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Oculoplasty

Outcome of Low Dose of Tamoxifen for Ocular Manifestations in Breast Cancer Patients

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Abstract **Original Research Article**

***Background*:** Tamoxifen, a non-steroidal triphenylethylene estrogen antagonist, serves as a crucial therapy, both alone and in conjunction with other treatments, for disseminated breast carcinomas due to its proven efficacy and minimal adverse effects in oncology. Despite its extensive use, ocular toxicity reports linked to tamoxifen remain relatively scarce in available literature. Given the limited studies in the Bangladeshi context, this investigation aims to explore ocular manifestations in breast cancer patients undergoing prolonged low-dose tamoxifen therapy for over two years. ***Methods*:** This longitudinal study was conducted at Dhaka Medical College Hospital between October 2019 and July 2020, involving 45 patients undergoing low-dose tamoxifen treatment for more than two years post-surgical intervention for breast carcinoma. Detailed patient histories were obtained, and thorough ophthalmic examinations were performed for each participant. Data were meticulously recorded in separate case files and analyzed using SPSS 22 to ensure accuracy and reliability. ***Observations and Results*:** The average age of the patients was 51.16 (±8.82) years, and 11.10% of the respondents exhibited ocular manifestations. These manifestations primarily comprised cataracts (6.70%), retinitis (2.20%), and optic neuritis (2.20%). Regarding eye-related conditions, cataracts are evident in patients 01, 02, and 03, while retinitis is observed in patients 04 and 05. Optic neuritis is specifically noted in patient 05. The data highlights occurrences of these conditions in relation to the duration of Tamoxifen treatment and the patients' ages, potentially suggesting associations worthy of further exploration regarding the impact of Tamoxifen on eye health in this demographic. ***Conclusion*:** This study revealed that approximately one-tenth of the patient cohort undergoing tamoxifen therapy for over two years experienced ocular manifestations. However, further in-depth investigations are strongly recommended to elucidate and comprehend the extent and nature of ocular complications associated with prolonged tamoxifen therapy in breast cancer patients.

Keywords: Tamoxifen, Ocular Manifestations, Breast Cancer Patients.

INTRODUCTION

Tamoxifen, a non-steroid estrogen antagonist, is a crucial therapy for disseminated breast carcinomas, notably estrogen receptor-positive cases and as adjuvant therapy post-surgery. Its mechanism involves disrupting estradiol binding to target tissues, primarily by depleting cytoplasmic receptors and competitively inhibiting receptor sites, establishing itself as the preferred hormonal therapy due to its efficacy and minimal adverse effects at standard doses of 10-20 mg twice daily. However, it's associated with systemic side effects like headaches, nausea, and minimal changes in blood cell counts, along with a notable increased risk of endometrial cancer [1-3].

Ocular manifestations linked to Tamoxifen were initially reported in high-dose cases, causing keratopathy and retinopathy. Although dosage reductions were made, retinopathy persisted even at lower doses of 20 mg/day. The prevalence of Tamoxifen-associated ocular manifestations, specifically retinopathy, ranges from 1.5% to 11.8% among breast carcinoma survivors using the standard dose over about 25 months. Detecting Tamoxifen retinopathy

photographically poses challenges due to its minute presence and potential interference from age-related fundus changes. Tamoxifen retinopathy typically involves small crystalline deposits, potentially leading to foveal cystoid spaces and subsequent macular holes, occurring at a higher rate in Tamoxifen users [4-6].

Moreover, Tamoxifen usage correlates with cataract induction, particularly posterior subcapsular cataracts, surpassing placebo groups in clinical trials. The mechanism involves blocking chloride channels in the lens, independent of estrogen receptors. Optic neuritis, although clinically evident in isolated cases, can often affect the optic nerve subclinically. Studies using scanning laser ophthalmoscopy indicate smaller optic cup dimensions in short-term middle-aged Tamoxifen users with breast carcinoma history. Corneal deposits, varying widely in prevalence from 0% to 72%, are also linked to Tamoxifen use, with the duration influencing their presence [7-10].

Tamoxifen's ocular effects, including retinopathy, cataract induction, optic neuritis, optic nerve alterations, and corneal deposits, pose considerable concerns despite its efficacy in treating breast carcinomas. The manifestation variability and potential subclinical impact emphasize the need for further research to elucidate their underlying mechanisms and devise effective monitoring strategies for patients undergoing Tamoxifen therapy.

Objective

To asses the Outcome of Low Dose of Tamoxifen for Ocular Manifestations in Breast Cancer Patients.

METHODOLOGY

Study Design: Longitudinal, single center follow-up study.

Place of Study: Department of Radiotherapy and Department of Ophthalmology, Dhaka Medical College Hospital, Dhaka.

Study Population

Patients with Breast Carcinoma taking low dose of Tamoxifen who are taking treatment for a duration of more than 2 (two) years by the department of Radiotherapy, Dhaka Medical College Hospital, Dhaka were included in this study.

Period of Study: October-2019 to July-2020.

Sampling Method: Purposive type of non-probability sampling technique was applied to enroll the patients.

Sample Size (n):

The sample size was determined by the following formula.

n= $z^2 \frac{pq}{e2}$

Here,- n- Sample size

P= expected proportion of event 6.3% = 0.063

(Prevalence of ocular manifestations in BC patient in tamoxifen is 1.5%- 11.8%

q= 1-p= 1-0.063= 0.937

Z= value of standard normal distribution = 1.96 (at 5% level of significance of 95% confidence level)

e= Acceptable error= 5%=0.05 (1% is not taken for large sample size for the place of study.

Putting the values in the equation the sample size n was estimated 90.7

As the period of study is too short so the sample size was taken 60-

Selection Criteria

Inclusion Criteria

1. Patients with Breast Carcinoma treated with low dose of Tamoxifen for a duration of more than 2(two) years post-surgically.
2. Clear refractive media without any opacity such as corneal opacity, lenticular opacity, vitreous opacity.
3. Patients with normal retinal findings in fundoscopy examination.

Exclusion Criteria

1. Patients with Breast Carcinoma taking Tamoxifen for a duration of less than 2 (two) years.
2. Patients with advanced stage of Breast Carcinoma.
3. Patients of Breast Carcinoma with any refractive media opacity.
4. Patients of Breast Carcinoma with previously diagnosed case of keratopathy, retinopathy, optic neuritis, or cataracts.

Study Procedure

Sixty patients were selected who present with Breast Carcinoma after surgery taking low dose of Tamoxifen for a duration of more than 2 (two) years in department of Radiotherapy, Dhaka Medical College Hospital, Dhaka. Detailed history of each patients were taken, including age, sex, chief complaints with duration, any history of keratopathy, retinopathy, optic neuritis, and history of cataract surgery were recorded. All patients with Breast Carcinoma underwent ophthalmic examination, including uncorrected and best spectacle corrected visual acuity by Snellen chart and near vision chart, slit lamp bio-microscopy to see eye lids, eyelashes, cornea, conjunctiva, pupil and lens, dilated fundus examination, CFP and OCT. A data sheet were filled up by interviewer by face to face interview. Laboratory data were recorded too. Collected data were checked for

errors and were analyzed using the statistical software SPSS 22.

Statistical Analysis

Data were cleaned and edited regularly. All data were processed by using SPSS program version 22. Descriptive analysis was presented by frequencies or percentages for qualitative values and mean (±SD) for quantitative values with normal distribution. After analysis, the findings were presented graphically in tables and charts.

RESULTS

The mean age of the patients was 51.16±8.82 years. Among the study subjects 04 (8.90%) were in ≤40 years age group, 16 (35.60%), 18 (40%) were in 51-60 years age group and 07 (15.60%) were in > 60 years age group.

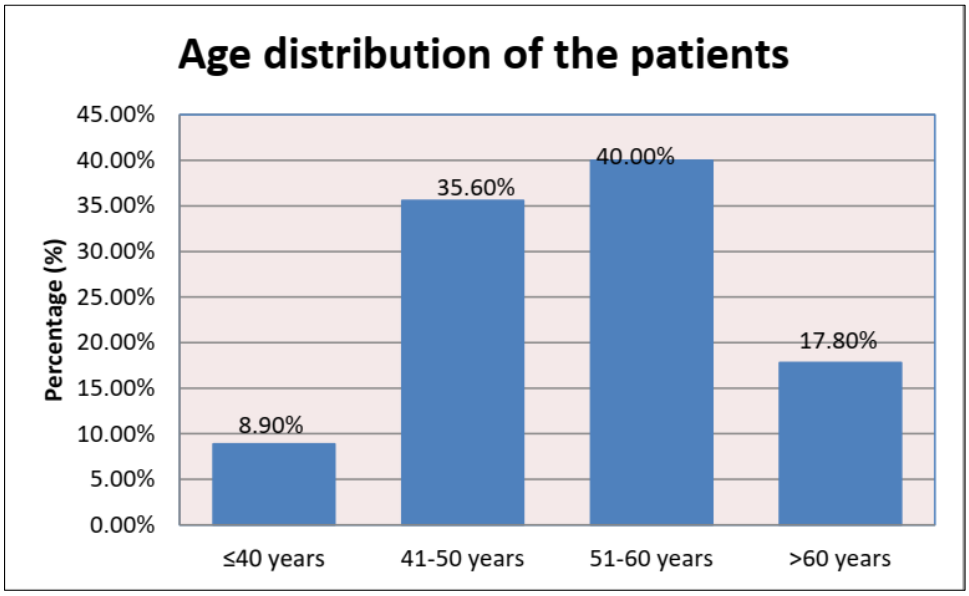

Figure 01: Age distribution of the patients (n=45).

On final follow up ocular manifestation was observed among 05 (11.10%) cases.

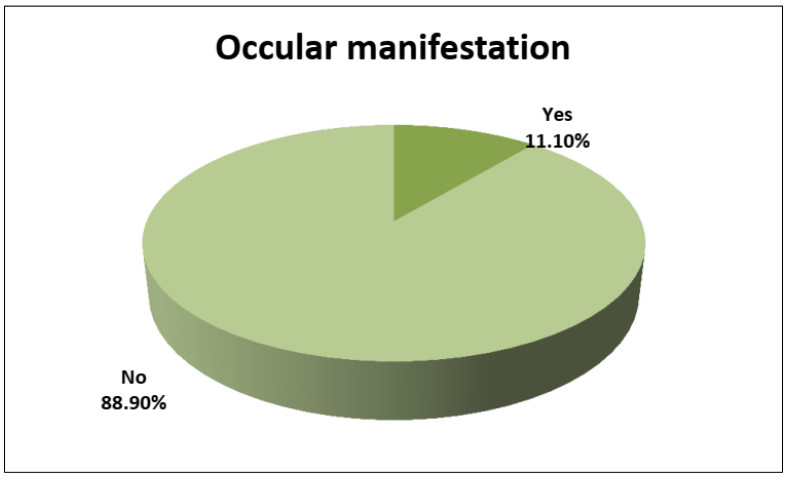

Figure 02: Prevalence of ocular manifestation among the patients (n=45).

Different ocular manifestation like cataract, retinitis and optic neuritis was observed among 03 (06.70%), 01 (02.20%) and 01 (02.20%) cases respectively.

Table I. Different ocular manifestation observed among the patients (n=45).

Ocular manifestation	Frequency (n)	Percentage (%)
Cataract	03	06.70
Retinitis	01	2.20

Optic neuritis	01	2.20

These patients, identified by serial numbers from 01 to 05, started the study between the ages of 38 and 47. Their duration on Tamoxifen spans 27 to 33 years. Regarding eye-related conditions, cataracts are evident in patients 01, 02, and 03, while retinitis is observed in patients 04 and 05. Optic neuritis is specifically noted in patient 05. The data highlights occurrences of these conditions in relation to the duration of Tamoxifen treatment and the patients' ages, potentially suggesting associations worthy of further exploration regarding the impact of Tamoxifen on eye health in this demographic.

Table II: Age and duration of Tamoxifen therapy in patients with occular manifestation.

Serial	Age of the patients (Years)	Time on Tamoxifen	Cataract	Retinitis	Optic neuritis
01	38	27	+		
02	42	30	+		
03	47	30	+		
04	44	33		+	
05	43	27			+

DISCUSSION

All of the study subjects of this study were women with a mean age of 51.16±8.82 years. Only 8.90% were in ≤ 40 years age group, maximum 40% were in 51-60 years age group, 35.60% were in 41-50 years age group and rest 17.80% were in >60 years age group. One report also found median age of their study cases 50 years and maximum of their study subjects aged between 50-59 years. 10 Study conducted by Zeeshan and colleagues found the median of their study subjects 50 years and both findings are nearly consistent to the finding of this study [11].

Maximum 26.70% of the study subjects were SSC passed followed by HSC (22.20%), primary education (17.80%), and graduation or above degree (11.10%). About 22.20% of the study subjects were illiterate. Majority (53.30%) of the study subjects were in middle socio-economic group followed by lower (28.90%) and higher (17.80%) socioeconomic group. Besides, maximum (73.30%) of them were housewife and only 13.30% were service holder. A study conducted by Gangane and associates found maximum of their study subjects housewife while 24% of them were illiterate and both finding are nearly consistent to the finding of this study [12].

Tamoxifen is a selective estrogen receptor modulator (SERM) and used as a hormonal therapy for breast carcinoma. It has mixed estrogenic and antiestrogenic activity in different tissues. In breast it has predominantly antiestrogenic effects [13]. Ocular toxicity of tamoxifen was reported by several studies since its first recognition in 1978 [14-3]. Concordant to that this study also revealed ocular manifestations among 05 (11.10%) tamoxifen using patients (using more than two years). Among these 05 cases 03 (06.70%) had developed cataract, 01 (02.20%) had developed retinitis and 01 (02.20%) had developed optic neuritis. The age of cataract developing three patients was 38, 42 and 47 years. The age of the patients having retinitis was 44 years and the age of the patients having optic neuritis was 43 years. Study conducted by Noureddin *et al*., observed ocular toxicity among their 12% cases. Noureuddin *et al*., observed cataract among their 10.77% study cases, retinopathy among their 4.62% study cases and optic neuritis among their 1.54% study cases 15 and Parkkari *et al*., observed 6.80% annual incidence of cataract among their cases and both are nearly consistent to the finding of this study.[16] Study conducted by Pavlidis *et al*., and Kaise-kapfer *et al*., also reported clear evidence of ocular toxicity following tamoxifen therapy in their respective study [16-14].

CONCLUSION

In this study, ocular manifestations was observed among one-tenth of tamoxifen using patients (using more than two years) which is consistent to other related studies. So, detailed ophthalmic evaluation in patients before starting tamoxifen therapy should be included in management plan. However, further larger study is recommended.

REFERENCE

1. Agarwal, G., & Ramakant, P. (2008). Breast cancer care in India: the current scenario and the challenges for the future. *Breast care*, *3*(1), 21-27.
2. Ashford, A. R., Donev, I., Tiwari, R. P., & Garrett, T. J. (1988). Reversible ocular toxicity related to tamoxifen therapy. *Cancer*, *61*(1), 33-35.
3. Bentley, C. R., Davies, G., & Aclimandos, W. A. (1992). Tamoxifen retinopathy: a rare but serious complication. *BMJ: British Medical Journal*, *304*(6825), 495.
4. Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185

countries. *CA: a cancer journal for clinicians*, *68*(6), 394-424.
5. Coughlin, S. S. (2019). Epidemiology of breast cancer in women. *Breast Cancer Metastasis and Drug Resistance: Challenges and Progress*, 9-29.
6. Craig, A. M., Mano, S., Johannes, B., & John, M. M. (2003). 'Tamoxifen retinopathy', *Bmj*, *327*, 7418, E77.
7. Doren, A., Vecchiola, A., Aguirre, B., & Villaseca, P. (2018). Gynecological–endocrinological aspects in women carriers of BRCA1/2 gene mutations. *Climacteric*, *21*(6), 529-535.
8. Early Breast Cancer Trialist's Collaborative Group. (1992). 'Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy', *The Lancet*, *339*(8785), 71–85.
9. Eisner, A., & Luoh, S. W. (2011). Breast cancer medications and vision: effects of treatments for early-stage disease. *Current eye research*, *36*(10), 867-885.
10. Manoharan, N., Nair, O., Shukla, N. K., & Rath, G. K. (2017). Descriptive epidemiology of female breast cancer in Delhi, India. *Asian Pacific journal of cancer prevention: APJCP*, *18*(4), 1015.
11. Zeeshan, S., Ali, B., Ahmad, K., Chagpar, A. B., & Sattar, A. K. (2019). Clinicopathological features of young versus older patients with breast cancer at a single Pakistani institution and a comparison with a national US database. *Journal of global oncology*, *5*, 1-6.
12. Gangane, N., Khairkar, P., Hurtig, A. K., & San Sebastián, M. (2017). Quality of life determinants in breast cancer patients in central rural India. *Asian Pacific journal of cancer prevention: APJCP*, *18*(12), 3325.
13. Jacobs, MCFTF (2020). Tamoxifen. https://www.ncbi.nlm.nih.gov/books/NBK532905/.
14. Kaiser-Kupfer, M. I., Kupfer, C., & Rodrigues, M. M. (1981). 1. Tamoxifen retinopathy: a clinicopathologic report. *Ophthalmology*, *88*(1), 89-93.
15. Noureddin, B. N., Seoud, M., Bashshur, Z., Salem, Z., Shamseddin, A., & Khalil, A. (1999). Ocular toxicity in low-dose tamoxifen: a prospective study. *Eye*, *13*(6), 729-733.
16. Parkkari, M., Paakkala, A. M., Salminen, L., Holli, K., & Finnish Breast Cancer Group (FBCG). (2003). Ocular side-effects in breast cancer patients treated with tamoxifen and toremifene: a randomized follow-up study. *Acta Ophthalmologica Scandinavica*, *81*(5), 495-499.