RESEARCH COMMUNICATION

Tamoxifen Use in Indian Women - Adverse Effects Revisited

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Abstract

Background: Tamoxifen is generally considered a safe drug for Indian women with breast cancer. Indian women seem to tolerate tamoxifen therapy better than western women, but there are no data regarding safety and local adverse effect profiles in typical Indian populations. Methods and Results: A total of 3,000 case records of patients who had received tamoxifen daily for any period of time, between January 1988 and December 2007, were identified for study. Hot flashes were reported by 800 (26%), mild vaginal dryness by 450 (15%) and vaginal discharge by 300 (10%), with vaginal bleeding experienced by 40 (1.3%) patients. A total of 1,100 (36.6%) asymptomatic patients had a thickened endometrium(defined as >8mm in thickness) on ultrasonography. Endometrial curettage was performed in all of these. None of the patients developed endometrial carcinoma. Fatty infiltration of liver was found in 1,440 (48%) patients with a mean time interval for development of 7 months (range 6-30 months). Conclusions: Fatty infiltration of liver is found in almost half of the Eastern Indian women who receive tamoxifen. Increased endometrial thickness, which remains asymptomatic, was documented in more than one third of patients on ultrasound examination. Tamoxifen seems to have a negligible potential for causation of uterine malignancies in eastern Indian women. Rates of hysterectomies in Indian patients on tamoxifen are substantially lower than those of western patients on tamoxifen.

Key Words: Indian breast cancer patients - tamoxifen - adverse effects

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Introduction

Cancer of the breast is the leading cause of cancer related deaths in Asia. In recent years breast cancer is emerging as the commonest female malignancy in developing Asian countries, overtaking cancer of uterine cervix in that respect (Aggarwal, 2007). In the management strategy of breast cancer, hormonal therapy is an integral part of the protocol both in early as well as advanced breast disease.Tamoxifen has been the most important hormonal agent used worldwide for the said purpose (Fisher et al., 2005; Chlebowski, 2008, Mathew et al., 2008). The continued importance of tamoxifen is reflected in the fact that it is the only hormonal agent approved by the USFDA for, the prevention of premenopausal breast cancer, the treatment of ductal carcinoma in situ (Fisher et al., 2002) and the treatment of surgically resected premenopausal ER positive breast cancer (Colleoni et al., 2006). Tamoxifen is an effective and widely used adjuvant therapy for women with breast cancer because it reduces recurrence rates and prolongs disease free survival. It is a partial oestrogen agonist in that it exhibits anti-oestrogenic activity in the breast, but has a stimulatory effect on the endometrium. This hormonal activity results in a higher incidence of post-menopausal vaginal bleeding and endometrial pathology such as endometrial polyps,hyperplasia and cancer (Barakat, 2000; Bergman et al., 2000; Neven et al., 2000).

With the advent of aromatase inhibitors, the focus of attention has shifted away from tamoxifen.Trial efficacy and safety analysis update of the ATAC trial has revealed that anastrazole has numerous noteworthy advantages in terms of tolerability as compared to tamoxifen (Howell et al., 2005; Buzdar et al., 2006). The problem in applications of the results of ATAC trial to the Indian patient population arises, because, the patient population studied in this trial, is mainly from the USA, the West and other developed countries. The Indian women,it seems,tolerate tamoxifen better than western population of patients,with a lesser incidence of life threatening side effects, like uterine cancer and venous thrombo-embolism. As of now, there are no available data regarding the safety and adverse effect profile of tamoxifen in Indian population. The present paper evaluates the tolerability and adverse effects of tamoxifen in breast cancer patients of eastern India.

Materials and Methods

This study was conducted at Chittaranjan National Cancer Institute, Kolkata; Eastern India. After obtaining institutional review board approval, a retrospective review of the case records of the patients between January 1988 and December 2007 was undertaken. Data were collected on patient demographics,and the time period for which

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each patient had received tamoxifen.The patients who had received tamoxifen 20 mg daily anytime during their followup period were included in the study.Follow up intervals were noted for all patients. Reasons of default,if any,were also recorded in the study. Commonly reported side effects like, hot flushes,menstrual abnormalities, vaginal bleeding and other genitourinary symptoms were looked for in every patient. Ultrasonography (abdominal/transvaginal) findings in case records, and the intervals at which ultrasonography was performed,were recorded for all patients. Patients who might have developed uterine malignancy, deep vein thrombosis,other adverse effects were looked for. Causes of drug default, stoppage against medical advice or change over to another drug were recorded for every patient.

Results

Overall 3,000 case records were identified. Of these 900 (30%) patients were in the age group of forty or less (<40) years. All the patients had received tamoxifen at 20 mg daily for relatively long periods (range 23 days-10 years) but 600 (20%) patients were reported to receive it. Follow up after starting tamoxifen was average 7.6 days (range 5-11 days) for the first three weeks, then 3.9 weeks(range 2-7weeks) for four to six months,then three monthly for four years and six monthly for the rest of the period.

Tamoxifen intolerance (adverse effects severe enough to lead to change to another hormonal agent) was not reported by any patient, during the period of follow up. Hot flashes were reported by 800 (26%) patients. The intensity of the hot flashes was not severe enough to lead to drug default by any of the patients, or switch over therapy.

Mild vaginal dryness was reported by 451 (15%) patients and vaginal discharge was reported by 300 (10%).Vaginal bleeding (without any underlying pathology) was reported by 12 (0.4%) patients, all of them were postmenopausal. Irregular menstrual cycles were reported by 357 (11.9%) patients.

1,970 (65.67%) patients had undergone ultrasound examination of abdomen, on an average 2.4 times (1-4 times) a year during follow up period and the rest 746 (24.8%) had undergone 1.6 times(range 0-5 times) a year during their follow up period .254 (8.4%) patients had undergone average 0.8 (range0-3)times during 1-7 months of followup. Indications of ultrasound were: six monthly screening,ureteric colic, cystitis, biliary colic, dyspepsia.864(28.8%) asymptomatic patients were reported to have thickened (> 8mm) endometrium on ultrasonography.Hysteroscopy with biopsy and/or endometrial curettage was performed in patients with reported thickened endometrium.

In none of the patients endometrial carcinoma was reported in the histopathological examination. Uterine fibromyomas were documented in 75(2.5%) on ultrasonography, out of whom 26 (26/75) patients were in the >40 age group, the rest (49/75) were in <40 age group. In 25 patients, fibromyomas had been diagnosed before receiving tamoxifen treatment. Ten out of 75 patients had demonstrated progression in the size of fibromyomas on serial USG evaluation on 3 monthly basis.Excessive or irregular menses were reported by 60 (80%, n=75) patients with fibromyoma.65 patients with fibromyomas of uterus had undergone operative treatment (26 from >40 years age group and 39 from <40 age group). In none of the operated patients malignancy was reported on histopathology. Asymptomatic ovarian cysts were found in 300(20%) patients, all in <40 years age group.

Overall 1,650 (55%) patients had fatty infiltration of liver.It was reported in 1,440 (48%) patients on ultrasound and 210 (7%) patients had evidence of hepatic steatosis on computerized tomograhic scanning. Average time interval of reporting of fatty infiltration of liver, from starting of tamoxifen, was 7 months (range 6-30 months). Evidence of recovery of this event was reported on ultrasound, within 6-12 months after the stoppage of tamoxifen. Deep vein thrombosis of the legs was found to be evident on Doppler scanning in only7 (0.2%) patients. Pulmonary thrombo-embolism, ocular toxicity, carcinosarcoma of uterus, hepato-cellular carcinoma or other GI malignancy were not reported in any of our series of patients.

Discussion

Although, the incidence of breast cancer in India is not as high as in the USA and the west, it is still a major public health concern. The incidence of breast cancer in India is estimated as 23 per 100,000 population, but in some metropolitan cities like Mumbai, it is higher than the national average (Jussuwala et al.,1993).The management of breast cancer comprises surgery, systemic chemotherapy, radiotherapy and hormonal therapy. The hormonal therapy is an integral part of the management of breast cancer, both in early as well as in advanced stages (Barakat et al., 2000; Bergman et al., 2000; Neven et al., 2000; Howell et al., 2005).Tamoxifen occupies a central position in the management protocol of breast cancer. A lot of work has been published by various authors, regarding the adverse effects and intolerability of tamoxifen in women.

The prominent side effect of tamoxifen therapy, reported in the literature, is hot flashes, being experienced by 50% of women (Hoda et al., 2003; Mathew et al., 2008). We did not find hot flashes to be the most common adverse effect of tamoxifen treatment.However, it was not an uncommon complaint and was reported by 800 (26.7%) in our study. In none of the patients, it had been severe enough to lead to drug default on the part of patients or switch over to other agent by the treating physician. All the cases had responded to reassurance only. Tamoxifen has been reported to increase the risk of endometrial carcinoma 2 to 5 fold (Smith et al., 2000).The incidence of endometrial carcinoma in long-term users has been found to be 2 per1000 patients per year (Fristch et al., 1994; Barakat, 1999; Barakat et al., 2000). Not only that, but also, the tamoxifen has been implicated as a possible etiological agent in the development of carcinosarcoma of the uterus (Baraket,1999; Fotios et al., 2000; Kloos et al., 2002; Wickerman et al., 2002; Arena et al., 2006).We

did not find an increased incidence of endometrial cancer or carcinosarcoma in the study group. Total number of hysterectomies performed were 66 (2.17%)patients (0.8%) were in >40 years age group and 49 patients (1.7%) were from <40 years age group. This is in contrast with the conclusions drawn by Buzdar et al (2006) that tamoxifen is associated with higher rates of hysterectomy(5%).This type of results can hold true in western scenario but Eastern Indian women seem to tolerate tamoxifen very well and the rates of hystrectomies associated with tamoxifen use are surprisingly low.

Veronesi et al (1998) and Mathew et al (2008) have reported a significant increase in vascular events in tamoxifen users. We did not come across significant increase in the evidence of vascular or cardiac events in the study group; however, hypertriglyceridemia could be documented in 600 (20%) patients. Fatty infiltration of liver and asymptomatic thickened endometrium (endometrial thickness >5mm in premenopausal and >8mm in post menopausal women) have been the most commonly reported USG findings in our patients, the former being reported in 55% while as the latter in 28.8% patients. Nishino et al (2003) have reported a highly significant effect of tamoxifen on hepatic fat content and development of hepatic steatosis. Nemoto et al (2002) have also reported higher rates of fatty infiltration of liver in tamoxifen users, proposing that tamoxifen is not merely an antagonist of estrogen but may also suppress the synthesis of estrogen as well. The majority of our patients (80%) have shown signs of recovery within 6 to 12 months of stoppage of tamoxifen.

As for as adverse effects are concerned, Indian women, seem to tolerate tamoxifen in a better way, as compared to western women. The number of patients <30 years age is substantially higher in Indian subcontinent than the west (25% vs10%),and as such, tamoxifen is remains to play a major role in the management of these patients (Agarwal et al., 2007).The unnecessary alarm regarding carcinogenic potential of tamoxifen, has to be clearly dealt with in the Indian context. Given the retrospective nature of our study, it is rather difficult to draw definite conclusions regarding the safety of tamoxifen vis-a-vis the safer carcinogenic profile of tamoxifen in Indian women.However,based on our data,it appears that tamoxifen does not lead to high rate of endometrial carcinoma in eastern Indian women and a prospective study is needed to settle the issue for Indian population of patients.

In conclusion, Tamoxifen appears to be a generally safe drug for Indian women with breast cancer,with acceptable side effect profile, as compared to that for western population. It seems to have a negligible potential for causation of endometrial cancer or other uterine malignancies in eastern Indian women. Fatty infiltration of liver is seen in more than half of the eastern Indian women who receive tamoxifen.Increased endometrial thickness, which remains asymptomatic, is documented in more than one third of patients on ultrasound examination. Rates of hysterectomies in Indian patients on tamoxifen are substantially lower than those of western patients on tamoxifen.

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