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Chemotherapy-induced Onycholysis

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CYTOTOXIC CHEMOTHERAPY has been shown to improve relapse-free and overall survival in early breast cancer [1] and palliate patients with metastatic disease. This benefit has to be balanced with any potential side-effects that may be caused by this treatment thereby limiting its potential value. In the treatment of breast cancer, mitozantrone has a low toxicity profile. In combination with methotrexate and mitomycin C, it has been shown, in metastatic breast cancer, to have equivalent activity as vincristine, doxorubicin and cyclophosphamide but with less side-effects [2]. One potential side-effect, of which there are only a few case reports of isolated cases, is onycholysis [3]. Onycholysis is a nail disorder caused by the premature separation of the nail plate that is occasionally seen in psoriasis, infection, thyroid disease and trauma. We report our experience of 13 cases of onycholysis in patients with breast cancer receiving chemotherapy, suggesting that this potential side-effect may be under-reported.

All 13 cases were women with primary breast cancer treated in our unit between January 1993 and June 1994. Table 1 summarises the characteristics of all cases. In 11 patients, chemotherapy involved a maximum of eight cycles of mitozantrone (11 mg/m^2) and methotrexate (35 mg/m^2) with tamoxifen 20 mg daily (MMT). One patient received mitozantrone (8 mg/m^2), methotrexate (35 mg/m^2) and mitomycin C (8 mg/m^2) without tamoxifen (MMM). A further patient received epirubicin (60 mg/m^2), cisplatin (60 mg/m^2) and 5-fluorouracil (200 mg/m^2 i.v. continuous infusion for 18 weeks) with no tamoxifen (ECF). Anti-emetics were administered with the above drugs mainly in the form of ondasentrone, dexamethasone and domperidone. None of the patients had pre-existing nail or skin disease. Nail changes appeared after several cycles (ranging from five to eight) of chemotherapy. In all patients, the main effect was on the big toes. There was thickening of the nails with discolouration and subsequent lifting of the nail plate. In four patients, scrapings were taken for fungal culture and proved negative. Improvement was not seen until 3–4 months after stopping chemotherapy (tamoxifen was continued) and took many months to return to normal. In several patients, the nail plate had completely separated. Two patients required avulsion of the affected toe nails. Nail dystrophy (thickening and ridging) of the other toe nails and finger nails was seen in some of these patients and any onycholysis observed in other nails was minor in comparison with the big toes.

Onycholysis occurring after treatment with cytotoxic drugs is uncommon. A search of the literature has revealed 4 cases of onycholysis after mitozantrone [3, 4] and 3 cases following treatment with doxorubicin [5]. Mitozantrone is an anthracenedione that has been used in the treatment of patients with breast cancer and non-Hodgkin's lymphoma. It is structurally related to the anthracyclines. Mitozantrone was administered to 12 of these patients and the other received epirubicin. It seems likely that these two agents were responsible for this side-effect. 12 patients also received methotrexate and 11 took tamoxifen, but onycholysis has never been reported with either of these drugs. An interaction cannot be excluded.

Considering all these patients were seen in a period of 18 months, it is rather surprising that so few cases have been previously reported. It seems likely that there is under-reporting

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Table 1. Patient characteristics and nail changes

Patient	Age (years)	Chemotherapy	Onycholysis of big toes	Other nail changes	No. of courses	Started to improve (months)
1	65	MMT	Yes	Discolouration of all nails	7	6
2	48	MMT	Yes	Koilonychia of all nails	7	3
3	54	MMT	Yes	None	5	6
4	65	MMT	Yes	None	6	3
5	55	MMT	Yes	Minor onycholysis of other nails	6	3
6	66	MMT	Yes	Koilonychia, discolouration	8	6
7	64	MMT	Yes	Minor onycholysis of thumb nails	6	3
8	41	MMT	Yes	None	6	1
9	62	MMT	Yes	Other nails dystrophic	2	3
10	45	MMT	Yes	None	6	2
11	53	MMT	Yes	Painful fingers	5	4
12	45	MMM	Yes	Ridging of thumb nails, other nails dystrophic	6	4
13	67	ECF	Yes	Minor onycholysis of other nails	5	4

CT, chemotherapy; MMT, mitozantrone, methotrexate, tamoxifen; MMM, mitoxantrone, methotrexate, mitomycin C; ECF, epirubicin, cisplatin, 5-fluorouracil.

of this potential side-effect. The treatment of early breast cancer with cytotoxic chemotherapy is aimed as a cure of a potentially fatal disease, and onycholysis of toe nails may well be acceptable to patients in view of the benefit. However, the treatment of metastatic breast cancer aims at palliation and in this situation careful consideration needs to be given to avoiding any side-effects that could potentially impair quality of life.

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Prevention of Second Primary Tumours With a Second Generation Retinoid in Squamous Cell Carcinoma of Oral Cavity and Oropharynx: Long Term Follow-up

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IT HAS been suggested that retinoids might be used as a pharmacological approach to the chemoprevention of cancer, because of their ability to exert a hormone-like control over normal cellular differentiation and proliferation, which may subsequently influence neoplastic development [1, 2]. Hong and associates and Benner and associates [3, 4] have shown that treatment with isotretinoin following primary therapy for squamous cell cancer of the head and neck reduces significantly the development of second primary tumours. In 1985, we launched a double-blind randomised study of T1/T2, N0/N1 < 3 cm, M0, clinical stage carcinoma of oral cavity and oropharynx trial by choosing etretinate, a second generation retinoid [5]; at that time, we had no data concerning the effect of etretinate on head and neck cancer or oral leukoplakia. 316 patients with histologically confirmed primary squamous cell carcinoma were randomly assigned to receive 2 years of therapy with either etretinate (156 patients) at a dose of 25 mg per day or placebo (160 patients). Eighty-two per cent of the tumours were located in the oral cavity. Five per cent of the patients in the etretinate group (8/156) and three per cent in the placebo group (5/160), were entered in the study but were not controlled after completion of primary treatment. In addition, 51 patients in the etretinate group (33%) and 36 in the placebo group (23%) did not complete the 24-month course of treatment because of clinical or biological toxicity, a relapse or other reasons; severe side-effects were described in detail in the initial report [6], based on a median follow-up of 41 months: the 5-year projected rates of development of second primary tumours were 38% in the etretinate group and 24% in the placebo group (NS).

We report here the long-term results based on 316 patients with a mean follow-up of 65 months. We found no difference in the survival curves of the two groups (log-rank NS): the 5-year survival rate (95% confidence interval) in the etretinate group is 65% (56–72) versus 74% (66%–81%) in the placebo group. There are no differences regarding local or regional relapses (log-rank NS) and distant metastasis (log-rank NS). 42 patients in the etretinate group and 40 in the placebo group developed a second primary tumour. In more than 75% of the cases, the second primary tumour occurred in the head and neck, oesophagus or lung, which is in keeping with the concept that the occurrence of neoplastic disease in these areas is tobacco-related [7]. The actuarial curves for occurrence of a second primary tumour are presented in Figure 1 (log-rank NS). The 3- and 5-year rates (95% confidence interval) are 18% (12–25%) and 35% (26%–45%) in the etretinate group versus 18% (13%–25%) and 26% (19%–35%) in the placebo

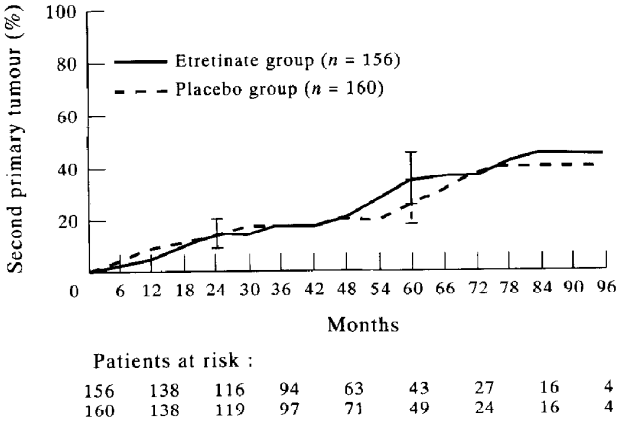

Figure 1. Second primary tumour (95% confidence interval).

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