RESEARCH COMMUNICATION

Uterine Malignancy following Tamoxifen Use in Breast Cancer Patients in Iran: Case Series and Literature Review

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Abstract

Background: This study evaluated tumor characteristics and survival in women with breast cancer who subsequently developed uterine cancer. Methods: Information about endometrial cancer in tamoxifen users following breast cancer refered to the gynecologic oncology clinic of Vali-Asr hospital between 1997-2007 was evaluated. Results: Among 330 patients with endometrial cancer, 5 were in women previously diagnosed with breast cancer. Two cancers were malignant mixed Mullerian tumors of the uterus (MMMT), 2 were endometrioid adenocarcinomas, and one was a papillary clear cell carcinoma. Patients received tamoxifen for 4-8 years. The endometrial cancers occurred 2-11 years after initial treatment for the breast cancers. Four of the endometrial cancers featured abnormal uterine bleeding and one of them had increased vaginal discharge and all were diagnosed on endometrial curetting. All patients received standard surgical staging for endometrial cancer and all except one were stage I. At laparotomy of one patient, an advanced stage MMMT was found with diffused peritoneal spread and ascites. In spite of the surgery, she died of disease, 3 months later. The other patients remain recurrence-free for breast cancer and uterine cancer after 6-120 months. Conclusion: Breast cancer patients who use tamoxifen and have early stage endometrial cancers demonstrate a good prognosis. Abnormal uterine bleeding or vaginal discharge is the most important symptom.

Key Words: Breast cancer - Tamoxifen - uterine malignancy - abnormal uterine bleeding

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Introduction

Tamoxifen is a non-steroidal antiestrogen that was synthesized in the United Kingdom in the 1960s as a contraceptive and was approved in 1977 by the US Food and Drug Administration (FDA) for the treatment of metastatic breast cancer in postmenopausal patients (Harper et al.,1966). Now it has been approved by FDA for adjuvant treatment of breast cancer, metastatic breast cancer and reduction in breast cancer incidence in high-risk women (Fisher et al.,1998; Early Breast Cancer Trialists Collaborative Group., 1999).

Tamoxifen is in fact a selective estrogen receptor modulator (SERM) with antiestrogenic properties in the breast and estrogenic effect in tissues such as bone, endometrium and the cardiovascular system (Neven and Vergote, 2001). The most common pathologic change encountered in uteri from patients treated with tamoxifen is the endometrial polyp (Deligdisch et al., 2000). Most studies have found that the relative risk of developing endometrial cancer for women taking tamoxifen is two to three fold that of age-matched populations (Bissett et al.,1994; Fisher et al.,1994; Sismondi et al.,1994).

In this study we evaluated characteristic of uterine cancer and survival of tamoxifen treated breast cancer patients.

Materials and Methods

Cases are patients with a histologically confirmed diagnosis of uterine cancer after a diagnosis of breast cancer. The gynecologic cancer ward of Vali Asr hospital admitted 330 uterine carcinoma between 1997-2007. Five patients had history of breast cancer and tamoxifen use. Data were obtained from patients' files, pathology records and calling to patients.

Information was collected about duration and dose of tamoxifen, other treatments for breast cancer, potential risk factors for endometrial cancer, uterine cancer histopathologic types, treatment of uterine cancer and survival.

Results

The clinical characteristics of the 5 uterine cancers following tamoxifen use for breast cancer are summarized

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in Table 1. Patient's age at the time of uterine cancer diagnosis was 48-81 years. Patients number 3 and 5 were diabetic (type II). All patients have been received standard chemotherapy and radiotherapy following surgical treatment for breast cancer and all of them received tamoxifen (20 mg daily) 4-8 years. Before diagnosis of breast cancer and initiation of tamoxifen use, two patients were menopause and others were premenopause. 4/5 of patients had abnormal uterine bleeding at the time of uterine cancer diagnosis and one patient had abnormal vaginal discharge. Uterine cancer diagnosed in two patients during tamoxifen use and in three patients 2, 4, and 6 years after discontinuation of tamoxifen. Interval between breast and uterine cancer diagnosis were 2-11 years.

Histopathologic findings of 5 uterine cancer following tamoxifen use for breast cancer are summarized in Table 2. Four patients had stage I and one had stage IV. Two cancers were uterine malignant mixed Mullerian tumor (MMMT), 2 patients were endometrioid adenocarcinomas, and one was endometrial papillary clear cell carcinoma. For all patients, diagnostic curettage was done before definite surgery. Histopathologic findings of uterine curettage were similar to hysterectomy in four patients; in one patient, atypical hyperplasia was reported in endometrial curettage, but evaluation of uterine sample was shown uterine MMMT.

Surgical staging, total abdominal hysterectomy, and bilateral salpingo-oophorectomy performed for patients. At laparotomy of one patient (81 years old), an advanced stage of MMMT (IVb) was found with diffused peritoneal spread and ascitis. In spite of the surgery, she died of disease, 3 months later. Clear cell adenocarcinoma, stage Ic dignosed in one patient. She received chemotherapy (Paclitaxel and Cisplatinium), external pelvic radiotherapy, and vaginal brachytheray following definite surgery. Two patients had endometrial adenocarcinoma stage Ia and grade I, therefore they didn't received adjuvant treatment. Last patient with uterine MMMT, stage Ib received external pelvic radiotherapy and chemotherapy (Paclitaxel, Adriamicin, and Cisplatinium) after surgery. Patients followed 3-120 months after treatment. Except one patient others are alive and recurrence-free for breast cancer and uterine cancer for 6-120 months.

Table 1. Clinical Characteristics of Uterine Cancers Following Tamoxifen Use

Patient number	1	2	3	4	5
Gravidity	1	3	5	6	2
Parity	1	3	5	6	1
Age at BC	46	38	70	53	43
Interval	2	10	11	9	5
Age at UC	48	48	81	62	48
Symptoms	AUBa	AUBa	AUBa	VDb	AUBa
Tamoxifen use	5	8	5	5	4
Tamoxifen dose	20	20	20	20	20
Menopausal	-	-	+	+	-

a: Abnormal Uterine Bleeding; b: Vaginal Discharge

Table 2. Histopathology and Survival of Uterine Cancers Following Tamoxifen Use

Patient number	1	2	3	4	5
Gravidity	1	3	5	6	2
FIGO staging	Ic	Ia	IVb	Ib	Ia
Histology	CC	EA	MMMT	MMMT	EA
DFS	52	120	0	6	12
Survival	52	120	3	6	12

CC, clear cell adenocarcinoma; DFS, Disease Free Survival (months); EA, Endometrioid adenocarcinoma; MMMT, malignant mixed Mullerian tumor

Discussion

This study reported all of uterine malignancies in tamoxifen user followed breast cancer patients in Iranian population. After a case report was published about a possible association between tamoxifen and the occurrence of endometrial cancer (Killackey et al.,1985), the study of Fornander et al found a 6.4-fold increased endometrial cancer risk in the tamoxifen group compared with controls(Fornander et al.,1989). A large cohort study by Curtis et al showed that both tamoxifen treated and nontreated breast cancer patients had an increased incidence of endometrial cancer compared with the incidence in the general population (Curtis et al.,1996). In a more recent update of all NSABP trials of patients with breast cancer, the rate of endometrial cancer was 1.26 per 1,000 patient years in women treated with tamoxifen versus 0.58 per 1,000 patient years in the placebo group (Wickerham et al. ,2002).

The clinicopathologic types of endometrial cancer in tamoxifen-treated compared with nontreated patients have given rise to controversy. In the retrospective study of Magriples et al, endometrial carcinoma in tamoxifen-treated patients was of a higher grade of malignancy than in untreated patients (Magriples et al.,1993). In a large French case-control study, was shown breast cancer patients who developed endometrial cancer and had received tamoxifen had a more advanced disease and a poorer prognosis than those with endometrial cancer without prior tamoxifen(Mignotte et al.,1998). However, other studies have shown that the histologic and International Federation of Gynecology and Obstetrics (FIGO) stage of endometrial carcinoma in tamoxifen-treated and untreated patients are comparable (Wickerham et al.,2002; Magriples et al.,1993; Mignotte et al.,1998; Silva et al.,1994). Some reports have indicated that women treated with a higher dosage of tamoxifen (40 mg/d) are more prone to develop more biologically aggressive tumors(Magriples et al.,1993). In this study 2 patients had mixed malignant mulerian tumor and one patient had clear cell carcinoma. So in our case series tamoxifen was associated to aggressive histological type of uteine malignancy.

Almost all endometrial carcinomas (95%) are detected by vaginal bleeding(Carter et al.,1993) and tamoxifen users with endometrial carcinoma present with postmenopausal bleeding in the same way as nonusers(Barakat et al.,1994; Seoud et al.,1999). In our study 4/5 of patients had abnormal uterine bleeding and one patient had abnormal vaginal discharge.

Several approaches have been explored for screening

asymptomatic women using tamoxifen for abnormal endometrial proliferation or endometrial cancer. Correlation is poor between ultrasonographic measurements of endometrial thickness and abnormal pathology in asymptomatic tamoxifen users because of tamoxifen-induced subepithelial stromal hypertrophy (Achiron et al.,1995). In up to 90% of postmenopausal tamoxifen users an increased endometrial thickness on transvaginal ultrasonography occurs with an irregular pattern of echogenicity (Swiss cheese appearance) suggestive of endometrial pathology(Mourits et al.,1999).

There is a tendency both in the United States and in Europe to advise clinicians to take less initiative in presymptomatic ultrasound screening and instead to educate patients to report vaginal bleeding and discharge (Hulka et al.,1993; Ismail, 1994; Mourits et al., 2000). Women taking tamoxifen should be informed about the risks of endometrial proliferation, endometrial hyperplasia, endometrial cancer, and uterine sarcomas. If atypical endometrial hyperplasia develops, appropriate gynecologic management should be instituted, and the use of tamoxifen should be reassessed. If tamoxifen therapy must be continued, hysterectomy should be considered in women with atypical endometrial hyperplasia. Tamoxifen use may be reinstituted following hysterectomy for endometrial carcinoma in consultation with the physician responsible for the woman's breast care(ACOG committee opinion 2006).

In conclusion, breast cancer patients who use tamoxifen have early stage of endometrial cancers had a good prognosis. Abnormal uterine bleeding or vaginal discharge are the most important symptoms indicative of lesion development.

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