Singapore Med J 1999; Vol 40(6):402-404

The Role of Endovaginal Ultrasonography and the Value of Endometrial Biopsy in Breast Cancer Patients on Tamoxifen Therapy

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ABSTRACT

Background: Endometrial changes have been observed when tamoxifen is used as an adjuvant therapy for carcinoma of the breast in postmenopausal women with positive estrogen receptors status.

Aim of Study: The aim of this study was to evaluate endometrial response in similar patients in Malaysia.

Patients: Between February – July 1995, 38 women who had been receiving tamoxifen therapy were analysed for endometrial thickness by transvaginal ultrasonography and histopathological changes in endometrial biopsy samples. The results were compared with a similar group of postmenopausal women who did not have carcinoma of the breast. In the study group, tamoxifen was administered daily at a dose of 20 – 40 mg. All patients were above 50 years of age. The mean duration of tamoxifen therapy was 21.2 months (range 8 – 36 months).

Results: Detectable differences in endometrial thickness were seen between tamoxifen and control groups. Eighteen (47%) patients in the study group had endometrial thickness in excess of 10 mm; the mean thickness being 10.7 mm (± 4.95 mm) which was significantly greater than the control group. Positive histological findings were found in 17 patients (45%) compared to 7 patients (18%) in the control group. Endometrium was reported to be atrophic when endometrial thickness was less than 5 mm. The study underscores the need for endometrial surveillance in breast cancer patients who are on continuous tamoxifen therapy for more than 12 months and have an endometrial thickness exceeding 8 mm.

Keywords: breast cancer, tamoxifen, endometrial biopsy, endovaginal ultrasonography

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INTRODUCTION

Tamoxifen has been successfully used with efficiency and safety for more than a decade as an adjuvant therapy for breast cancer in postmenopausal women with positive estrogen receptor proteins after conventional primary treatment[1]. Against the good response rate in these patients[2], an increasing number of reports have appeared, implicating the induction of endometrial changes with continued use of tamoxifen in women with intact uteri[3-5].

Although tamoxifen has been used in the management of breast cancer patients in Malaysia, there is little documentation on the occurrence of endometrial pathology in our local context. The aim of this study was to assess the possible consequences of tamoxifen upon the endometrium of unselected asymptomatic postmenopausal women managed at the breast cancer clinic, and to correlate endometrial thickness imaged by endovaginal ultrasonography with endometrial pathology.

MATERIALS AND METHODS

Breast cancer is traditionally managed by general surgeons at the Breast Clinic. A cross-sectional study was carried out at the Breast Clinic at the Ipoh Hospital and the Kuala Lumpur Hospital over a 6-month period between February – July 1995. Thirty-eight consecutive non-hysterectomised postmenopausal consenting breast cancer patients receiving tamoxifen for a minimum period of six months were included in the study. These women were free of overt gynaecological diseases. They were primarily treated surgically (ie. either modified radical mastectomy or lumpectomy with axillary node dissection). Tamoxifen therapy was initiated at a dose of 20 – 40 mg daily for periods ranging from 8 – 36 months in the presence of estrogen receptors. Radiotherapy and chemotherapy were administered according to staging and further evolution. Surgical or radiotherapic castration was not carried out in any of the patients.

Another group of 38 postmenopausal women attending the gynaecological clinic with intact uterus, not receiving hormonal treatment and presenting with age related problems like minor uterovaginal prolapse and stress incontinence, served as the control group. Both study and control groups had similar demographic characteristics. All patients consented to a full gynaecological examination, transvaginal sonography and outpatient endometrial biopsy by the principal investigators.

Following digital bimanual pelvic examination and routine cervical smears for cytology, transvaginal ultrasonography was performed using 5.0 Mhz vaginal probe. After emptying the bladder, the uterus was scanned both sagitally and coronally to assess the thickness and regularity of the endometrium. The

antero-posterior diameter of the endometrial image, obtained in the long axis view was measured between the outermost edges of the line separating the hyperechogenic endometrium from the myometrium. The maximum width was recorded.

An outpatient endometrial biopsy was obtained in all patients in both the study and control groups following transvaginal ultrasonography using a Pipelle endometrial biopsy sampler without dilatation or anaesthesia. Endometrial tissue obtained from this procedure was fixed immediately in 10% formaldehyde and despatched for histopathological examination.

Patients who were on hormone replacement therapy were not included in the study. Complete procidentia and patients who were known to have benign or malignant genital tumours were also excluded.

Statistical analysis was performed using chi-squared test, Fisher exact test and unpaired student t-test. The level of significance was set at a probability of less than 0.05.

RESULTS

Of 58 patients interviewed, 38 fullfilled the criteria and were recruited. There were another 38 postmenopausal patients in the contol group. Selected demographic data of these two groups is shown in Tables I, II and III. Ten patients (26%) in the study group and 5 in the control group had concomitant non-insulin dependent diabetes mellitus. All were controlled with oral hypoglycemics. Tamoxifen therapy ranged from 8 – 36 months (mean 21.24 months).

Table I – Age distribution of asymptomatic postmenopausal tamoxifen-treated patients and controls

Age distribution (years)	Tamoxifen group (n = 38)	Control group (n = 38)	p value (chi-square)
50 – 59	30 (79%)	26 (69%)	NS
60 – 69	5 (13%)	7 (18%)	NS
> 69	3 (8%)	5 (13%)	NS
Mean (SD)	58.53 (± 6.11)	58.67 (± 7.23)	NS

Note: NS – Not significant
SD – Standard deviation

Table II – Parity among asymptomatic postmenopausal tamoxifen treated patients and controls

Parity	Tamoxifen group (n = 38)	Control group (n = 38)	p value (chi-square)
Nulliparous	3 (8%)	1 (3%)	NS
1 – 3	16 (42%)	20 (52%)	NS
> 3	19 (50%)	17 (45%)	NS
Mean (SD)	3.66 (± 1.98)	3.84 (± 2.22)	NS

Table IV shows the endometrial thickness in both groups. The mean thickness in the study group of 10.74 mm (± 4.95 mm) was significantly higher than the control group. In the tamoxifen group, 10 (26%) patients had endometrial thickness of less than 5 mm. A significant proportion had endometrial thickness greater than 10 mm (47%).

Endometrial biopsy was available in all the patients. Except for slight discomfort in most patients, no complications were documented. Positive histological findings were found in 17 patients (45%) in the tamoxifen group compared to 7 (18%) in the control group as shown in Table V.

Benign cystic hyperplasia was seen in an equal proportion of patients both in the tamoxifen treated and control groups. However, atypical hyperplasia (2/38), adenomatous hyperplasia (1/38) and endometrial polyp (8/38) were documented only in the study population. Atypical hyperplasia referred to endometrial hyperplasia with focal atypia. There was no record of endometrial carcinoma in the series. Seventeen patients who exhibited endometrial thickness determined by endovaginal scanning, showed a width greater than 8 mm range (8.9 mm – 20.0 mm) with a mean of 12.74 mm (± 3.73 mm). Correspondingly, in the control group, no evaluable endometrial tissue was obtained in 31 women. Seven women who exhibited proliferative endometrium had a mean endometrial thickness of 8.30 mm (6.9 mm – 11.2mm).

When the duration of tamoxifen (mean 21.2 months) therapy was analysed with respect to positive histopathological findings, no correlation between duration of tamoxifen therapy and the appearance of specific pathology was noted. In both groups, no endometrial pathology was evident when the endometrial thickness was less than 5 mm.

DISCUSSION

Tamoxifen, an antiestrogen, has been the treatment of choice for postmenopausal breast cancer patients as it significantly improves both recurrence-free intervals as well as overall survival rate when used as an adjuvant therapy[6]. Its antineoplastic effect is exerted by its high affinity for estrogen receptor proteins in the cytoplasm of hormone dependant cells especially in breast tissue[7]. However, tamoxifen has shown to function as an estrogen agonist in a low estradiol environment typical of the postmenopausal age[8].

The possible association of tamoxifen therapy and induction of various endometrial pathologies have been reported over the last few years[3-5]. Information on this relationship has been scarce in Malaysia. In this small study, nearly 45% of asymptomatic postmenopausal breast cancer patients on tamoxifen therapy ranging from 8 – 36 months appear to present with some degree of endometrial 'response'. If we excluded proliferative benign cystic hyperplasia from both groups, as they occurred with equal frequency, various other types of more sinister endometrial pathology, viz. atypical, adenomatous hyperplasia and endometrial polyp, were obvious in 11 patients.

Table III – Distribution of duration since menopause among asymptomatic postmenopausal tamoxifen treated patients and controls

Duration since menopause (years)	Tamoxifen group (n = 38)	Control group (n = 38)	p value (chi-square)
> 1	0	3 (8%)	p < 0.01
1 – 5	20 (53%)	21 (55%)	NS
6 – 10	10 (26%)	6 (16%)	NS
> 10	8 (21%)	8 (21%)	NS
Mean (SD)	7.71 (± 5.53)	7.46 (± 4.38)	NS

Table IV – Distribution of endometrial thickness among asymptomatic postmenopausal tamoxifen treated patients and controls

Endometrial thickness (mm)	Tamoxifen group (n = 38)	Control group (n = 38)	p value (chi-square)
< 5	10 (26%)	27 (71%)	p < 0.001
5 – 10	10 (26%)	9 (24%)	NS
> 10	18 (47%)	2 (5%)	p < 0.01
Mean (SD)	10.74 (± 4.95)	4.62 (± 2.12)	p < 0.05

Table V – Histopathological findings of the endometrium in asymptomatic postmenopausal tamoxifen treated patients and controls

Histopathology	Tamoxifen group (n = 38)	Control group (n = 38)	p value (chi-square)
Atophic endometrium	21 (55%)	31 (82%)	p < 0.05
Proliferative benign cystic hyperplasia	6 (16%)	7 (18%)	NS
Atypical hyperplasia	2 (5%)	0	NS
Adenomatous hyperplasia	1 (3%)	0	NS
Endometrial polyps	8 (21%)	0	NS

Endometrial hyperplasia, endometrial polyps and endometrial carcinoma[3-5] have been documented in the literature with respect to tamoxifen therapy in breast cancer patients. Inspite of the small number of cases in the tamoxifen group, one needs to draw attention to the fact that the above lesions are precursors of endometrial carcinoma[9]. Continuous unopposed estrogen stimulation has been described in the eventual development of adenomatous hyperplasia, atypical hyperplasia and carcinoma in postmenopausal women with intact uteri[10,11]. Since none of the patients were on estrogen replacement therapy, one can surmise that the pathological changes in the endometrium were due to continuous unopposed exposure of the endometrium to tamoxifen.

When correlated with endometrial thickness established by transvaginal sonography, 17(45%) patients in the tamoxifen group had histologically detectable endometrial pathology when endometrial width exceeded 8 mm. However, no relationship was noted with regards to endometrial thickness (when it exceeded 8 mm) with specific endometrial pathology. We were also unable to correlate duration of tamoxifen therapy with the development of endometrial pathology. However, all patients who ultimately developed endometrial changes had been exposed to tamoxifen for over 12 months. None of the patients who had endometrial thickness of less than 5 mm with endovaginal scan demonstrated endometrial changes in histopathological examination. This study illustrates the usefulness of endovaginal scanning to determine endometrial thickening of postmenopausal patients who are on tamoxifen therapy for carcinoma of the breast. As shown by other workers[3-5], when endometrial thickness exceeds 5 mm; an outpatient endometrial biopsy is advised for breast cancer patients being continuously treated with tamoxifen, for periods exceeding 12 months, as part of gynaecological examination rendered to all postmenopausal patients.

ACKNOWLEDGEMENT

The authors wish to thank the Director General of the Ministry of Health for permission to publish this article. They also wish to thank the staff of the Breast Clinic, Ipoh and Kuala Lumpur Hospitals for their assistance with this study.

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