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Original Research Article

Tamoxifen treatment and its outcome in breast cancer patients at a hospital-based cancer registry in Kerala

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ABSTRACT

Background: Endocrine therapy for breast cancer is directed at reducing oestrogen synthesis or alternatively blocking oestrogen receptors (ER) in tumour-sensitive tumors. Despite side effects, the use of systemic adjuvant therapy after local management of breast cancer substantially improves survival and reduces the risk of relapse. The study objective was to assess the recurrence of breast cancer and the complications seen in breast cancer patients on tamoxifen therapy at a hospital-based cancer registry, Thrissur, Kerala.
Methods: After obtaining institutional ethical clearance, included 75 patients of histologically diagnosed breast carcinoma currently on tamoxifen, diagnosed in the year of 2016. Data was obtained from the patient files and by personal intimation.
Results: Of the 75 patients on tamoxifen, four (5.33%) patients had history of recurrence. 22.6% of patients on tamoxifen were noted to have increased endometrial thickness. Other side effects noted were weight gain, TIA, bone pain and vaginal discharge.
Conclusions: It was found that the recurrence rate at three years for the study population was 5.33%. More studies from developing countries, with larger sample size and clinical trials will give us more accurate information regarding the efficacy of the drug.

Keywords: Breast cancer, Tamoxifen, Hospital based cancer registry, Kerala

INTRODUCTION

Breast cancer is a hormone-dependent malignant proliferation of epithelial cells lining the ducts or lobules of the breast.[1] Breast cancer is usually treated through a combined approach including surgery, chemotherapy, radiotherapy and hormone therapy. The use of systemic adjuvant therapy subsequent to local management of breast cancer markedly improves survival and reduces the risk of relapse.[1]

Many human breast cancers are shown to possess a multitude of receptors and methods have been developed to measure the hormone receptors in tumor specimens. Hormone therapy has been indicated in estrogen receptor/ progesterone receptor (PR) positive patients in all age groups; its advantages being that it's easy to administer, patient compliance can be assured and that it's relatively safe to use.[2]

The likelihood of a tumour responding to endocrine manipulation is increased by the type of hormone receptors present. Studies show that the presence of both ER and PR receptors improves the chance of response up to approximately 75% but unfortunately only 35% of patients have both ER, PR positive tumors. It has also been seen that about 55-60% of patients whose tumor contains ERs will respond to hormone therapy as opposed

to less than 5% for those with no receptor.[3,4] It is now generally agreed that tumors lacking ERs recur earlier than those possessing ERs.[5,6]

With this knowledge, the oncologist should be able to carefully select or reject endocrine therapy for a patient after noting available clinical prognostic factors such as menopausal status, site of primary lesion, disease-free interval and especially, response to previous hormonal therapies.[4]

Hormone therapy gives prophylaxis against carcinoma of opposite breast and is also useful in metastatic breast carcinomas. Hormone therapy includes the following modalities-ER antagonists, Oral aromatase inhibitors, PR antagonists, Androgens, Luteinizing hormone releasing hormone agonists, Aminoglutethimide Progestogens, Bilateral oophorectomy, Adrenalectomy and Hypophysectomy.[7]

Tamoxifen is the most commonly prescribed drug as the systemic adjuvant therapy of breast cancer. The drug is a non-steroidal antiestrogen that binds to ER and displays both estrogen-antagonist as well as estrogen-agonist properties. It exerts it's chief antiestrogenic effects by competitively blocking the binding of estrogen to ER. The net result is a blockade of cell cycle transit in G_1 phase, a slight increase in cell loss and inhibition of tumor growth. A reduction in serum insulin-like growth factor (IGF-1) concentration and an increase in IGF-binding protein levels acts as another mechanism for tumor growth inhibition.[8]

Some evidence suggests that duration of tamoxifen treatment may influence response by menopausal status and that prolonged treatment for 5 years or more may add to the benefit in premenopausal women. Indirect comparison of trials with different tamoxifen durations suggest that tamoxifen taken for longer than two years is superior to tamoxifen taken for two years or less in premenopausal but not postmenopausal women.[9]

The meta-analysis of the National surgical adjuvant breast and bowel project (NSABP) trial B14 which was a trial focused on patients on adjuvant tamoxifen with histologically negative axillary nodes, suggests that the benefit with adjuvant tamoxifen is similar for both node-negative and node-positive patients. The reduction in the annual odds of recurrence was 26±4% for node-negative patients and 28±2% for node-positive patients .[10] The Nolvadex adjuvant trial organization (NATO) trial measure ER on a proportion of their patients and this study found a correlation between the histologic grade, which can be thought of as a surrogate marker for ER status and tamoxifen response. Patients with grade 1 and 2 tumors, which are more likely ER-positive, benefitted from tamoxifen, whereas those with grade 3 tumors did not.[11]

On literature, the side-effects usually associated with tamoxifen therapy are hot flushes, tachycardia, bone pain, weight gain, genitourinary abnormalities and thromboembolic events. Tamoxifen has been shown to increase the endometrial thickness and predispose to endometrial carcinoma, so patients must be examined for pre-existing endometrial carcinoma before initiating tamoxifen. Tamoxifen does not prevent the growth of endometrial tumours. History of spotting and vaginal bleeding in postmenopausal patients taking tamoxifen should be followed up with a thorough gynaecological examination with ultrasonography. The incidence rate of endometrial cancer for tamoxifen-treated patients is 2/1000 patients per year. More than 80% of detected endometrial tumours are stage 1 disease and can be cured by hysterectomy.[12]

The efficiency and adverse effects of tamoxifen has been studied only to a limited extent in South India. Cconducted a research with the objective to assess the recurrence of breast cancer and the complications seen in breast cancer patients on tamoxifen therapy at a hospital-based cancer registry in Thrissur, Kerala.

Tamoxifen intake showed a good outcome in Indian women in most ER/PR positive breast cancers, irrespective of menopausal and nodal status, with negligible adverse effects.

METHODS

A retrospective cohort study was conducted at Amala Institute of Medical Sciences-a hospital-based cancer registry centre in Thrissur District, Kerala from June-2019 to December-2019. Histopathology registry was used as the source for data retrieval in the current study. All breast cancer cases diagnosed histopathologically in the year 2016 has been included in the study, which was 202 cases. A sub cohort was formed among them, which was 75 cases who were on tamoxifen and these 75 patients were followed up. After obtaining institutional ethical board approval (REF. No: 25/IEC/19/ AIMS - 6), data was collected from hospital records, on patient demographics, treatment modalities taken, characters of the tumour, history of recurrence and metastasis and the time period for which each patient had received tamoxifen. The patients who had received tamoxifen 20 mg daily anytime during their follow up period were included in the study. Follow up intervals were noted for all patients. Commonly reported side effects like, hot flushes, vaginal discharge, bone pain and other genitourinary symptoms were looked for in every patient. Ultrasonography (abdominal/transvaginal) findings in case records, and any change-over to another drug or default in the intake of the drug was noted. Patients who might have developed uterine malignancy, deep vein thrombosis, other adverse effects were looked for. Current status of the patient was obtained after directly contacting the patient/care-giver and taking their

approval. The data collected was entered in Microsoft excel and analysed using SPSS version 23 software.

RESULTS

The hospital records containing IHC reports and biopsy report of 202 breast cancer patients who presented to this hospital in the year 2016 was obtained, and among them, 75 patients who were on tamoxifen were selected as the sample population, which included patients from 10 districts of Kerala, India. Mean age of the study population was 52.8±8.9 years. Majority were in the age group 46-55 (38%). The age distribution of the study population is depicted in table 1. 74 cases in our study were females (98.67%) and one was a male (1.33%).

Table 2 depicts the menopausal status, grade at diagnosis, histological subtype and nodal status of the study population. Out of 74 female patients, 47 (63.5%) were post-menopausal. Out of 75 cases, 58 (77.3%) were diagnosed at grade II. 71 (94.6%) of the cases were invasive breast carcinoma and regarding the nodal status 35 (46.6%) were node negative and 40 (53.3%) were node positive.

The correlation between the receptor statuses and history of recurrence of breast cancer and metastasis after taking tamoxifen is depicted in table 3. The results show that a greater number of recurrences were seen in ER/PR negative tumors as opposed to ER/PR positive tumors, which was expected since tamoxifen primarily works on ER and tumors. History of metastasis of tumors after taking tamoxifen were seen in both ER/PR positive and negative tumors, but the incidence was lesser in ER/PR positive tumors.

75 patients, four (5.33%) patients who were on tamoxifen gives history of recurrence after taking tamoxifen and ten (13.33%) patients gives history of metastasis after taking tamoxifen.

After correlating with the duration of treatment, most cases of recurrence and metastasis were seen to occur within the first three years of taking the treatment.

Adverse effects of tamoxifen according to literature, were surveyed and recorded and is depicted in figure 1. The most common side effect was an increase in endometrial thickness seen in 17 (22.6%) of patients. Other adverse effects seen were weight gain, flushing, tachycardia, thromboembolic events and vaginal discharge. No cases of endometrial cancer were seen. 12 (16%) of the patients were shifted from tamoxifen to letrozole after experiencing adverse effects.

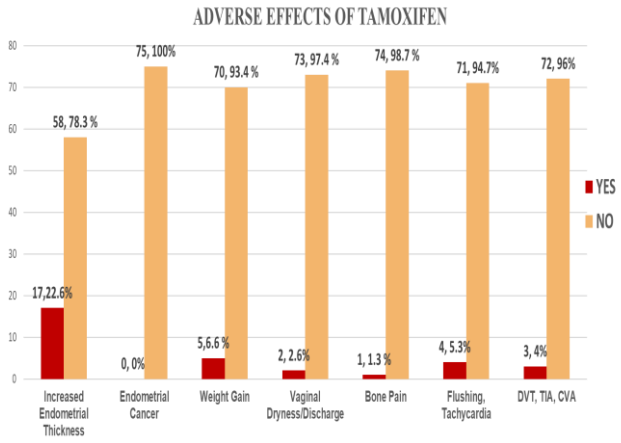

Figure 1: Adverse effects seen after taking tamoxifen (n=75).

Table 1: Demographic details of study population (n=75).

Age (years)	Frequency	Percentage (%)
≤45	18	24.0
46-55	29	38.67
56-65	23	30.67
≥65	5	6.67

Table 2: Clinical findings of patients on tamoxifen (n=75).

Variables	Categories	Frequency	Percentage (%)
Menopausal status	Pre-menopausal	28	37.3
	Post-menopausal	47	62.6
Grade at diagnosis	Grade I	8	10.6
	Grade II	58	77.3
	Grade III	9	12.0
Histological subtype	Invasive ductal carcinoma	71	94.6
	Lobular carcinoma in situ	1	1.3
	Mucinous carcinoma	3	4.0
Nodal status	Node-positive	35	46.6
	Node-negative	40	53.3

Table 3: History of recurrence and metastasis after taking tamoxifen (n=75).

	Frequency	Percentage (%)
History of recurrence		
Yes	4	5.33
No	71	94.67
History of metastasis		
Yes	10	13.33
No	65	86.67

Table 4: Correlation between receptor status and history of recurrence and metastasis (n=75).

Immunohistochemistry	No. of patients on tamoxifen (%)	No. with history of recurrence of breast cancer	No. with history of metastasis
ER-PR-Her 2+	16 (21.33)	2	2
ER-PR-Her 2 (2+)	7 (9.33)	1	2
ER-PR-Her 2+	4 (5.33)	-	1
ER-PR-Her 2(2+)	2 (2.66)	-	-
ER-PR-Her 2-	34 (45.33)	-	3
ER-PR-Her 2-	7 (9.33)	-	1
ER-PR-Her 2+	2 (2.66)	1	1
ER-PR-Her 2+	1 (1.33)	-	-
ERPR- Her2 (2+)	2 (2.66)	-	-
Total	75 (100.0)	4	10

*2+ → Equivocal status; additional investigations required

DISCUSSION

Major trials regarding efficiency of tamoxifen in combination with other treatment modalities have been mostly done abroad, the most famous being the NSABP B-14 trial in United States and the Royal Marsden trial in London.[10,11] These were incidence rate studies wherein tamoxifen was given prophylactically to determine the incidence of primary breast cancer after taking tamoxifen as opposed to our study where recurrence rate was calculated in patients who already had a history of breast cancer.

In this study, 5.33% of recurrence was seen in patients who were on tamoxifen and undergoing other treatment modalities. A higher incidence was seen in ER/PR negative tumours as opposed to ER/PR positive tumours.

The adverse effects of patients on tamoxifen have been studied in the Royal Marsden trial that took place in London and in Kolkata by Ashraf and Biswas.[11,13]

Studies reports that 50% of women experience hot flashes as the most prominent side effect .[15,16] Did not find hot flashes to be the most common adverse effect of tamoxifen treatment. The most common adverse effect seen in our study was an increase in endometrial thickness in 22.6% of the patients. A similar result was obtained in a study done in Kolkata by Ashraf and Biswas, where 36.6% of the sample population were seen to have an increase in endometrial thickness. In the Royal Marsden trial done in London, the most common adverse effect recorded were flushing and tachycardia seen in 48.3% of the sample population. The second most common adverse effect seen in our population was weight gain (6.6%), but this cannot be solely attributed to the intake of tamoxifen, as weight gain can be caused due to lifestyle, comorbidities present and due to other drugs being taken.

As far as adverse effects are concerned, Indian women, seem to tolerate tamoxifen in a better way, as compared to western women. The number of women <30 years age is substantially higher in Indian subcontinent than the west (25 vs 10%), and as such, tamoxifen remains to play a major role in the management of these patients .[17] It is difficult to draw definite conclusions regarding the safety of tamoxifen, given the retrospective nature of this study. However, based on our data, it appears that tamoxifen does not lead to high rate of endometrial carcinoma in southern Indian women and a prospective study is needed to confirm the findings. Also, since the patients routinely take ultrasound scans during follow-ups, any change in the endometrial thickness are detected quickly and the drug can be changed as needed as seen in 16% of the patients in this study.

CONCLUSION

Out of 75 patients on tamoxifen and undergoing other treatment modalities, four patients were seen to have a recurrence of breast cancer, most being ER/PR negative in immunohistochemistry. Recurrence rate among the study population was 5.33%. This result is important

since previous studies have focused on the incidence rate of breast cancer after starting Tamoxifen as opposed to the recurrence rate of breast cancer in a patient who's taking tamoxifen as a local adjuvant therapy. The most common adverse effect noted on taking tamoxifen was increase in endometrial thickness, seen in 22.6% of the patients. Other adverse effects noted were weight gain, bone pain, thromboembolic incidents, vaginal dryness/discharge and flushing. No incidence of endometrial cancer has been recorded. Tamoxifen appears to be a generally safe drug for Indian women with breast cancer, with an acceptable side effect profile that can be easily monitored, as compared to that for western population and can be easily administered by medical personnel with minimal training and experience.

Target-oriented research is needed to identify the optimal methods for delivering chemotherapeutic drugs and tamoxifen. Clinical research on the definition of optimal duration of treatment and known adverse effects and their incidence is still required. More research can be done regarding the use of tamoxifen in Indian population. Newer agents such as raloxifene and aromatase inhibitors need to be evaluated.

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