COMMENTARY

Prevention of Endometrial Cancer in Breast Cancer Patients Taking Tamoxifen : The Gynecologists' Role

Supat Sinawat

Abstract

Breast cancer is among the commonest malignant diseases in women. Over the past two decades tamoxifen has been generally accepted as an endocrine therapy of choice for prevention of breast cancer recurrence. Although tamoxifen was thought to have only a few adverse effects, several reports indicate that it is associated with an increase incidence of proliferative and neoplastic changes in the endometrium, with a 1.3 to 7.5 relative risk of developing endometrial carcinoma. The increased risk of endometrial cancer following the use of tamoxifen has stimulated studies on endometrial diagnostic screening methods. During the past ten years several reports have shown the benefits of transvaginal ultrasonography in detecting endometrial pathologies in patients receiving tamoxifen. Sonohysterography has been claimed to be a useful diagnostic tool on differentiating space-occupying lesion, eg. endometrial polyp, from abnormal endometrial-myometrial junction while the contribution of pulsed flow velocity in diagnosis of endometrial pathologies seems to be inconclusive. More recently a few factors have been identified as risk of developing endometrial cancer after tamoxifen use. These include pre-existing endometrial pathologies, obesity, and prior ERT use. This information provides us a more sensible way in following breast cancer patients receiving tamoxifen. It is proposed here that postmenopausal breast cancer patients intend to have tamoxifen treatment should receive a "two - step evaluation". The pretreatment evaluation is aimed to classify patients at risk of later development of endometrial pathologies after being exposed to tamoxifen while the ongoing evaluation is designed to closely follow the patents after the initiation of tamoxifen in hope that this will provide a tool for early diagnosis or hopefully a protective measure against endometrial carcinoma associated with tamoxifen therapy.

Key Words: Breast cancer - tamoxifen - endometrial carcinoma - gynecologist

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Introduction

Breast cancer is among the commonest malignancies in women. In western world it accounts for approximately one-third of all cancers found in women and the incidence has been found to be increasing globally (Parker et al., 1996). Since the early 1980s, tamoxifen has become the standard adjuvant therapy for patients with breast cancer and it is estimated that over one million women worldwide are now using tamoxifen to reduce the risk of the recurrence of breast cancer (Fisher and Costantino, 1989). Although tamoxifen was thought to have only a few side effects, reports indicated that it is associated with an increased incidence of proliferative and neoplastic changes in the endometrium, with a 1.3 to 7.5 relative risk of developing endometrial cancer (Daniel et al., 1996). It is, therefore, the responsibility of the gynecologists to provide a reliable surveillance method in hope that this will result in an early detection or even prevention of endometrial pathologies associated with tamoxifen treatment in breast cancer patients.

Tamoxifen and Reproductive Tract

Tamoxifen is a nonsteroidal antiestrogen. It was approved by the American Food and Drug Administration (FDA) to be used as an adjuvant therapy in all stages of breast cancer. The current recommendation for tamoxifen treatment is five years and the potential indication for tamoxifen use in the future is for prophylaxis against breast cancer in high-risk population (Fisher et al., 1998). It has been clear that tamoxifen provides several beneficial effects to breast cancer patients both in terms of the disease itself and to general health status. Tamoxifen prolongs disease-free survival and reduces mortality rate due to breast cancer. In addition, it

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provides a 30 to 50 % reduction in the development of contralateral breast cancer. Moreover, tamoxifen has been demonstrated to decrease total and LDL-cholesterol; reduce hip, radius, and spine fractures; alleviate urinary frequency, urgency, dysuria , and dyspareunia due to vaginitis; and it also increases the level of HDL cholesterol, and thus provides a protective effect on cardiovascular system (Benshushan and Brzezinski, 1999). Besides its wide ranges of benefits, tamoxifen also exhibits several drawbacks mostly involving reproductive organs. The adverse effects of tamoxifen on reproductive tract can be categorized into two groups, the first of which is benign alterations such as the development of endometrial polyp, endometrial hyperplasia, adenofibroma of endometrium, ovarian cyst and the progress in the size of uterine fibroid (Baldini et al., 1996; Huang et al., 1996). The second change associated with tamoxifen use is malignant transformation such as endometrial carcinoma, uterine sarcoma and malignant mixed tumor of the uterus (Treilleux et al., 1999; Kenedy et al., 1999)..

Tamoxifen and Endometrial Cancer

Over the past decade, it has been reported that postmenopausal breast cancer patients who have been treated for more than 12 months with tamoxifen are at increase risk of endometrial carcinoma (Van Leeuwen et al., 1994). The incidence of endometrial cancer during postmenopausal tamoxifen therapy is estimated to be approximately 2 per 1000 annually and the relative risk of developing endometrial cancer in this group of patients was 1.3 to 7.5 compared to the age-matched tamoxifen non-exposing group (Daniel et al., 1996).

So far there is no precise explanation regarding the development of endometrial cancer in tamoxifen users. Several pathogeneses, however, have been proposed. These include its partial estrogenic effect on the endometrium (Hatchisuga et al.,1999), its anti-estrogenic, gestagen-like action (Dallenbach et al., 1996), the changes of endometrial steroid receptors (Schwartz et al.,1997), inactivation of p53 tumor suppressor gene due to tamoxifen (Isaksson et al., 1999), and its action as genotoxicity (Shibutani et al., 1999).

Surveillance for Endometrial Cancer in Women Receiving Tamoxifen

Since the risk of developing endometrial cancer in breast cancer patients taking tamoxifen is real, efforts have been put in several studies involving endometrial diagnostic screening methods. Most investigators agree that close follow up in this group of patients is recommended in order to prevent the development of endometrial pathologies, however, controversies still exist in several aspects such as: who should be monitored, when to start monitoring, how to monitor these patients, and how often shall the monitoring be performed? This article will provide the most up to date information regarding several questions mentioned above and discuss the practical approach to these poor patients in a real setting of developing countries.

Who should be monitored?

Recent study by Bertelli and his colleagues revealed clearly that postmenopausal breast cancer patients on tamoxifen had significantly thicker endometrium, larger uterine volume and higher incidence of endometrial abnormalities. There were, however, no significant differences in either ultrasound or biopsy findings in the pre- and peri-menopausal group between those being treated with tamoxifen and the control (non-exposure) group (Bertelli et al., 1998). It is thus sensible to propose surveillance measure for endometrial pathologies only in postmenopausal breast cancer patients taking tamoxifen.

When should the monitoring be started?

It has been shown that 93 % of pathological changes of endometrium occurred after 12 months of tamoxifen treatment (Uziely, Lewin, Brufman, 1993). However, recent study by Berliere in 1998 interestingly demonstrated that 17 % of postmenopausal breast cancer patients were found to have abnormally thick endometrium (greater than 4 mm) before initiation of tamoxifen therapy and up to 74 % of these patients with thickened endometrium revealed abnormal pathological findings upon biopsy (Berliere et al., 1998). Moreover, the same study pointed out that 80 % of patients who subsequently developed premalignant or malignant lesions of the endometrium had received a diagnosis of endometrial lesion before initiation of tamoxifen treatment. More recently, the study by Bernstein indicated that the risk of developing endometrial diseases increases with the duration of tamoxifen use (Bernstein et al., 1999). It seems, therefore, very reasonable to recommend pre-treatment evaluation of pelvic organs, especially the endometrium, in order to classify the patients at risk of developing endometrial lesions subsequent to tamoxifen treatment. After initiation of tamoxifen therapy, a yearly follow up scheme should also be applied in hope that this will provide us a protective tool against the development of pelvic pathologies.

How should these patients be monitored?

During the past decade several reports were published regarding diagnostic screening methods to detect endometrial pathologies in breast cancer patients taking tamoxifen. The methods being evaluated include endometrial sampling, ultrasonography, sonohysterography, doppler studies and office hysteroscopy.

Regarding as a screening method in this group of patients, endometrial sampling was not found to be a cost-effective diagnostic tool since it detects only 1.7 cases of cancer per 1000 person-year (Koss et al., 1984). Moreover, recent study has found that endometrial abnormalities occurring in the setting of tamoxifen use seem to be more heterogeneous than is usual, with focal hyperplastic lesions coexisting in a background of atrophy (Cohen et al., 1997), therefore, the false-negative rate of endometrial sampling may be higher

in these patients.

Several studies have examined the use of ultrasonography followed by endometrial biopsy in patients taking tamoxifen. Kedar and colleagues demonstrated that among postmenopausal women receiving 20 mg/day of tamoxifen for 24 months, 49 % were found to have abnormally thick endometrium on transvaginal ultrasound scan(endometrial thickness greater than 5 mm). The incidence of premalignant and malignant changes in this study was 16 % and the author concluded that endometrial thickness greater than 8 mm on ultrasonography had a 100 % positive predictive value for endometrial disease (Kedar, et al., 1994). The study undertaken by our group in Khon Kaen, Thailand preliminarily revealed that among 33 postmenopausal breast cancer patients taking 20 mg/day of tamoxifen for at least six months, 59.46 % were found to have endometrial thickness greater than 5 mm. One in twenty (5%) of these abnormally thick endometrium patients revealed endometrioid adenocarcinoma of endometrium (Sinawat et al., 2001). The recent review by Elizabeth demonstrated that there were no cases in which endometrial cancer was found in a patient with an endometrial lining measurement of 8 mm or less (Elizabeth and Suh-Burgmann, 1999).

Sonohysterography has been shown to enhance the differentiation between space-occupying lesions, eg. endometrial polyp from abnormal endometrial-myometrium junction commonly found in tamoxifen-primed endometrium (Tepper, Beyth and Altaras, 1997) whereas the contribution of pulsed doppler flow in diagnosis of endometrial pathologies seems to be inconclusive since the changes in either pulsatility index or resistance index have not been predictive of significant endometrial abnormalities (Kurjak et al., 1993). Another effective method of evaluating endometrium is office hysteroscopy, which allows direct visualization of the uterine cavity. Although this method is comparable to transvaginal ultrasonography in terms of sensitivity and specificity, hysteroscopy may not be as well accepted by the patients (Saidi and Salder, 1997).

Taking all these information discussed above together, it should sound justified to propose a transvaginal ultrasonography (using endometrial thickness greater than 8 mm as a cut-off point for further evaluation) as a diagnostic tool in evaluating endometrial pathologies in postmenopausal patients taking tamoxifen

How often should the monitoring be performed?

So far there is no general consensus on the appropriate interval of gynecologic follow up in these patients. According to the Canadian steering committee on clinical practice for the care and treatment of breast cancer, the recommended interval for gynecologic evaluation in asymptomatic postmenopausal breast cancer patients taking tamoxifen is one year whereas in cases presenting with gynecologic symptoms such as abnormal vaginal discharge or bleeding per vagina, a prompt report to the gynecologists is indicated.(The steering committee on clinical practice for the care and treatment of breast cancer, 1998)

Conclusion

Since it is obvious that long-term tamoxifen treatment does produce detrimental effects on the female reproductive tract, especially in those who are in postmenopausal period.

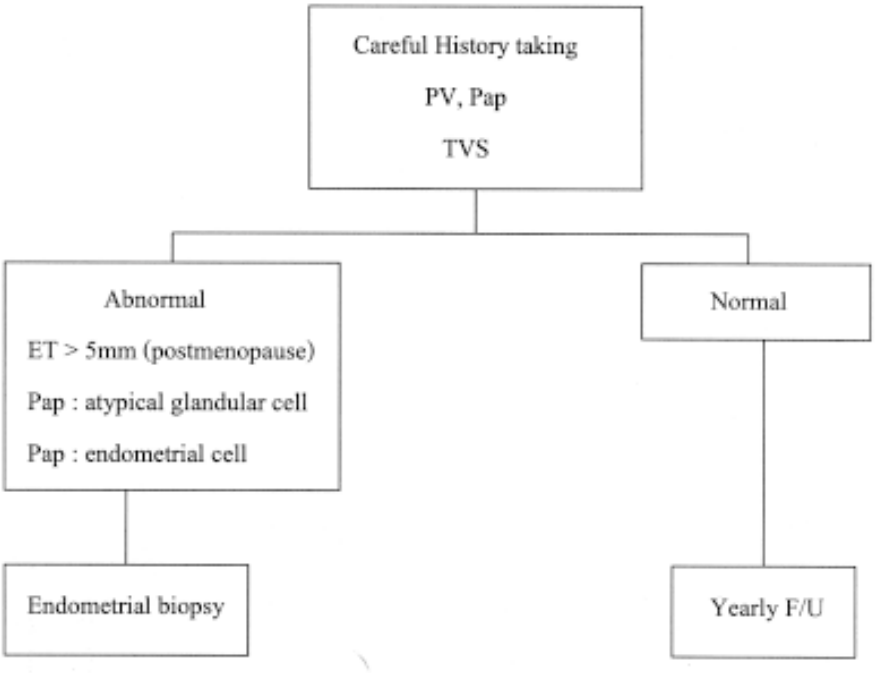

Figure 1. Pretreatment Evaluation

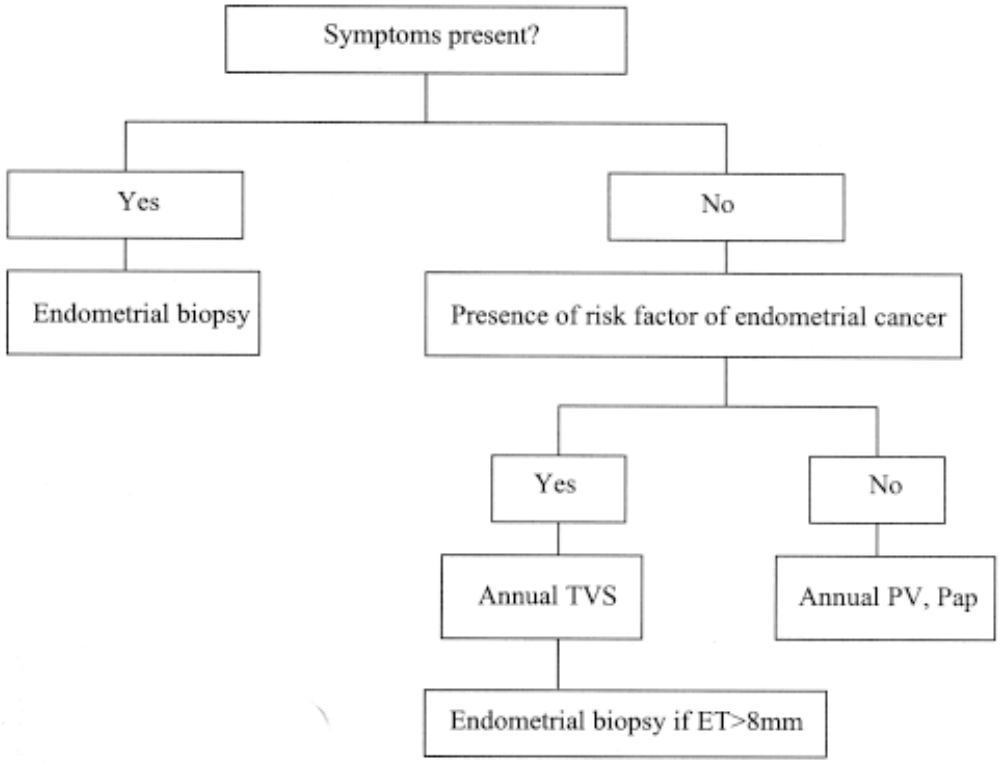

Figure 2. Ongoing-treatment Evaluation.

The appropriate surveillance methods, therefore, is required to make the most benefit out of tamoxifen therapy. Due to the vast varieties in both genetic background of the patients and availability of the medical facilities necessary for surveillance procedure, no general consensus regarding surveillance method has yet been established. Providing the setting of the developing world, the two – step strategy is being proposed in postmenopausal breast cancer patients taking tamoxifen. The first step or "pretreatment evaluation" is aimed to identify patients at risk of later development of endometrial pathologies, such as those presenting with pre-existing endometrial lesions before initiation of tamoxifen. This step of evaluation includes careful gynecologic history taking, pelvic examination, Papanicolaou smear and transvaginal ultrasonography. Endometrial biopsy is recommended if the endometrial cell or atypical gladular cell are found in Pap smear or the transvaginal ultrasound scan reveals greater than 5 mm thickness of endometrium in postmenopausal patients (figure 1).

The second evaluating step (figure 2) or "ongoing treatment evaluation", comprising of the same methods of surveillance (history taking, pelvic examination, Pap smear and transvaginal ultrasonography), is performed annually in asymptomatic patient who is found to have risk factor for endometrial cancer such as obesity, late menopause, chronic anovulation, familial cancer syndrome, nulliparity or previous pelvic irradiation. Endometrial biopsy is suggested when endometrial thickness greater than 8 mm on transvaginal ultrasound scan is detected in postmenopausal women or in any patient presenting with gynecologic symptoms such as abnormal discharge or bleeding per vagina. Using this two – step evaluating strategy, it is hoped that endometrial cancer arising after long term tamoxifen treatment will be early detected or even prevented.

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Personal profile : Supat Sinawat

Dr. Supat Sinawat was born in Khon Kaen, Thailand in 1969. After obtaining his medical degree with honours in 1992 he proceeded his training in the Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University. He finished his specialist training in 1996 and went to the United Kingdom for further study in the area of Reproductive Medicine. He obtained the degree of Master of Science (MSc) with distiction in Reproductive Biology

from the Centre for Reproductive Biology, University of Edinburgh in 1998 and did some further training in Reproductive Medicine at the Department of Obstetrics and Gynecology, University of Cambridge under the supervision of Professor SK Smith. Besides focusing on Reproductive Endocrinology, Dr. Sinawat also entends his interests into Reproductiver Genetics and cancer prevention. He was awarded the FIGO international fellowship from the International Federation of Obstetricains and Gynecologists (FIGO) in 2000 to serve as a visiting fellow in Reproductive Genetics at Baylor College of Medicine in Houston, Texas. He also recently attended the training course in cancer prevention organized by JICA at Aichi cancer center in Nagoya, Japan. Dr. Sinawat is now an assistant professor in the Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University located in the Northeastern region of Thailand.