Tamoxifen-induced endometrial cancer

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Summary

Objective: Tamoxifen-induced endometrial changes in postmenopausal women with breast carcinoma are well-known. Due to the popularity of postoperative chemotherapy for breast cancer, chemotherapy-induced early menopause in women with breast cancer on tamoxifen treatment needs more attention, because these women have higher risk for endometrial cancers than premenopausal women.

Subject: From May 1995 to May 1997, three premenopausal women aged 46, 43, and 39 with breast cancer were treated in our center. All patients received standard surgery for their breast cancers followed by six courses of adjuvant chemotherapy and 5-year tamoxifen treatment. All patients were regularly followed-up at the Breast Cancer Center and evaluated annually at the gynecological clinics including pelvic examination, Pap smear and transvaginal sonography.

Results: All patients became menopausal after six courses of chemotherapy ranging from three months to 14 months. The endometrial cancers occurred at 36 months, 28 months, and 33 months, respectively, after initial treatment for the breast cancers. Their last gynecologic examinations performed at six months, eight months and five months before the diagnosis of endometrial cancer showed nothing remarkable. Only one patient complained of vaginal spotting before diagnosis and the other two patients only complained of increasing purulent vaginal discharge. All patients received standard treatment for endometrial cancer and none of them died of their disease but one patient died of recurrent breast cancer 52 months later.

Conclusion: Women with breast cancer on tamoxifen treatment need more attention and frequent evaluation of their reproductive organs, especially postmenopausal (either spontaneous or chemotherapy induced) women, although the American College of Obstetricians and Gynecologists (ACOG) comments that no more than annual pelvic exams with Pap smears are needed in asymptomatic women.

Key words: Breast cancer; Endometrial cancer; Tamoxifen.

Introduction

Tamoxifen, the first clinically available selective estrogen receptor modulator (SERM), was developed in 1966 and approved efficacious in all settings of breast cancer. However, a series of case reports announced an association between tamoxifen therapy in women with breast cancer and the development of endometrial carcinoma in the mid-to-late 1980s [1]. Passing through more than 20 years, it seems that the occurrence of endometrial cancer in women with breast cancer on tamoxifen treatment persists. The ACOG Committee Opinion No. 169 recommends that evaluations be limited to an annual pelvic examination and Pap smear unless there is any abnormal bleeding [2]. However, some extra messages which are very important may be omitted when we do not take heed of the additional information. First, the opinion acknowledges the following: Practitioners should be alert to the increased incidence of endometrial malignancy [2]. Second, screening procedures or diagnostic tests should be performed at the discretion of the individual gynecologist [2]. The following case reports would emphasize the importance of frequent evaluation for postmenopausal women with breast cancer on tamoxifen treatment.

Revised manuscript accepted for publication November 4, 2002

Patients

From May 1995 to May 1997, three premenopausal women aged 46, 43, and 39 with breast cancer were treated in our center. None of them had a remarkable history for their family, medicine, surgery or obstetrics and gynecology. All patients received modified radical mastectomy and superficial lymph node dissection and split thickness skin grafts for their breast cancers. Pathology showed that they were localized diseases without any lymph-node metastases or distant metastases. Patients were administered six courses of postoperatively adjuvant chemotherapy (FEC regimen- 5-FU 500mg/m^2 + epirubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2) and daily 20 mg tamoxifen treatment. All patients tolerated treatment well and were regularly followed-up at the breast cancer center. At the same time, they were evaluated annually at the gynecological clinics including pelvic examination, Pap smear and transvaginal ultrasound.

Results

All patients became menopausal after six courses of chemotherapy ranging from three months to 14 months. Their last gynecologic examinations were performed six months, eight months and five months before the diagnosis of endometrial cancer and showed nothing remarkable. Symptoms or signs of the patients were non-specific before detecting endometrial cancers. Only one patient complained of vaginal spotting before diagnosis and the other two patients complained of increa-

sed purulent vaginal discharge. Transvaginal sonography (TVS) in three patients demonstrated 1.2 × 1.1 cm polyp-like lesions in the uterine cavity, 13 mm of endometrial thickness, and 7 mm of the endometrial thickness, respectively. All patients were intensively arranged to receive diagnostic dilatation and curettage (D & C). Two endometrial cancers were diagnosed at the first time of D & C but the third patient (7 mm) failed to get an accurate diagnosis because of inadequate tissue. This patient was finally diagnosed with endometrial cancer three months later by repeat D & C because she suffered from intermittent vaginal spotting after the first D & C procedure. Therefore, the endometrial cancers were detected at 36 months, 28 months, and 33 months, respectively, after initial treatment for the breast cancers. All patients were treated with standard staging surgery including washing cytology, total hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal lymph-node sampling and biopsy for any suspicious lesions. The final surgical-pathological stage was endometrioid-type endometrial cancer Stage IB, grade 1; Stage 1B, grade 2; and Stage 1A, grade 1, respectively. None of them received further postoperative adjuvant therapy for their endometrial cancers. They continued to take 20 mg daily tamoxifen for their breast cancer as usual. None of them died of endometrial cancer but one patient died of recurrent breast cancer 52 months later.

Discussion

The effect of the tamoxifen on the endometrium seems to be age-dependent (the cut value is 50, because women under 50 are presumed to be premenopausal and women over 50 are presumed to be postmenopausal). According to the results from Brest Cancer Prevention Trial (BCPT) of the study on the endometrial effects of tamoxifen in healthy women [3], in women under 50 there was no statistically significant difference in the incidence of endometrial cancer between the tamoxifen and placebo groups. However, the risk was significantly present in women over 50 [3]. In our patients, none were regarded as a high-risk group for endometrial cancer because all of them were younger than 50 and all were premenopausal when they were diagnosed with breast cancers. However, after receiving a complete course of chemotherapy, all women ended with menopause although the occurrence of time delay ranged from three months to 14 months. In this situation they became a high-risk group when they were treated with tamoxifen for the breast cancer.

All the patients in our report were followed-up regularly for annual gynecologic examination. The last follow-up of the patients had also showed negative. Unfortunately, endometrial cancers were found six months, eight months and five months after their last gynecological outpatient evaluation. It seemed that something was missed in our routine annual gynecological examination because we did not detect any abnormality at the last outpatient clinics.

For endometrial cancer screening, many screening procedures have been reported; however, so far there are no definitive conclusions with regard to the effectiveness of screening procedures, including pelvic examination, TVS, Pap smear, hysteroscopy, and standard test-endometrial biopsy or more invasive procedure - D & C. Cohen *et al.*, pointed out the significance of secondary ultrasonographic endometrial thickness in postmenopausal tamoxifen-treated women because they found that a significant increase (> 50%) in secondary endometrial thickening, measured ultrasonographically in postmenopausal tamoxifen-treated patients, was associated with a high rate of endometrial pathologies, including endometrial cancer [4]. The conflicting data argued the effectiveness of TVS in the assessment of the endometrium in these patients [5, 6] because TVS showed a high percentage of false-positive rates. In addition, Juneja et al. found a large number of postmenopausal women with breast cancer on tamoxifen treatment had an endometrial thickness of > 5 mm [7], but no endometrial cancer was found. Since TVS is not a good tool for screening, what about the pelvic exam and Pap smear? Unfortunately, the effectiveness of pelvic examinations and Pap smears seems to be much worse not only due to false positives but also false negatives. Less than 30% of endometrial cancers could be detected by routine Pap smears [8]. In addition, endometrial cancers are very difficult to detect by pelvic examination. The non-invasive procedures did not provide us with a good enough screening tool. We considered the possible value of a minimally invasive procedure – the standard procedure is endometrial biopsy – which is also fraught with difficulties and is of limited utility in screening women being treated with tamoxifen [1] because of its high false-negative rate and a high percentage of patients present with cervical stenosis which can preclude outpatient sampling [9]. All indications are that powerful screening tools for evaluating women with breast cancer on tamoxifen treatment are not yet available. Although it is disappointing for women with breast cancer on tamoxifen treatment, we can not underestimate the risk of these patients having future endometrial problems. Thus we should emphasize the importance of individual close follow-up for these women, especially when they are menopausal (either spontaneous or chemotherapy induced).

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