ORIGINAL ARTICLE

Radiation Recall

Another Call With Tamoxifen

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Tamoxifen, a nonsteroidal antioestrogen, has been used as an adjuvant therapy in patients with oestrogen-receptor positive breast cancer for more than 10 years. Few cutaneous adverse side-effects of the skin are found with this therapy. In this study we present 20 cases of adverse skin effects in relation to tamoxifen during 1979–1997 reported to the Swedish Adverse Drug Reaction Register and 1160 skin side-effects reported to he World Health Organisation's International Collaborative Programme on Drug Monitoring. One new case report of radiation recall in conjunction to tamoxifen, with no sign of reactivation despite 18 months treatment with the tamoxifen analogue toremifene is also discussed in detail. This case illustrates that toremifene can be used as a second-line therapy in patients who have received radiation recall, on tamoxifen.

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The indications for using tamoxifen, a non-steroidal antioestrogen, have increased in recent years. The use of tamoxifen as an adjuvant therapy with chemotherapy was approved in 1986 by the Food and Drug Administration, and as an adjuvant therapy alone in 1988 in node-positive postmenopausal patients, and in pre-/postmenopausal node-negative patients with oestrogen receptor-positive disease in 1990 (1, 2). In Sweden the sales figures for tamoxifen have steadily increased (Fig. 1). The incidence of acute adverse effects associated with tamoxifen therapy is generally low, and less than 5% of the patients have to stop tamoxifen therapy because of side effects. The most common adverse effect on skin, with an incidence of 17–67%, is vasomotor instability with hot flushes (1), but more severe types of skin reactions caused by tamoxifen are rare (3).

In 1992, a letter in the Lancet presented the first case of radiation recall dermatitis induced by tamoxifen (4). Radiation recall dermatitis is an inflammatory reaction, possibly a delayed form of radiosensitization developing on previously ionized irradiated skin (5) and associated with the intake of cytostatics, e.g. doxorubicin (5), actinomycin-D (6), paclitaxel (7, 8), dactinomycin (5), or exposure to sunlight (9). The reaction may or may not be preceded by clinically apparent radiation damage in the involved skin and may occur months to years after completion of radiotherapy (5).

In this report we present a second case of radiation recall dermatitis associated with tamoxifen therapy. In addition, we have evaluated all the adverse skin reactions in connection with tamoxifen therapy reported to the Swedish Adverse Drug Reaction Register (ADR-register) during the period 1979–1997, and the cumulative reports collected by the World Health Organization's International Collaborative Programme on Drug Monitoring during the Period 1976 to February 1998.

Case report. A 48-year-old, previously healthy, woman had a partial mastectomy in 1994 for a left-sided breast cancer. Histopathology revealed an 8×9 mm, highly differentiated tubuloductal breast cancer with an Elaston-Ellis score of IV points. Biochemical determination revealed the presence of oestrogen as well as progesterone receptors; flow cytometry demonstrated a diploid tumour with a high S-phase. The breast parenchyma was treated with postoperative radiotherapy, 2 Gy fractions to a total of 54 Gy. No further adjuvant therapy was given. No sign of recurrence was noticed until January 1997, when a second invasive breast cancer, measuring 8×7 mm, was removed. This tumour was also a highly differentiated tubuloductal carcinoma, with V malignancy points according to Elaston-Ellis. Adjacent to the tumour, minor areas of ductal carcinoma in situ grade II were detected. Biochemical receptor analysis revealed an intermediate level of oestrogen receptors and a high progesterone receptor content. Flow cytometry revealed a diploid tumour with a low S-phase. Whether this tumour represents a truly new tumour or a relapse is not known. Based on the biology, the patient was recommended adjuvant therapy with tamox-

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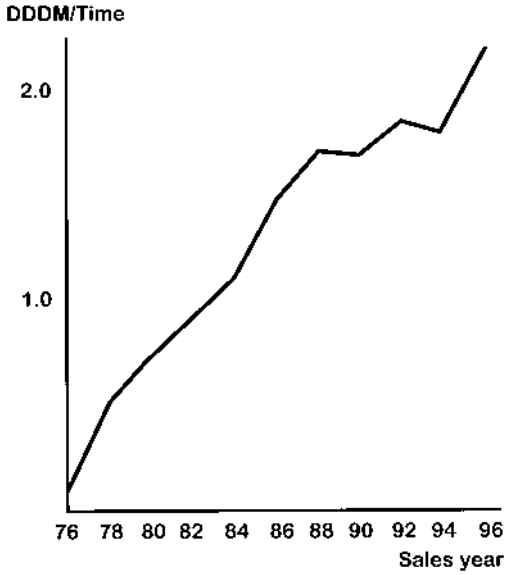

Fig. 1. The total drug sale of tamoxifen in Sweden 1976–1996 is expressed as daily dose (DDD) per thousand inhibitants and days over a 12-month period. Data available from the Swedish ADR register's computerized drug information system.

ifen 20 mg/day for 5 years. Two months after initiating the therapy, a painful progressive erythema developed in the previously irradiated mastectomy area. The erythematous skin measured 17×19 cm (Fig. 2) and demonstrated some scattered hyperpigmentation and increased feeling of heat. Seven 3-mm punch biopsies were taken in the erythematous area, all negative for recurrence of the breast cancer.

The histopathological picture demonstrated dermal blood and lymph vessels in conjunction with a few inflammatory cells and fibrosis. The biopsies showed no signs of fungus, foreign body reaction, eczema or erythema chronicum migrans. The sedimentation rate was 6 mm, CRP < 10 mg/L, WBC 5.6×10^9/L. However, bacterial infection could not be completely ruled out and clindamycin was administered orally for 2 weeks. For symptomatic relief, a potent local steroid cream, mometasone furoate (Elocon®) was applied once daily for 10 days. Owing to lack of response to topical steroid and clindamycin treatment in combination with absence of inflammatory blood parameters and the inconclusive histopathological picture, an adverse skin reaction was suspected. Seven weeks after cessation of the tamoxifen therapy the skin gradually appeared almost normal (Fig. 3). After 8 weeks without tamoxifen, the patient was restarted on toremifene, a tamoxifen-related substance. After 18 months of continuous treatment with toremifene, there has been no sign of recurrence of the skin reaction.

Fig. 2. Two months after initiation of tamoxifen, a painful progressive erythema developed.

Fig. 3. Seven weeks after cessation of the tamoxifen, the skin gradually almost normalized.

Adverse effects of the skin in association with tamoxifen reported to the Swedish ADR register and the WHO Collaborative Programme on Drug Monitoring.

Voluntary reporting of suspected adverse drug reactions to the Swedish ADR register began in 1965. Since, 1975, reporting of fatal, otherwise serious, and new reactions are compulsory. The reports are scrutinized by a medical officer and discussed in a working group. Finally, the probability of a causal relationship is evaluated by the full committee, which includes representatives from several clinical specialities.

By definition, the causality of the reports is classified as 1) probable: if there is a reasonable time to administration of the drug, with a reasonable response to withdrawal (dechallenge) and if the reaction is unlikely to be attributed to other drugs or diseases, 2) possible: if there is a reasonable time of administration, but there is lack of information on withdrawl and/or the reaction can also be explained by concurrent diseases, and 3) as unclassifiable: when more data are needed for a proper assessment.

In 1979–1997 only 20 cases of suspected adverse skin effects in association with tamoxifen therapy were reported (Table 1), 19 of them were females and one male (mean age 63.8 years, range 39–74 years) all with a history of breast cancer. The treatment duration before initiation of the skin reactions ranged from 1 day to 1.5 years. The

causality of these suspected adverse reactions was evaluated as probable in 2 cases, possible in 15 cases, while 3 cases were unclassifiable (Table 1).

As shown in Table 1, there are various types of adverse skin reactions reported on tamoxifen. Only one case represents a local skin reaction in the operated area. A 72-year-old woman had surgery for a left-sided breast cancer in 1984 and presented a local tumour recurrence on the left side of the thoracic wall in 1985. After only one dose of 40 mg tamoxifen, a localized skin lesion flared up on the previously irradiated breast. The skin lesions faded after cessation of the therapy, but flared up again after rechallenge. When the tamoxifen dose later was divided into two doses (20 mg twice a day), the erythema decreased sufficiently to allow the patient to continue on the drug.

The main function of the World Health Organization's International Collaborative Program on Drug Monitoring (officially in operation since 1971) is to provide a reliable early warning of possible health hazards caused by medicines (10). Between the years 1976 and February 1998, 1160 adverse drug reactions of the skin in patients on tamoxifen were reported to the WHO collaborating centre (Table 2). However, it should be noted that these reports may sometimes be registered twice, owing to factors such as reports being sent in by physicians and companies separately. The causality of the reports to the WHO centre is not further classified.

Discussion. Tamoxifen was the first drug developed within the group of oestrogen receptor modulators. The effect in the breast is that of an oestrogen receptor antagonist, while the effect in some other organs could be described as oestrogen agonism (1). This dissimilarity of effect may be due to the different forms of oestrogen receptors. This may also explain some of the tamoxifen-related adverse effects. The positive effects of this drug can be summarized as follows: tamoxifen can reduce the risk of developing an oestrogen receptor positive breast cancer (11); when used in the adjuvant setting tamoxifen significantly reduces the mortality in breast cancer patients (especially for patients with receptor positive breast cancer); and it can induce objective remission for 50–70% of patients with metastatic, receptor-positive cancer (2).

There seem to be few adverse reactions of the skin related to tamoxifen (3), the most common reactions reported to the WHO collaborating centre being rashes, alopecia/hypotrichosis and pruritus (Table 2). Only 20 cases have been reported to the Swedish ADR register. The most frequently reported reactions were toxicodermia, eczema and photosensibility (Table 1). One case of erythema occurring locally on the thoracic wall was reported. The history of this patient fits well with a tumour flare that can be seen during tamoxifen therapy (3). No cases of diagnosed radiation recall have been reported to either of these registries.

Radiotherapy is, with variable incidence, associated with acute and late side effects (12). These are partly related to the fraction size, fraction schedule, total dose and differences in individual inherent radiosensitivity (14). Activation within the previously irradiated area may occur when cytostatics are given relatively soon after the radiotherapy

Table 1

Adverse skin reaction to tamoxifen reported to the Swedish ADR register during 1979–1997

Adverse reaction	Localization	Onset	Treatment
Toxicodermia	Arms/legs/chest	5 days	Discontinued, no rechallenge
Toxicodermia		<14 days	Discontinued, no rechallenge
Toxicodermia	Chest	11/2 yrs	Reversible, rechallenge negative
Pruritus, eczema		>6 months	Reversible, changed to toremifene
Maculopapular eczema		3 yrs	Discontinued
Maculopapular exanthema		<1 month	Discontinued, reversible
Oedema, discolouration	Arms/legs	14 months	Discontinued, reversible
Seborrhoic dermatitis**	Head/neck	1 month	Rechallenge pos, reversible
Photosensitivity	Arms	2 yrs?	Continued with reduced dose
Photosensitivity*		?	Continued, no reversible
Photosensitivity**	Face/neck	3 yrs	Discontinued, rechallenge pos.
Photosensitivity		<1 yr	Continued
Pruritus, Quincke?	Face	4 days	Discontinued, reversible
Erythema*	Neck	<1 week	Discontinued
Urticaria	Neck	4 days	Discontinued, reversible, Multiple cytostatics involved
Defluvidum	Arms/legs	<4 months	Discontinued
Alopecia	Head	?	Discontinued, reversible
Hypertrichosis	Face	1.5 yrs	
Local erythema	Breast	Immediately	Poss. Rechallenge, splitting the dose, fewer symptoms
Discolouration*	Arms/legs	19 days	Discontinued, not reversible

* Indicates unclassifiable.

** Probable and unmarked adverse reaction indicates possible.

Table 2

Adverse skin reactions reported to the WHO centra during the years 1976–1998 (Feb.)

Adverse skin reaction	n
Rash	317
Alopecia/hypotrichosis	205
Pruritus	140
Angioedema/urticaria/dermographia	73
Macular oedema	
Sweating increased	62
Hypertricosis	60
Photosensitivity	45
Nail disorders	34
Acne/rosacea/seborrhea	23
Other hair disorders (texture, colour)	19
Bullous disorders	18
Steven Johnson syndrome/epidermal	18
Nekrolysis/exfoliative dermatitis	
Psoriasis	12
Dry skin/rhagades	12
Abnormal pigmentation (vitiligo, hypo, hyper)	
Erythema multiforme	11
Erythema nodosum	11
Eczema	10
Skin uleration	7
Lichenoid dermatitis	7
Abnormal odour	4
Malignant melanoma	3
Purpuric rash	3
Scleroderma	2
Fungal dermatitis	2
Naevus	2
Skin atrophy	2
Fixed eruption	1
Papilloma	1
Cold clammy	1
Erythema exudativum	1
Contact dermatitis	1
Skin discolouration	20
Skin disorders	17
Dermatitis	5
Total	1160

course or in connection with exposure to ultraviolet light (9). The mechanism of activation is not fully understood. The incidence of radiation recall seems to decrease with time between radiotherapy and the agent causing this phenomenon. It can be speculated that the radiation recall phenomenon may be partly explained by the altered conditions post-radiotherapy within the irradiated area. This could be due to altered vascularization, decreased immunological competence in combination with increased fibrosis in the tissue, at the expense of the morphological structures normally present. The acute irradiation side effects are partly related to the endothelial cell damage and the long-term effects are associated with capillary proliferation in conjunction with increased fibrosis (12).

These changes may have the potential to alter the distribution of cytostatics and tamoxifen within the irradiated area, compared with the surrounding tissues. Radiotherapy-induced vascular changes can progress for up to 10 years after irradiation (14). One case of radiation recall on tamoxifen was previously reported to have been induced 2 years after radiotherapy and 5 days after initiation of the drug. After discontinuation of the tamoxifen therapy, the reaction disappeared within 2 weeks. Rechallenge with the drug resulted in an additional skin reaction and the therapy had to be stopped (4).

In our patient, the radiation recall phenomenon was seen 2 months after initiation of the tamoxifen therapy and 28 months after postoperative radiotherapy. The disappearance of the recall dermatitis was delayed many weeks, most likely explained by the very long half-life of tamoxifen (2 weeks for the main metabolite, N-desmethyltamoxifen). More than 30% of the metabolite can be detected in the body after 2 weeks (15).

There have been no signs of reactivation of the recall phenomenon despite 18 months' treatment with the tamoxifen analogue, toremifene. Accordingly, a similar finding was reported to the Swedish ADR register (Table 1). A patient with eczema and pruritus was later transferred to toremifene, without any further skin symptoms. This is interesting, as the compounds are structurally similar, with the exception of a chloride atom in the toremifene molecule (16). Toremifene is not usually recommended as a second-line therapy after tamoxifen because of the risk of cross-resistance (17).

In conclusion, there seem to be few serious adverse skin reactions associated with tamoxifen. Radiation recall can appear late after radiotherapy in conjunction with tamoxifen. Toremifene may be an alternative in these cases.

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