20]. The mechanism is not known with certainty, but in the present study erythema developed throughout the area perfused by the internal mammary artery.

Pleural effusions have been reported in only 4% of patients with breast cancer who undergo i. a. chemotherapy [11], and there are no previous reports of diaphragmatic paralysis. In addition to supplying blood to the breast and chest wall, the internal mammary artery also perfuses areas of the visceral pleura and mediastinum [13]. A marked inflammatory response in the visceral pleura and mediastinum, similar to that observed in the skin, would explain the pleural reaction and phrenic nerve damage seen in two of our patients.

Our schedule for i. a. doxorubicin is similar to one that is well tolerated by patients with limb sarcoma. However, blood flow is considerably lower in the internal mammary artery than in the major limb vessels involved in the treatment of limb sarcomas; therefore, when doxorubicin is given through the internal mammary artery, the drug concentrations achieved are correspondingly greater [5] and the risk of local toxicity, higher. This study was stopped because of the unacceptable local toxicity; thus, we cannot assess the activity of doxorubicin given in this way.

We conclude that patients with locally advanced breast cancer can be treated with i. a. chemotherapy given through the internal mammary artery using a catheter introduced percutaneously under local anaesthetic. In these patients, treatment with 35 mg/m^2 doxorubicin given as a 6-h i. a. infusion on 2 successive days is unacceptably toxic. If this approach to local control is to be tested further in patients with locally advanced breast cancer, either lower doses of doxorubicin should be given or different cytotoxic drugs should be used.

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