RETINAL CHANGES ASSOCIATED WITH TAMOXIFEN TREATMENT FOR BREAST CANCER

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SUMMARY

Purpose: **This study was undertaken to estimate the incidence of retinal changes and determine the prevalence of ocular toxicity associated with tamoxifen treatment in a breast cancer population.**

Methods: **The study was based on a population cross-sectional survey, including 290 patients taking tamoxifen from 6 months to 12 years; 274 patients were analysed. The main outcome measures were the incidence of retinal changes and visual impairment.**

Results: **The incidence of retinal changes was 0.9% (3 of 274 patients). All 3 patients were asymptomatic. The length of tamoxifen treatment ranged from 39 months to 120 months in the affected patients, with cumulative tamoxifen doses ranging from 23.7 g to 73 g.**

Conclusions: **Retinopathy in patients receiving low doses of tamoxifen is rare and, in our study, did not result in changes in visual acuity. We found no retinopathy in patients receiving tamoxifen within the first 3 years of treatment or in patients receiving a total tamoxifen dosage of less than 23.7 g. Although retinopathy can occur in a tamoxifen-treated population, its low incidence and an associated good prognosis for vision does not merit special screening for this problem.**

Tamoxifen (Nolvadex), a non-steroidal oestrogen antagonist, has proved to be an effective adjuvant hormonal therapy in the treatment of breast cancer.[1] This triphenylethylene derivative exerts its anti-oestrogenic properties by competitively binding to cytoplasmic oestrogen receptors, thus arresting the cell in G_1 phase.

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The ocular side effects of tamoxifen were first reported in 1978 by Kaiser-Kupfer and Lippman,[2] who described white refractive retinal opacities and subepithelial opacities in the cornea in patients receiving high doses (up to 320 mg/day) of the medication. In several subsequent studies,[3–10] tamoxifen-induced ocular toxicity, including optic neuritis, was reported. Pavlidis *et al.*[11] described similar toxicity in patients taking low doses of tamoxifen (20 mg/day); however, Beck and Mills[12] and Longstaff *et al.*[13] found no evidence of ocular side effects associated with the drug.

Tamoxifen is the most commonly prescribed agent for the treatment of breast cancer; and since major benefits are observed with treatment for 5 years or longer, it is important to evaluate the ocular toxicity associated with the chronic use of this drug. We present the results of ocular examinations in 290 breast cancer patients who received standard doses (20 mg/day) of tamoxifen.

PATIENTS AND METHODS

A total of 290 patients receiving 20 mg/day of tamoxifen had ocular examinations; records of the length of tamoxifen treatment were available for 274 patients. Patients were selected from three centres: 80 were recruited from the Ocular Oncology Service, Wills Eye Hospital, Philadelphia, PA (J.S.); 90 were from a private ophthalmology practice, Houston, TX (R.T.); and the remaining 120 patients were recruited from a private oncology practice, Oklahoma City, OK (J.H.). The mean age in the Oklahoma City group was 66 years, and the mean age in the Houston group was 58 years.

Criteria for enrolment in the study included diagnosis of breast cancer, treatment with tamoxifen, and agreement to an ophthalmological examination. Ophthalmic complaints were not a requirement for

Table I. Treatment duration and results by groups

	No. of patients	Duration of treatment (months) Mean ± SD	Tamoxifen dosage (g) Mean ± SD	Patients with retinal changes
Philadelphia	73	18.42 ± 17.42	11.4 ± 10.4	0
Houston	81	22.11 ± 20.47	13.3 ± 12.3	0
Oklahoma City	120	55.29 ± 38.0	33.18 ± 22.8	3
Total	274	35.66 ± 33.80	21.4 ± 20.28	3

inclusion; neither was there a specified length of tamoxifen treatment.

Eye examinations were concentrated on the fundus. The examination comprised the following: visual acuity, Amsler grid testing, applanation tonometry and full dilated funduscopic examination with both the direct and indirect ophthalmoscope. Fundus photography documented all retinal pathology.

RESULTS

Crystalline deposits in the posterior pole consistent with previously described tamoxifen retinopathy were found in 3 patients (0.9%) (Table I). No other ocular abnormalities were evident, and visual acuity was not affected in any of the 3 patients. The length of tamoxifen treatment in these 3 patients ranged from 39 months to 120 months, and the total dosage of tamoxifen ranged from 23.7 g to 73 g (Table II). All 3 patients with retinal changes were found in the Oklahoma City group, which had the longest mean duration of treatment (55 months) and the highest total dosage of tamoxifen (72 g).

DISCUSSION

Tamoxifen has proved to be beneficial in the treatment of advanced breast cancer. In recent years there have been reports indicating its beneficial effects in the early stages of breast cancer as well. Recently, the Early Breast Cancer Trialists' Collaborative Group reported the results of a meta-analysis involving more than 30 000 patients in 40 clinical trials in which tamoxifen therapy was used in the early stages of breast cancer.[14] A significant survival and disease-free interval was shown in tamoxifen-treated patients versus controls. The standard practice is to treat breast cancer patients for 5 years or longer.[14] In this report, greater benefit was observed with a longer duration of therapy.

Tamoxifen is remarkably well tolerated, with fewer than 3% of patients withdrawing from clinical trials. Although most of the toxicity is related to the anti-oestrogenic properties of the drug, ocular toxicity has also been reported – specifically a tamoxifen-induced retinopathy.

A review of tamoxifen-induced retinopathy reported in the literature is shown in Table III. Retinopathy is a rare occurrence in patients receiving 20 mg daily of tamoxifen; in our study it was not associated with changes in visual acuity or visual function. We found no evidence of tamoxifen retinopathy during the first 3 years of treatment or with a total dosage of less than 23.7 g. Some patients treated with higher doses (180 mg or more daily) have been found to develop a reversible crystalline maculopathy and, occasionally, a keratopathy.[2] The clinical significance of these crystalline deposits in the retina is unknown. Although they have been found in the outer plexiform layer,[3] their exact location is still a matter of debate. Given the chemical composition of tamoxifen and its structural similarity to other toxic ocular agents with cationic, amphophilic properties such as chloroquine, amiodarone and phenothiazine,[16] tamoxifen may be expected to accumulate as a drug–lipid complex in the lysosomes of the cornea and retina – most probably at the level of the retinal pigment epithelium. This chemical similarity lets us also speculate that its toxicity may be dose related rather than idiosyncratic. A cumulative dosage effect is also supported by the fact that we found no abnormalities in patients taking a total dosage of less than 23.7 g, which is equivalent to 3 years of treatment.

Patients who have visual complaints while undergoing tamoxifen therapy should see their ophthalmologist for evaluation. Together, the ophthalmologist and oncologist can best coordinate the continuation of treatment based on the visual complaint and ocular examination.

The clinical significance of retinal findings in the absence of visual changes remains unknown. The results of this study suggest that annual eye examinations during the first 3 years of treatment are unlikely to reveal retinal damage secondary to tamoxifen.

Table II. Clinical factors associated with retinal changes

Patient	Age (years)	Total dosage of tamoxifen (g)	Duration of treatment (months)	Visual acuity
1	69	23.7	39	20/20
2	56	73	120	20/20
3	73	73	120	20/20

Table III. Tamoxifen-induced retinopathy: review of the literature

Author/Year/Reference	No. of patients		Dosage of tamoxifen		Duration (months)	Retinal changes
	Total	Retinopathy	Daily	Total		
Kaiser-Kupfer and Lippman, 1978[2]	4	4	240–320 mg	108–320 g	17–27	White refractile retinal opacities, posterior pole. White, subepithelial corneal opacities
Beck and Mills, 1979[12]	19	0	40 mg	—	3–48	No retinal changes
Kaiser-Kupfer *et al.*, 1981[3]	1[a]	–	40–240 mg	—	42	Superficial lesions overlying retinal vessels. Post-mortem: lesions confined to retinal nerve fibre and inner plexiform layer
McKeown *et al.*, 1981[4]	1	1	180 mg	158 g	30	Bilateral retinal opacities; cystoid macular oedema
Vinding and Nielsen, 1983[5]	17	2	20–30 mg	5.8–15 g	7–25	Yellowish-white opacities, posterior pole of retina[b]
Pugesgaard *et al.*, 1986[6]	1	1	30–40 mg	6 g	6	Bilateral optic neuritis
Griffiths, 1987[7]	1	1	20 mg	7.7 g	7	Decreased visual acuity; macular oedema by fluorescein angiography[c]
Ashford *et al.*, 1988[8]	1	1	20 mg	0.4 g	3 wk	Bilateral optic disc swelling; retinal haemorrhages[c]
Longstaff *et al.*, 1989[13]	79	0	20–60 mg	24.3 g (mean)	27 (mean)	No retinal changes
Gerner, 1989[9]	1	1	30–40 mg	22.8 g	26	Refractile opacities, inner retinal layer at paramacular area; bilateral cystic macular changes[b]
Pavlidis *et al.*, 1992[11]	63	4	20 mg	3.6–30 g	6–51	Decreased visual acuity; macular oedema; yellow-white opacities in paramacular and foveal areas. Corneal opacities (1 patient)[b]
Chern and Davis, 1993[10]	1	1	20 mg	—	36	Refractile opacities, paramacular area of left eye. Increase of deposits at 8 months; macular changes in right eye at 13 months[d]
Heier *et al.*, 1994[15]	135	2	20 mg	17.2 g (mean)	2–244	Intraretinal refractile crystals; no visual symptoms or visual loss, continued 3 month follow-up intervals

[a]This patient was reported in the 1978 study.
[b]Retinal changes persisted after discontinuation of the drug.
[c]Retinal changes regressed after discontinuation of the drug.
[d]Patient was lost to follow-up.

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Key words: Cancer, Breast, Retina, Tamoxifen.

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