Scleroderma in association with the use of docetaxel (taxotere) for breast cancer

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Received on August 24, 2000; accepted in revised form of January 17, 2001.

Key words: Scleroderma, Taxotere, malignancy, drug-induced scleroderma.

ABSTRACT

The taxanes, paclitaxel (Taxol) and docetaxal (Taxotere), are a new class of anti-microtubule agents which have shown cytotoxic activity in a number of solid tumours. Phase I and II trials confirm that docetaxal is highly active in the treatment of metastatic breast cancer. Reported toxicities of docetaxel include, dose limiting neutropenia, alopecia, skin reactions and fluid retention. Here we report the first case of rapid onset, diffuse scleroderma-like illness, which occurred in a 59-year-old female receiving treatment with docetaxel for locally invasive and advanced metastatic breast cancer.

Introduction

In the 1990's a new class of antimicrotubule agents, the taxanes, became available for the treatment of solid tumours. These drugs promote the polymerization of tubulin into stable microtubules and inhibit depolymerization of formed polymers, thereby inducing the formation of stable microtubule bundles (1). These microtubule bundles then accumulate, interfere with cell division and result in cell death. The first taxane described was paclitaxel, an extract from the bark of the Pacific yew, Taxus Brevifolia, which showed encouraging results in breast cancer (2). However, it was difficult to isolate, extract and formulate and this led to the development of docetaxel, a semisynthetic analogue of paclitaxel extracted from the needles of the European yew, Taxus Baccata (3).

In Phase I trials, the major dose limiting toxicity of docetaxel was neutropenia and mucositis. Other toxicities included generalized alopecia, neuropathies, acute cutaneous reactions and fluid retention. Cutaneous reactions due to docetaxel are often asymptomatic or only mildly symptomatic, rarely impair function, and routinely resolve within days to weeks (4). They occur in up to 80% of patients, and can consist of palmar-plantar erythrodysesthesia, erythematous macules, papules and plaques, and various nail changes, including onycholysis, thinning and ridging of the nail plates, subungal erythema and subungal haemorrhage. Fluid retention can occur and includes peripheral odema, ascites and pleural effusions or a combination of these, and was a frequent cause (30-60%) for premature treatment discontinuation (5, 6). Fluid retention appears to be related to the cumulative dose of docetaxel, increasing in incidence at cumulative doses of ≥ 400 mg/m^2 (7). Pre-medication with corticosteroids has been shown to delay the onset of the fluid retention syndrome, reduce the incidence of peripheral odema, and decrease the severity of fluid retention but does not alter the incidence of cutaneous reactions (8). The relative roles of the drug itself or the delivery vehicle (Tween 80) in the etiology of this phenomenon remains unclear. Previously, Battafarano *et al.* have reported limited scleroderma-like changes of the lower extremities associated with docetaxel use in 3 patients (9). They suggested that docetaxel should be added to the list of exogenous agents capable of inducing scleroderma-like disease.

In Phase II trials, docetaxel as a first line chemotherapy agent for metastatic and/or locally advanced breast cancer has response rates of between 57-87%, and thus provides hopeful advances in the treatment of this subgroup of patients (7). Ongoing trials will potentially involve large numbers of patients, as phase III trials begin to compare docetaxel to standard therapies for the treatment of breast cancer. We report here a case of diffuse scleroderma-like illness occurring during treatment with docetaxel for metastatic breast cancer.

Case report

The patient, a 59-year-old female, with no significant past history, presented with locally advanced carcinoma of her right breast, having noted swelling, redness and nipple retraction one year prior presentation,and a tender lump of the breast dating back 6 years. A fine needle aspiration biopsy was performed which showed estrogen and progesterone receptor positive adenocarcinoma. A staging chest x-ray and pulmonary CT scan, showed multiple pulmonary and a solitary hepatic metastases, of which she was asymptomatic. She was a single, retired clerical assis-

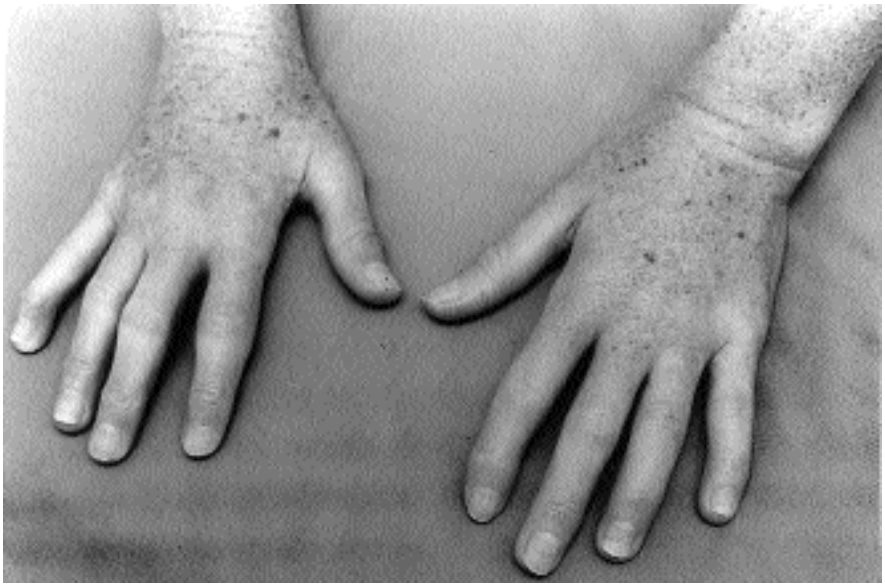

Fig. 1. Photograph of the patient's hands demonstrating thickened skin, flexion contractures of DIP joints, swelling of PIP joints, and ridging of nails.

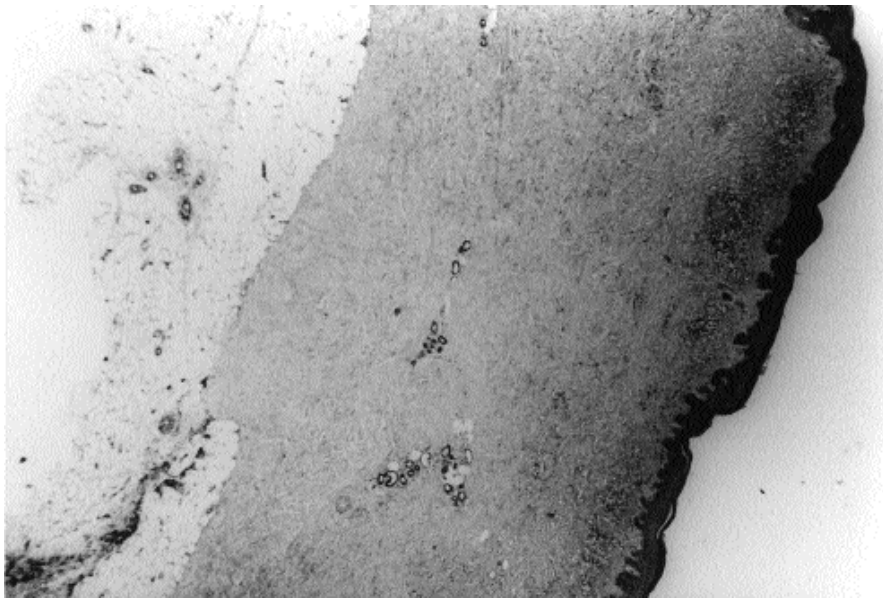

Fig. 2. Histological features of a skin biopsy specimen taken from an affected area of the patient's left forearm (haematoxylin and eosin stained). The epidermis shows hyperkeratosis. The dermis is increased in thickness and is composed of broad sclerotic collagen bands with a straight dermal-subcutaneous interface (original magnification x100).

tant, nonsmoker, with no significant medical or surgical past history and no family history of breast cancer or rheumatic diseases.

Oral tamoxifen 20 mg daily was commenced, which was well tolerated. However, after three months of treatment there was symptomatic breast discomfort and progression of local disease. Chemotherapy with cyclophosphamide, methotrexate and 5-Fluorouracil (CMF) was commenced with a proposed 6 cycles planned. After three cycles were completed, local breast disease continued to progress, and CMF was ceased. Whilst receiving the CMF she reported the onset of cold white hands, unrelated to cold exposure, which subsequently subsided on the cessation of CMF treament. There was no classical description of Raynaud's phenomenon before or after treatment was ceased.

The patient entered a Phase II taxotere trial subsequently, receiving taxotere 100 mg/m^2 intravenously, and dexamethasone 8 mg orally twice daily for three days, beginning the day prior to taxotere, every three weeks. After the first cycle, the patient was admitted to hospital for febrile neutropenia and a generalised maculopapular rash, and in subsequent cycles granulocyte colony stimulating factor was given at 263 mcg subcutaneously for 7 days. Peripheral odema was not observed. Local disease regressed by greater than 50% prior to the third cycle. Post the fourth cycle she was noted to have thickening of the skin of the fingers, dorsum of the hands and forearms. Prior to completion of the sixth cycle latter that year, she noted a decrease in her mouth aperture and increased pigmentation of her tightened skin.

Three months post completion of taxotere, she noticed progressive hardening of the skin, involving arms, face, anterior chest wall, abdomen and upper thighs, with limitation in the ability to close her hands. Pruritis, painful thigh muscles, and painful PIP joints were also prominent symptoms. There was no dysphagia, indigestion or diarrheoa to suggest gastro-intestinal organ involvement. She was commenced on Anastrazole for the ongoing management of her breast cancer.

On examination vital signs were within normal limits. There was scleroderma extending from the fingers up to the shoulders, of the face, lower limbs and onto the lower abdomen. The skin was hidebound, with increased pigmentation. The mouth aperture was markedly reduced and facial telangectasia were present. The fingers revealed dilated nailfold capillaries, synovitis in a number of PIP joints, minor DIP flexion deformities, fibrosis of the skin overlying the fingers, very few telangectasia and no calcinosis (Fig. 1). Ridging of the nails secondary to receiving chemotherapy was evident. Tenderness was elicited on squeezing her thigh muscles, but no evidence of a myopathy. Examination of the cardiovascular system, chest and abdomen was unremarkable. There was marked induration and retraction of the right breast, but no ulceration.

The following investigations were normal or negative: full blood count, urea and electrolytes, liver function tests, creatinine kinase, thyroid function tests, rheumatoid factor, erythrocyte sedimentation rate, complement levels and double stranded DNA. The antinuclear antibodies showed a speckled pattern of 1 in 2560, with a negative extractable nuclear antigen.

Skin biopsies were taken from multiple sites. A representative biopsy of the forearm (Fig. 2) demonstrated, increased thickness and sclerotic collagen bands in the dermis which extended to the underlying subcutis. Collagen replaced the fat around the sweat glands and atrophy of the eccrine sweat glands was noted. Some of the walls of small blood vessels showed narrowing of their lumen secondary to fibro-mucinous intimal thickening. A very mild perivascular chronic inflammatory infiltrate was noted. The appearances were consistent with scleroderma, and there was no evidence of malignancy in the tissue examined. Direct immunofluorescence studies of involved skin were negative.

Prednisolone (30 mg/day), d-penicillamine (62.5 mg/day), enalapril (10 mg/day) and diclofenac (50 mg tds) were commenced. On review at 6 months, on prednisolone (5 mg/day) and d-penicillamine (125 mg/day) there was regression of the skin tightness over the abdomen and legs, with noted softening of the skin around the shoulders, chest and face. There was no evidence of fibrosis. However, sclerodactyly was a persistent clinical finding.

Discussion

We report here the first case of diffuse scleroderma-like illness in a female patient with metastatic breast cancer receiving docetaxel as part of a Phase II trial. Prior to the commencement of docetaxel, the only suggestive symptom of an underlying connective tissue disease was that of cold hands, recalled on specific rheumatological questioning, experienced whilst receiving CMF chemotherapy. The description was not classical of Raynaud's phenomenon, resolved on cessation of CMF and did not recur with the onset of skin tightening whilst receiving docetaxel. Neither cyclophosphamide, methotrexate nor 5-FU have previously been reported to be associated with scleroderma. There was no family history, occupational or other drug history that may have placed her at risk for the development of scleroderma. The temporal relationship of the rapid development of scleroderma and the administration of docetaxel, implicates the drug or its delivery agent Tween-80, as an inducing agent.

The association between docetaxel, cutaneous reactions and fluid retention has been previously well documented (4, 7). A series of three patients with different underlying malignancies who had received multiple cycles of docetaxel and who had developed sclerodema-like changes of the lower extremities was reported by Battafarano *et al.* (9) All these patients had documented pitting odema of the lower extremities and weight gain, with the subsequent sclerodermatous areas being localized to the lower limbs. The upper limbs were unaffected, despite docetaxel being infused via peripheral veins of the arms. Nailfold capillaroscopy, clinical features of CREST and autoantibodies were absent in all patients. Skin biopsies in two patients showed scleroderma-like changes. Two patients had persistent skin pathology one year post discontinuation of docetaxel, and in the remaining patient there were no residual changes at five months. Prednisolone was not administered in these patients.

Only one other taxotere trial has reported scleroderma-like changes of the skin. This was a Phase I trial, in which five patients receiving the highest cumulative doses of docetaxel developed diffuse subcutaneous odema. Out of four skin biopsies obtained from these patients, two were reported on histological examination to be consistent with nonspecific toxidermic cutaneous reaction or scleroderma-like patterns (10). In this trial study they found that cutaneous toxicity was not reduced by the administration of corticosteroids or antihistamines, but did not look specifically at its effect on fluid retention or scleroderma-like changes. The sclerodermatous changes in our patient involved the upper and lower extremities, the trunk and face, and were not related to fluid retention.

The presence of anti-nuclear antibodies, nailfold capillary dropout, synovitis, and telangiectasia, raise the possibility of an idiopathic diffuse scleroderma coincidentally developing or becoming clinically overt in our patient whilst receiving taxotere. In support of this, skin involvement initially progressed despite completion of the Taxotere trial, as one might expect of the natural history of idiopathic scleroderma. However, as in the cases reported by Battafarano *et al.*, skin involvement did not progress to fibrosis, and had actually softened and regressed when we reviewed this patient nine months post completion of the Taxotere trial and six months following the institution of prednisolone and d-penicillamine. This rapid resolution of sclerodermatous skin changes and lack of progression to fibrosis is not consistent with the usual clinical course of idiopathic disease. In case reports of bleomycin induced scleroderma-like disease, cessation of drug and administration of corticosteroid resulted in a similar clinical picture (11).

The relationship between scleroderma and the development of malignancy and vice versa, in particular lung cancer and breast cancer, has been examined in both case series and epidemiologic studies, but remains an area of debate, with mixed results (12-14). Most series have estimated an incidence of cancer occurring in patients with scleroderma to be comparable to the incidence in the general population, and that breast cancer does not occur with increased frequency. In a number of case reports there has been a close temporal relationship between the onset of breast cancer and scleroderma (15-17). In a case series reported by Forbes *et al.* (17), 2 out of 4 patients had onset of sclerodermatous skin changes within 18 months of mastectomy for breast cancer. Both were ANA positive, with diffuse scleroderma, similar to our case. Similarly Lee *et al.* (16) reported that 2 out of 4 patients had changes within 6 months,and 2 out

of 4 within 24 months of their diagnosis of breast cancer. Only one patient was ANA positive. A definite worsening of the scleroderma was noted in one case after recurrence of the malignancy with widespread metastases. Improvement of skin changes has been observed after the treatment of the breast cancer (13). In our patient the scleroderma developed several years after clinically detectable disease, and continued to progress on chemotherapy, suggesting that whilst these may be a chance association, an etiological relationship between breast cancer and scleroderma in this case is unlikely.

In summary, we describe here the first case of diffuse sclerodermatous development in a patient receiving taxotere chemotherapy. Although there may be a number of confounding issues, the temporal relationship and the unusual clinical progression, imply a drug effect.With increasing clinical use of taxotere, we should be aware of its potential to lead to clinical variants of scleroderma.

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