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Original Research Article

Effect of Anastrozole for Breast Cancer Prevention

Abhijeet Ramesh Dhawale

MD, Pathology, Associate Professor, Vedantaa Institute of Medical Sciences, Saswand, Dahanu(Palghar) Maharashtra

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Corresponding author: Abhijeet Ramesh Dhawale
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Abstract

Introduction: Breast cancer is quite prevalent in India with 25.8 per 100,000 women and mortality 12.7 per 100,000 women. In India, there are several factors that cause increase of the cancer incidence which also includes environmental factors. Delayed visit to the hospital results in increase mortality rate. There is epidemiological and pathophysiological evidence that the breast cancer is vulnerable in post-menopausal females.

Aims and Objectives: The study intends to find the preventive efficacy of anastrozole in females with high risk of breast cancer.

Materials and Methods: The study derived 100 patients who are of high risk individuals and randomly classified them into 2 groups, of which one of them was given anastrozole and another was given placebo. This treatment phase went on for 3 years and after that, histological examination evaluated the presence of breast cancer and its type and also studied the adverse effects in both the groups. Hazard Ratio was determined and Fisher exact test was employed for effective statistical analysis.

Results: The study has found that there significant difference ($p<0.05$) between anastrozole and placebo group in terms of getting invasive type of carcinoma in which the placebo group is significantly more vulnerable to be affected by breast carcinoma as compared to the patients who received anastrozole for 3 years.

Conclusion: The study concluded that there is preventive effect of anastrozole treatment in breast cancer among high risk post-menopausal females. The effect of anastrozole, specially in Invasive estrogen receptor-positive type, is significant as compared to the placebo.

Keywords: Anastrozole, Breast Carcinoma, Breast Cancer Prevention, Estrogen Receptor-Positive.

Introduction

With an estimated 1.67 million new cancer cases identified in 2012, breast cancer is the most prevalent cancer in women worldwide, accounting for almost a quarter (25%) of all cancer cases. In comparison to more developed locations (794 000), women from less developed areas (883 000 instances) had a small number of cases [1]. Although India's age-adjusted incidence rate of breast cancer is lower than the United Kingdom's (95 per 100 000), its mortality rate is comparable to the United Kingdom (12.7 vs. 17.1 per 100 000) [2]. According to international and Indian studies [3–7], the incidence of cancer, as well as cancer-related morbidity and death, has significantly increased in the Indian subcontinent. Although cervical cancer continues to be the most prevalent cancer in rural India, breast cancer

incidence has exceeded cervical cancer in recent years and is now the primary cause of cancer mortality [8].

For incidence and mortality rates, data reports from the most recent national cancer registries were compared. It was discovered that Delhi had the highest age-adjusted incidence rate of breast cancer at 41 per 100,000 women, followed by Chennai (37.9), Bangalore (34.4), and Thiruvananthapuram District (33.7) [9]. All of the PBCRs, including Bangalore (annual percentage change: 2.84%), Barshi (1.87%), Bhopal (2.00%), Chennai (2.44%), Delhi (1.44%), and Mumbai (1.42%), showed a statistically significant rise in age-adjusted rates over the study period (1982-2014). In rural registries, the mortality-to-incidence ratio reached a maximum of 66, while it was only 8 in urban registries [10]. In addition, it has been discovered that young age is a significant risk factor for breast cancer in Indian women [11]. According to projections, there could be 1797900 cases of breast cancer in India by the year 2020. A more favorable and optimistic clinical picture would result across the nation if breast cancer screening programs and treatment facilities were more readily available [12].

The incidence and death of breast cancer are growing across all PBCRs in India, mostly as a result of the country's fast urbanization, industrialization, population increase, and aging population [13]. In India, factors such as marital status, geographic region (urban/rural), BMI, breast-feeding, waist-to-hip ratio, low parity, obesity, alcohol consumption, tobacco chewing, smoking, lack of exercise, diet, and environmental factors were major risk factors that contributed to an increase in cancer incidence; however, the cause of the high incidence of breast cancer in younger women is unknown [14]. In some places of India, delayed disease presentation caused by illiteracy, a lack of awareness, and financial constraints result in late diagnosis, which therefore raises the death rate [15].

The disadvantages causing an increase in breast cancer incidence also include a lack of coordinated programs for breast cancer screening, a lack of diagnostic tools, and a general disregard for the health of women in the mostly patriarchal Indian society. The majority of patients in this location are therefore still receiving treatment at locally progressed and metastatic stages [16].

The majority of breast tumors express the estrogen receptor and are growth-dependent on estradiol (E2). Utilizing either aromatase inhibitors (AI), which prevent the aromatase-dependent synthesis of E2, or selective estrogen receptor modulators (SERM), which prevent the binding of E2 to its receptor (ER), hormonal therapy seeks to prevent estrogen signaling. Patients who are premenopausal or postmenopausal should take SERMs, whereas postmenopausal patients should only take AIs. The SERM Tamoxifen has been the "gold standard" for treating hormone receptor-positive breast tumors for the past 20 years. Third-generation AIs like anastrozole, which show better efficacy in the adjuvant environment in numerous recently reported trials [17], are increasingly challenging the role of tamoxifen.

Mechanisms of Action of Anastrozole

Depending on its makeup and mode of operation, artificial intelligence is categorized as type-I or type-II. Exemestane is an example of a type-I inhibitor, while type-II inhibitors are non-steroidal substances (such as letrozole and anastrozole). Both classes of medications work by imitating androgens to prevent aromatase from interacting with the enzyme. When type-I inhibitors create covalent connections with the aromatase, the enzyme is permanently inhibited and can only be recovered by producing new aromatase. [18] Type-II inhibitors, on the other hand, are rival inhibitors. An

example is the benzyltriazole derivative anastrozole (2,2-[5-(1H-1,2,4-triazol-1ylmethyl)-1,3-phenylene]-bis(2-methyl-propiononitrile)), which binds reversibly to the heme iron of the aromatase enzyme and inhibits it from functioning. As a result of this reversible interaction with the enzyme, anastrozole needs to be present continuously to block aromatase [18].

Materials and Methods

Study Design

This is a prospective Randomized Control Trial (RCT) which was conducted during the period of November 2021 to October 2022. The study has considered post-menopausal patients aged from 45 years to 70 years old who can be considered under high risk individuals for breast cancer. After final inclusion of these patients, they were assigned randomly to two groups. One group was planned to receive oral anastrozole at the dosage of 1 mg per day and another group was planned to receive placebo daily for 3 years. After the treatment phase, data was collected regarding the outcomes like incidence of breast cancer among the whole study population, death, major adverse occurrences like fractures, cardiovascular events. The occurrence of breast cancer was the primary outcome, as considered by this study.

Sampling and Data Management

The patients were considered according to the inclusion and exclusion criteria. At the beginning of the study, the demographic details of the patients were obtained from the patients while taking their history. Then they were randomly assigned to any of the groups and after 3 years of treatment, they underwent Fine Needle Aspiration Cytology (FNAC) for histological evaluation of the breast tissue. Further classification was also done by the histological examination. Other examinations were also carried out including blood examination and X-ray to evaluate the cardiovascular consequences and presence of fractures, respectively. The evaluation of the outcome of this study was based on the results of these diagnosis. The study finally considered 100 patients for evaluation and the number of patients maintained in the anastrozole group and control group was maintained at 1:1.

Inclusion and Exclusion Criteria

The post-menopausal female patients from the outpatient department of our hospital who visited for breast cancer screening and can be classified as high risk individuals were considered for this study. The patients aged between 45 years and 70 years old were included. The included patients also needed to cooperate with the whole study process.

The patients who had breast cancer previously, those who are current users of tamoxifen or raloxifen or used previously, those who had scheduled mastectomy prophylactically, were excluded. The patients who did not complete or left the study process in the middle, were also excluded. After applying inclusion and exclusion criteria, the study considered 100 patients.

Ethical Approval

The authors explained the study process and intention to each patient clearly and written consent was obtained from each patient. The study was conducted according to the Declaration of Helsinki (World Medical Association).

Statistical Analysis

The study used SPSS 25 and excel software to conduct the statistical analysis and other calculation, respectively. Analysis of the outcome were evaluated by using Hazard Ratio which was determined by Cox Proportional Hazard models with corresponding 95% confidence interval. The significance was determined by Fisher Exact test. The descriptive measurements were expressed as

mean±standarddeviation. The level of significance was considered as α=0.05.

Results

The study has summarized the findings of baseline characteristics in each group (anastrozole and placebo). These baseline characteristics were obtained at the beginning of the study. Table 1 gives the detailed findings in each group.

Table 1: The baseline characteristics in each group before the study

Characteristic	Anastrozole group N = 50	Placebo group N = 50
Age (years)	66.2±12.67	67.58±12.85
Body Mass Index (BMI)	24.9±2.1	25.1±1.8
Family history of breast cancer	25	26
Presence of bone weakness	0	0
Abnormal Mammography	0	0
Chronic condition present		
Diabetes	4	5
Cardiovascular	6	5
Neurological	1	1
Respiratory	3	2

After 3 years of treatment (either with anastrozole or placebo), FNAC was conducted again on all the patients and finding the confirmed histological presence of breast cancer. Both the invasive and non-invasive types were considered. Table 2 shows the outcomes that are found in this study after 3 years of treatment and Hazard Ratio which was determined for the assessment of the study. The study has found that there significant difference (p<0.05) between anastrozole and placebo group in terms of getting invasive type of carcinoma in which the placebo group is significantly more vulnerable to be affected by breast carcinoma as compared to the patients who received anastrozole for 3 years.

Table 2: The outcomes of the study in each group after 3 years of anastrozole treatment and Hazard Ratio between the patients received anastrazole and those who received placebo

Outcome	Anastrozole group N = 50	Placebo group N = 50	Hazard Ratio*	*p*-value
Invasive estrogen receptor-positive	12 (24)	36 (72)	0.41±0.12	p<0.05
All ductal type (Carcinoma in-situ)	6 (12)	11	0.28±0.4	0.017

*95% Confidence Interval

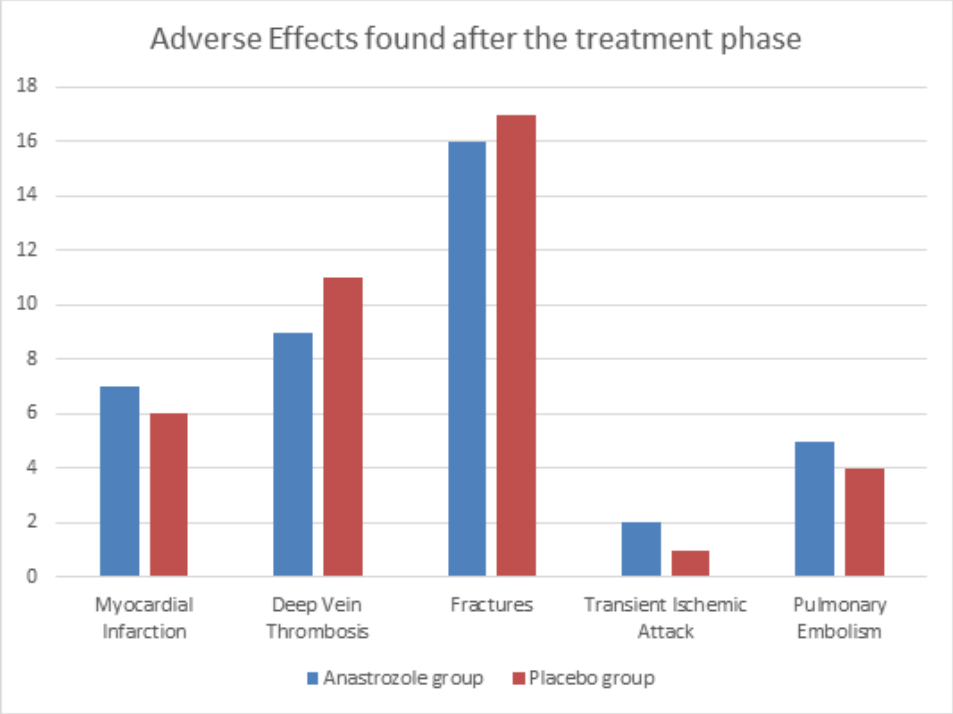

Figure 1: The adverse effects of the patients in each group after the treatment phase

The study also found that there was 3 deaths in anastrozole group and 7 deaths in placebo group. Hazard Ratio was determined between the two groups. Table 3 shows the detailed findings about the death of the patients after the treatment phase in each group.

Table 3: The death of the patients after the treatment phase in each group

Cause of death	Anastrozole group	Placebo group	Hazard Ratio*
Breast carcinoma	2	4	0.63±1.2
Cardiovascular	1	2	0.78±0.8
Pulmonary	0	1	0.58±0.1
Total	3	7	

*95% confidence interval

Discussion

Cuzick et al. [19] undertook a study to examine the long-term effects of using anastrozole for breast cancer prevention (IBIS-II). The use of anastrozole for high-risk postmenopausal women to prevent breast cancer is further supported by this updated analysis of the IBIS-II study. The significant 61% decrease in breast cancer incidence in the first five years has been sustained throughout the subsequent 12-year follow-up. While not significantly smaller than during treatment, the considerable 36% reduction observed during post-treatment follow-up was nevertheless more than that seen with tamoxifen, which has caused a relatively steady 29% reduction over 20 years. During the first 12 years of follow-up, 29 patients were required for treatment to prevent one breast cancer, which contrasts well with the 58 required for tamoxifen at the time [20].

Although there have been very few breast cancer-related deaths to date, it is still too early to predict a change in this outcome, which is a drawback of this investigation. Since estrogen receptor-positive tumors accounted for the majority of the anastrozole reduction, the effect on mortality is likely to be less significant than that on incidence. The estrogen

receptor-positive tumors were most affected, but an unexpected and non-significant 27% drop was also observed for the receptor-negative malignancies, which will need more research to confirm [20].

The 5 years of anastrozole treatment in high-risk postmenopausal women has been shown to have a long-term effect on avoiding breast cancer, according to these latest results. No new major adverse events were identified. After five years of follow-up, statistics significantly support the conclusions from our initial research [21].

The findings of four newly released research on breast cancer risk assessment techniques revealed low discriminatory accuracy in estimating the likelihood of breast cancer in specific women, which is consistent with earlier studies. The majority of techniques barely outperformed age as a risk predictor. According to these studies, it is most likely inaccurate to choose women for risk-reducing medications based on a modified 5-year Gail score of 1.66% or higher, as is the case for inclusion criteria in primary prevention trials and US Food and Drug Administration approval of Tamoxifen and Raloxifene for risk reduction. Without any other risk factors, the majority of women in their 60s would fall under this cutoff just by age. Furthermore, studies do not offer professional advice on the best ages or frequency for risk assessment because these factors have not yet been examined [22].

New research on the benefits and drawbacks of aromatase inhibitors for lowering the risk of breast cancer is presented in primary prevention studies of anastrozole and exemestane. However, there are no long-term follow-up data available to assess whether side effects such as fractures and cardiovascular events that were seen in therapy studies for women with noninvasive and early-stage breast cancer apply to risk reduction [23, 24]. Anastrozole (1mg/d) and tamoxifen (20mg/d) were compared for 5 years with a median follow-up of 7.2 years in an RCT of 2980 women with locally excised estrogen receptor-positive ductal carcinoma in situ [25]. The findings showed that anastrozole and tamoxifen both increased the risk of venous thromboembolic events and fractures (odds ratio, 1.36 [95% CI, 1.03-1.80]) and stroke (odds ratio, 3.36 [95% CI, 1.04-14.18]).

Women who used tamoxifen, raloxifene, or aromatase inhibitors had a decreased risk of developing primary invasive breast cancer, but they also experienced side effects that varied between the drugs. Methods for risk stratification that were used to identify patients at higher risk for breast cancer had poor specificity.

Khosrow-Khavar et al study [26] that examined the relationship between aromatase inhibitors and a cardiovascular prognosis in breast cancer patients is debatable. Initiating an endocrine treatment with an AI was linked to an 86% higher risk of heart failure and a 50% higher risk of cardiovascular mortality in this population-based analysis of breast cancer patients. A tendency toward an elevated risk of myocardial infarction and ischemic stroke was also seen. Multiple sensitivity analyses showed that these results remained constant. [27]

The reported study has several advantages. As far as we are aware, this is the largest observational study that has explicitly contrasted the risk of cardiovascular events between AIs and Tamoxifen among breast cancer patients. The connection between AIs and clinically significant endpoints, such as myocardial infarction, ischemic stroke, heart failure, and cardiovascular mortality, was also thoroughly investigated in this study. Second, the result misclassification was probably reduced by linking to the HES and ONS databases [26]. Third, the new-user, active-comparator approach probably eliminated user bias at the design stage while reducing confusion [26]. Fourth, sensitivity studies designed to account for

various types of bias did not change our findings. Last but not least, because our study is population-based, patients treated in real-world settings are likely to be represented among our study population.

Conclusion

The study concluded that there is preventive effect of anastrozole treatment in breast cancer among high risk post-menopausal females. The study had some limitations. The study was bound to 3 years and limited number of patients were available. So, the author suggests that there should be more studies be conducted with varied and larger population. However, this study has highlighted an important finding and the clinical significance of the conclusion of this study is very high. Anastrozole also proved to have lesser adverse effects which increases the clinical significance of anastrozole. The death occurred in anastrozole group and placebo group is insignificant. The effect of anastrozole, especially in Invasive estrogen receptor-positive type, is significant as compared to the placebo. The study also claimed that there is probability that the risk of breast cancer among the high risk individuals can be reduced by anastrozole therapy for 5 years whose beneficial effect can be remain beyond 5 years.

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