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A Controlled Study of the Ocular Effects of Tamoxifen in Conventional Dosage in the Treatment of Breast Carcinoma

SIMON LONGSTAFF, HAROLD SIGURDSSON, MICHAEL O'KEEFFE, SIMON OGSTON and PAUL PREECE

Department of Ophthalmology, Surgery and Community Medicine, Ninewells Hospital, Dundee, U.K.

Abstract—*The use of tamoxifen is expanding in its application in the treatment of breast carcinoma, and proposed prophylactic use. Tamoxifen in high dosage and in some reports at conventional dosage is associated with ocular toxicity. This study in a single blind fashion examined 79 patients receiving tamoxifen for varying treatment durations at conventional dosage and 115 patients not receiving tamoxifen. No ocular toxicity was found. Further follow up studies are required to ensure no toxicity develops in patients receiving high cumulative dosage on conventional therapy.*

INTRODUCTION

THE anti-oestrogen drug, tamoxifen (Nolvadex), has been, and is currently, used for treating breast cancer in post-menopausal women. For such it has an established place as the drug of first choice in advanced breast cancer [1]. It is useful as the sole primary treatment of localized breast cancer in the elderly [2]. It has been shown to delay recurrence [3] and prolong survival [4] of post-menopausal women given it as therapy adjuvant to mastectomy performed for apparently local disease.

Use of the drug has been associated with a low incidence of side-effects, less than 3% of patients having been withdrawn from therapy due to intolerance [5].

Ocular toxicity has been noted [6] then refuted [7]. These effects were attributed to high doses of the drug [6, 8, 9] but subsequently a retinotoxic effect has claimed to follow low dosage [10].

This study aims to investigate in a controlled manner these important aspects of a valuable drug, the indications for which appear to be widening and the use of which is increasing.

MATERIALS AND METHODS

Patients attending the surgical out-patient breast clinic were invited to participate in the study.

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Correspondence and reprint requests to: Mr S. Longstaff, M.B.Ch.B. F.R.C.S.E., Department of Ophthalmalogy, Royal Hallamshire Hospital, Sheffield, U.K.
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Two groups of patients were studied: Group I, those patients who had never received tamoxifen; Group II, those patients taking tamoxifen in conventional dosage (10–20 mg two or three times daily) for varying treatment durations.

Following a full explanation of the purpose of the study, patients underwent a single ocular examination, the study was carried out in a single blind fashion, the examiner being unaware of any oral medication the patient might be taking.

Corrected visual acuity was recorded using the Snellen chart followed by central visual field red thresholds using the Friedmann visual field analyser.

Corneal sensitivity using the Cochet-Bonnet Aesthesiometer and Schirmer's test for tear production were measured.

All patients underwent slit lamp anterior segment examination and assessment of tear film break-up time (>20 s taken as normal). Lens opacities were graded as anterior or posterior subcapsular, cortical and nuclear. All patients underwent dilated full fundal examination with direct and indirect ophthalmoscopy.

Provision was made within the protocol to carry out fluorescein angiography and elecrophysiology if fundal abnormalities were noted.

RESULTS

One hundred and ninety-four patients took part in the study, 115 patients in Group I and 79 patients in Group II. Table 1 and 2 summarize the clinical staging of the two groups and the subsequent treatment.

Table 1. Breast carcinoma staging of Groups I and II

Clinical stage	Group I	Group II
I	16	6
IIa	47	34
IIb	31	24
IIIa	6	5
IIIb	9	4
IV	3	6
Pagets	2	0
Intraduct	1	0

Table 2. Additional treatment of patients in Groups I and II

Treatment	Group I	Group II
Mastectomy	92	35
Radiotherapy	5	3
Radiotherapy and mastectomy	4	2
Conservative	13	39
Microdochotomy	1	

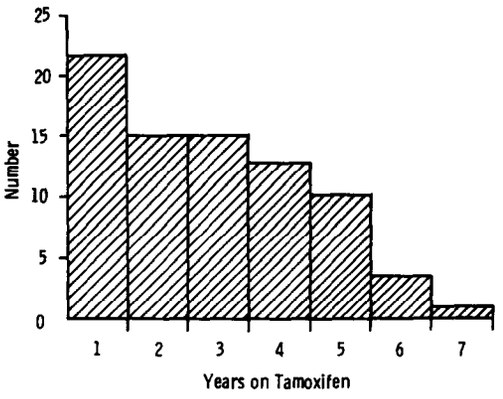

Fig. 1. Treatment duration distribution for Group II.

The average duration of tamoxifen treatment in Group II was 2 years 3 months with a maximum of 6 years 4 months. Figure 1 shows the distribution of treatment durations for the group.

The average cumulative dose of tamoxifen was 24.3 g, with a maximum of 85 g.

Table 3 shows the age distribution of the two groups. There is a significant difference in ages between Groups I and II. The average age of Group I is 57 years 6 months, that of Group II is 67 years 10 months. This follows the inclusion in Group II of a number of elderly women receiving tamoxifen as primary therapy for breast carcinoma. This age difference is adjusted for in subsequent analysis. Those patients who did not achieve corrected visual acuity of 6/9 or better had identifiable ocular causes not related to tamoxifen treatment. Table 4 summarizes the clinical findings for Groups I and II.

To account for the age differences between the two groups when analysing the results for corneal

Table 3. Age distribution of Groups I and II

	Group I		Group II	
Age	Number	%	Number	%
0 – 45	13	11.4	2	2.6
46 – 55	28	23.7	5	6.4
56 – 65	48	42.1	22	28.2
66 – 75	21	18.4	28	34.6
76 – 85	5	4.4	18	23.1
86+	0	0	4	5.1

Table 4. Ocular pathology of Groups I and II

	Group I	Group II
Lens opacities	7	14
Senile macular degeneration	3	5
Glaucoma	3	
Uveal metastases	2	

sensitivity, tear production and Friedmann central visual field red thresholds, all patients were placed in three groups. Group I — those patients not receiving tamoxifen, Group IIa — total doses of tamoxifen 0–20 g and Group IIb — total dose of tamoxifen 20–80 g.

Analysis of covariance and F test were used to assess the differences between the three groups. Calculations done using the GLIM computer program [11].

Table 5 shows mean values for each group after adjusting to age 60. Tear production measured by Schirmer test $F(2; 185) = 1.98$ ($P > 0.1$); corneal sensitivity $F(2; 183) = 1.85$ ($P > 0.1$); Friedmann central visual field red thresholds $F(2; 181) = 0.867$ ($P > 0.1$).

There was also no significant difference between the groups for tear film stability ($P > 0.1$). There was no significant difference in the incidence of lens opacities or senile macular degeneration between the groups.

DISCUSSION

The use of tamoxifen in high daily dosage (>180 mg a day) is associated with retinotoxicity and corneal changes [6, 8, 9].

The retinotoxicity is characterized by white refractile intraretinal deposits distributed mainly at the posterior pole. The retinal lesions at both light and electron microscopy level are located in the inner retinal layers, predominantly the nerve fibre layer. The lesions also have a predilection for the paramacular area and they diminish in number towards the peripheral retina [8]. In the early stages, vision may be unaffected but development of macular oedema leads to a reduction in central

Table 5. Mean values for tear production, central visual field thresholds and corneal sensitivity for Groups I and II

	Schirmer (mm in 5 min)	Friedmann (log units)	Corneal sensitivity (mm)
I	16.1	0.40	56.0
IIa	17.3	0.43	56.8
IIb	12.8	0.37	51.6
Pooled standard deviation	10.2	0.186	12.8

vision. Dyschromatopsia is also reported with no specific polarity [6, 8, 9].

Corneal changes are described as whorl like subepithelial opacities, occurring together with retinal changes [6].

A small uncontrolled study of 19 patients receiving (average treatment duration 15 months) tamoxifen in standard dosage (20 mg bd) showed no clinical ocular toxicity [7]. A further small uncontrolled study (17 patients, average treatment duration 16 months) found characteristic retinal deposits in two patients receiving 30 mg of tamoxifen daily for 9–14 months [10]. There have been further case reports suggesting tamoxifen-induced optic neuritis [12, 13] and macula oedema [14] in patients on conventional low dose regimes.

Tamoxifen is an important therapeutic agent and its use is increasing greatly, firstly as systemic adjuvant therapy in operable breast carcinoma [15–18], secondly in the treatment of benign breast disease [19, 20]; it is even being mooted as a possible agent for the prophylaxis of breast cancer [13].

With the initial success of adjuvant tamoxifen a number of studies are evaluating the use of tamoxifen out to 5 years and even proposing indefinite ingestion of tamoxifen [17, 22].

This expanded role of tamoxifen both increases the number of patients treated and the duration of treatment at conventional dosage, with high cumulative dosage expected.

Numerous papers, correspondence and editorials [19, 21, 23, 24] have drawn attention to the need for adequate toxicity studies of tamoxifen prior to its use in benign breast disease or prophylaxis.

This is the first controlled study into the potential ocular toxicity to be carried out using tamoxifen in conventional dosage. The study has demonstrated no toxic effects although no patient has received at conventional dosage levels a cumulative amount known to be associated with ocular toxicity in high dosage.

Tamoxifen is an amphiphilic cationic compound and its ability to induce a generalized intracellular lipidosis has been demonstrated [25]. Chloroquine, a drug with established ocular toxicity, is pharmalogically similar and produces a similar intracellular lipidosis [26].

Studies have demonstrated that high cumulative amounts of chloroquine cause ocular toxicity but that if the daily dose of the drug is kept low (<4 mg/kg/day) then very high cumulative doses may be given with no sight-threatening ocular toxicity [27].

It appears that in conventional dosage tamoxifen is not associated with any ocular toxicity. Further studies are required to establish that high cumulative doses are acceptable over many years as proposed in tamoxifen's use for non-neoplastic conditions, and for prophylaxis, however in view of the similarity with the pharmacology of chloroquine this would not be expected to lead to any problems.

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