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Effectiveness of Low-Dose Tamoxifen for Managing Ocular Manifestations in Breast Cancer Patients

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Abstract **Original Research Article**

Background: Breast cancer remains one of the most common malignancies worldwide, with hormonal therapies like tamoxifen significantly improving survival rates in hormone receptor-positive cases. However, tamoxifen's systemic effects can lead to adverse outcomes, including ocular manifestations such as cataracts, retinopathy, and optic neuritis. These complications, although rare, may impact quality of life, prompting a focus on low-dose tamoxifen to mitigate risks while preserving efficacy. ***Objective:*** This study evaluates the ocular outcomes of low-dose tamoxifen in breast cancer patients, aiming to explore its safety and implications for long-term therapy. ***Methods:*** A longitudinal study was conducted at Dhaka Medical College Hospital between October 2019 and July 2020. Sixty breast cancer patients treated with low-dose tamoxifen for more than two years were evaluated through detailed ophthalmic examinations, including visual acuity tests, slit lamp biomicroscopy, color fundus photography (CFP), and optical coherence tomography (OCT). Data were analyzed using SPSS software. ***Results:*** Among the participants, 11.1% (n=5) exhibited ocular manifestations, including cataracts (6.7%), retinitis (2.2%), and optic neuritis (2.2%). These complications were associated with extended tamoxifen therapy (27–33 months). The findings suggest a correlation between prolonged tamoxifen use and ocular toxicity, although the prevalence was relatively low. ***Conclusion:*** Low-dose tamoxifen was associated with minimal ocular side effects, supporting its viability as a safer alternative for long-term therapy in breast cancer patients. Comprehensive ophthalmic evaluation before and during treatment is recommended to ensure early detection and management of potential complications.

Keywords: Breast cancer, tamoxifen, low-dose therapy, ocular manifestations, cataracts, retinitis, optic neuritis.

INTRODUCTION

Breast cancer remains one of the most prevalent malignancies worldwide, significantly impacting women's health. The use of hormonal therapies, particularly tamoxifen, has revolutionized the management of hormone receptor-positive breast cancer by reducing the risk of recurrence and improving survival rates [1-2]. Tamoxifen, a selective estrogen receptor modulator (SERM), exhibits its therapeutic effects by blocking estrogen's influence on breast tissue, a key driver of tumor growth. However, its systemic actions extend beyond the breast, leading to both therapeutic benefits and potential adverse effects in various tissues, including the eyes [3].

Ocular side effects of tamoxifen, though less common than other adverse events, can significantly affect a patient's quality of life. These side effects may include keratopathy, retinopathy, and lens opacities. Such complications have raised concerns about the long-term use of tamoxifen, particularly in high doses. While these manifestations are generally considered rare, their potential severity underscores the importance of exploring safer dosing strategies without compromising the drug's efficacy [4-7].

Recent studies have shifted focus toward the use of low-dose tamoxifen as an alternative approach to maintain therapeutic efficacy while minimizing adverse effects. This dosage adjustment has demonstrated promising results in reducing systemic and ocular toxicities. For breast cancer patients prone to ocular complications or those already presenting with mild symptoms, the adoption of a lower tamoxifen dose could serve as a viable strategy to enhance treatment tolerability [8-10].

The interplay between tamoxifen dosage and ocular health remains an area of active investigation.

Understanding the mechanisms through which tamoxifen induces ocular changes is essential for refining dosing strategies and optimizing patient outcomes. Such insights are crucial for balancing the dual objectives of achieving effective breast cancer control and preserving patients' quality of life.

Objective

This study aims to evaluate the outcomes of low-dose tamoxifen therapy in breast cancer patients with a focus on its ocular manifestations. By examining clinical data and patient-reported experiences, we seek to provide evidence-based recommendations for incorporating low-dose tamoxifen into treatment regimens.

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.

Variables:

i. Demographic variables
   1. Age
   2. Sex
   3. Occupation
   4. Educational status
   5. Socio-economic status

ii. Clinical variables
   1. Visual acquity
   2. Slit lamp bio-microscopy
   3. Ant-segment photograph
   4. Tonometry
   5. Post-segment
   6. Color Fundus Photograph
   7. OCT

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.

Ethical Implications

The following points were considered during the study-

1. Patients (subjects) and key relatives were clearly informed about the scope and limitations of the study.
2. Written consent was obtained from the patients (subjects).
3. Confidentiality of the patients about personal information was strictly maintained.
4. The study did cause any physical, mental, financial or social harm to patients. If any problem would arise during study, hospital was responsible to manage.
5. The study did not interfere his/her current treatment.
6. Ethical clearance was sought from ethical review committee.

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.

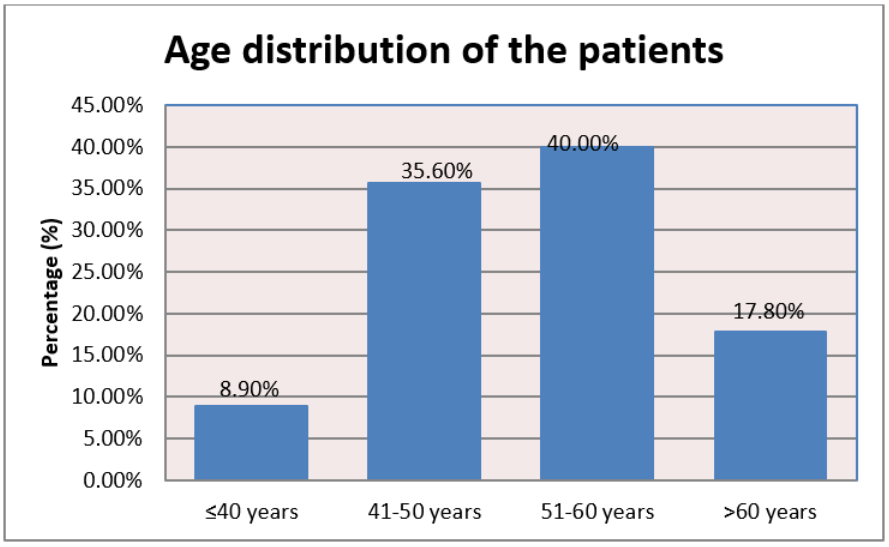

Figure 1: Age distribution of the patients (n=45).

Among the study subjects 10 (22.20%) had stage I tumour, 21 (46.70%) had stage II tumour, 13 (28.90%) had stage III tumour and 01 (2.20%) had stage IV tumour.

Table I: Stage of the breast cancer (n=45)

Stage of the breast cancer	Number	Percentage
Stage I	10	22.20
Stage II	21	46.70
Stage III	13	28.90
Stage IV	01	2.20

Among the study subjects 24 (53.30%) underwent mastectomy and 21 (46.70%) underwent segmental resection.

Table II: Primary treatment of the patients (n=45)

Primary treatment	Frequency (n)	Percentage (%)
Mastectomy	24	53.30
Segmental resection	21	46.70

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

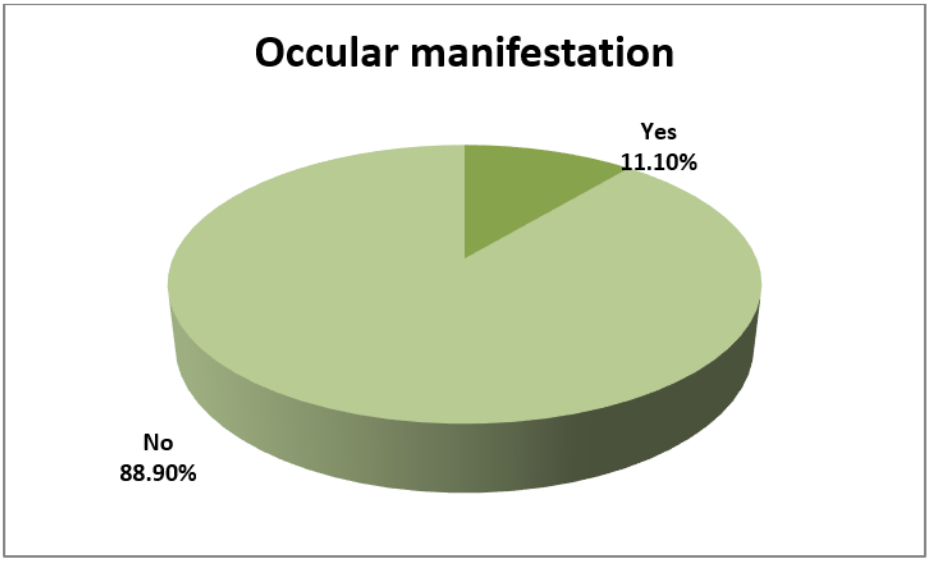

Figure 2: Prevalence of ocular manifestation among the patients (n=45)

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 III: 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

The analysis of ocular manifestations in breast cancer patients on tamoxifen therapy, as summarized in Table IV, reveals a pattern associated with age and duration of treatment. Among the five patients studied, cataracts were observed in three individuals aged 38, 42, and 47 years, all of whom had been on tamoxifen for 27 to 30 months. Retinitis was identified in one patient aged 44 years, after 33 months of therapy, while optic neuritis was reported in one patient aged 43 years, following 27 months of treatment. These findings suggest a correlation between the duration of tamoxifen use and the onset of ocular complications, emphasizing the need for vigilant monitoring, particularly in patients undergoing long-term therapy.

Table IV: 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

Breast cancer is the most prevalent cancer in women which increasing alarmingly both in developing and developed world with an estimated 1.8 million new cases in 2013 [7]. It is estimated that, in 2018, 627,000 women were died worldwide due to breast cancer which is nearly 15% of all cancer mortality in women [8]. Different surgical approach including mastectomy and segmental resection followed by radiotherapy and chemotherapy are the mainstream of treatment of breast carcinoma [9]. Tamoxifen is a widely used chemotherapeutic agent for breast carcinoma which has some unavoidable adverse effects on patients overall wellbeing [10]. This study was aimed to find out the ocular effects in Breast Carcinoma patients treated with low dose of Tamoxifen for a long duration.

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. Other study also found median age of their study cases 50 years and maximum of their study subjects aged between 50-59 years [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.

Maximum (46.70%) of the study subjects of this study had grade II cancer followed by stage III (28.90%), stage I (22.20%) and stage IV (02.20%) cancer. And maximum (53.30%) of them underwent mastectomy and rest 46.70% underwent segmental resection. A study also found maximum of their breast carcinoma cases in stage II [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. Ocular toxicity of tamoxifen was reported by several studies since its first recognition in 1978 [13]. Concordant to that this study also revealed ocular manifestations among 05 (11.10%) tamoxifen using patients (using more than two years). Among this 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. A study observed cataract among their 10.77% study cases, retinopathy among their 4.62% study cases and optic neuritis among their 1.54% study cases [14].

The mechanism of Tamoxifen associated ocular toxicity is unresolved. But this ocular manifestation may be due to blockage of swelling-activated chloride channel in the lens and the interfering in the lipid catabolism by tamoxifen in eye [15]. Tamoxifen has structure similarity with chloroquine, chlorpromazine, amiodarone, and triparanol. Some of these compound form tight reversible bond with lipids causing accumulation of drug-lipid complexes in lysosomes [16]. These drugs have hydrophobic moietry and a positively charged side chain with hydrophilic characteristics (this amphiphilic nature of this drug allows binding with polar lipids and interfering its metabolism) [17].

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.

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