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Tamoxifen in the Management of Breast Cancer: A Case Presented in Multidisciplinary Session With Clinical Discussion and Decision-Making

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ABSTRACT

Background: Selective estrogen receptor modulators (SERMs) have been shown to reduce the risk of developing estrogen-positive breast cancer. Tamoxifen, a potent SERM, has been successfully administered as adjuvant therapy for breast cancer. However, uterine pathologic changes may develop due to the effect of tamoxifen as both an agonist and antagonist of estrogen on the uterus. Here, we discuss a case of breast cancer treated with tamoxifen to clarify one of the most important complications, namely, endometrial hyperplasia.

Case Presentation: A 51-year-old woman presented with left breast mass and axillary lymphadenopathy. Mammography showed a 26-mm spiculated mass consistent with invasive ductal carcinoma in core needle biopsy. Immunohistochemical analysis revealed that the tumor was ER- and PR-positive, HER2-negative. Adjuvant chemotherapy was completed, and the patient was referred to undergo adjuvant radiotherapy (RT). After the completion of RT, treatment with tamoxifen was initiated at the recommended dose of 20 mg/day.

Questions: The questions are when to use tamoxifen as adjuvant therapy for breast cancer, how to follow the patient treated with tamoxifen, and when to discontinue tamoxifen therapy.

Conclusion: Use of tamoxifen for at least 5 years after diagnosis is a reasonable option for the prevention of breast cancer or its recurrence in high-risk patients.. For premenopausal women taking tamoxifen, irregular vaginal bleeding should be evaluated by hysteroscopy or uterine ultrasonography, and, if the etiology remains unclear, a biopsy should be done. There are no evidence-based recommendations for uterine malignancy screening in patients who take tamoxifen. Current recommendations are annual gynecologic examination and evaluation of any abnormal vaginal bleeding.

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Introduction

Selective estrogen receptor modulators (SERMs) have been shown to reduce the risk of developing estrogen-positive breast cancer.[1] Tamoxifen, a potent SERM, has been successfully administered as adjuvant therapy for breast cancer. However, the

effect of tamoxifen as both an agonist and antagonist of estrogen may cause pathologic changes in the uterus.[2-4] The agonist effect may stimulate endometrial proliferation leading to endometrial polyps, hyperplasia, and, rarely, endometrial cancers.[5-9] The use of tamoxifen for more than 5 years does not seem to increase its efficacy. Moreover, the risk of endometrial cancers seems to increase for up to at least 10 years of treatment.[10] These patients must be evaluated carefully; however, the method of choice for screening is controversial.[11, 12] Here, we discuss a case of breast cancer treated with tamoxifen to clarify one of the most important complications, namely, endometrial hyperplasia.

Case Presentation

A 51-year-old woman presented with left breast mass and axillary lymphadenopathy. Mammography showed a 26-mm spiculated mass consistent with invasive ductal carcinoma in core needle biopsy. Immunohistochemical analysis revealed that the tumor was ER- and PR-positive, HER2-negative, and P53-negative. Metastatic workup was negative. Due to axillary lymph node involvement (N2), the patient was referred for neoadjuvant therapy.

After 4 cycles of epirubicin and cyclophosphamide (EC), modified radical mastectomy was performed. The pathology report after surgery did not show definite size reduction after chemotherapy (partial response), although none of the 11 dissected lymph nodes were involved. Adjuvant chemotherapy was completed, and the patient was referred to undergo adjuvant radiotherapy (RT). After the completion of RT, treatment with tamoxifen was initiated at the recommended dose of 20 mg/day. This was a case of nonmetastatic, hormone-positive invasive ductal carcinoma, and it has been shown that its recurrence risk can be reduced by adjuvant tamoxifen. In the follow-up, she did not have any sign or symptom of disease recurrence. Her menstrual cycle was stopped after the first chemotherapy course. Uterus and ovarian sonography were performed annually to detect any mass or endometrial hyperplasia. After 3 years of tamoxifen initiation, uterus sonography revealed endometrial cystic hyperplasia (15 mm) with coarse echo pattern. Because the patient had no vaginal bleeding, the multidisciplinary team decided that she did not need further evaluation. However, since endometrial thickness was above 9 mm (15 mm in our patient), tamoxifen was discontinued and replaced by an aromatase inhibitor (AI), letrozole, and a GnRH agonist, triptorelin. Endometrial hyperplasia reversed subsequently and reached 7 mm after 2 years.

Questions

The above case was presented in Imam Khomeini Hospital breast multidisciplinary team session. The questions are when to use tamoxifen as adjuvant therapy for breast cancer, how to follow the patient treated with tamoxifen, and when to discontinue tamoxifen therapy.

Discussion

Tamoxifen is a selective estrogen receptor modulator (SERM) that blocks the signaling of endogenous estrogen in normal and malignant breast tissue and is a reasonable option for the prevention of breast cancer or its recurrence in high-risk patients including those with atypical breast tissue hyperplasia, history of lobular carcinoma in situ (LCIS), five-year breast cancer risk ≥ 1.7% according to the modified Gail model, and adjuvant therapy in nonmetastatic hormone-positive breast cancer.[13] Tamoxifen possesses estrogen-like effects on the uterus, bone, liver, and coagulation system.[14] Recent studies demonstrated that tamoxifen is associated with an increased risk of both endometrial cancer and uterine sarcoma depending on the duration of its usage. Other risk factors, such as body mass index and prior estrogen replacement therapy for preventing endometrial cancer while using tamoxifen, were also evaluated. The duration of treatment should also be taken into account. Previous studies showed using tamoxifen for more than 5 years increases the risk of endometrial cancers.[15] The ATLAS trial showed a reduced risk of breast cancer recurrence, but an increased risk of endometrial cancer, among patients taking tamoxifen for more than 5 years.[16] The US National Comprehensive Cancer Network (NCCN) guidelines recommend the following for postmenopausal women: (1) an AI as initial adjuvant therapy for 5 years, with consideration of an additional 5 years on AI therapy; (2) an AI for 2 to 3 years followed by tamoxifen to complete 5 years of endocrine therapy; (3) tamoxifen for 2 to 3 years followed by either an AI to complete 5 years of adjuvant endocrine therapy or 5 years of AI therapy; or (4) tamoxifen for 4.5 to 6 years followed by 5 years of an AI, or consideration of tamoxifen for up to 10 years. In postmenopausal breast cancer patients, a tamoxifen-alone treatment regimen is only admissible when the patient refuses to take AI or there is a contraindication to AI use. The NCCN guidelines recommend 5 years of tamoxifen with or without ovarian suppression, or ovarian suppression plus an AI for 5 years in premenopausal women. For the women who become amenorrheic with chemotherapy, periodic assessment of luteinizing hormone, follicle-stimulating hormone, and estradiol is mandatory to be assigned to AI treatment.[17]

Tamoxifen leads to subendometrial gland enlargement and endometrial hyperplasia in the absence of malignancy; therefore, endometrial thickening in the absence of abnormal vaginal bleeding does not indicate further evaluation like a biopsy.[18] According to the American College of Obstetricians and Gynecologists, just taking tamoxifen is not a

reason to perform endometrial sampling or routine ultrasonography.[19] In premenopausal women taking tamoxifen who present with abnormal uterine bleeding, transvaginal ultrasonography (TVUS) is recommended. If the endometrial thickness is ≤ 4 mm, there is no need for endometrial sampling, and the routine follow-up is recommended. Endometrial biopsy is contingent on the continuation of abnormal uterine bleeding. If endometrial thickening is present in TVUS, then hysteroscopy or saline infusion sonohysterography is recommended.[20] In this group of patients, if endometrial biopsy confirms hyperplasia, it is recommended that tamoxifen be discontinued and cyclic progestin therapy be initiated. In the case of no desire for fertility, hysterectomy may be an option.[21] Some other experts recommend that for premenopusal women, taking tamoxifen, irregular vaginal bleeding should be evaluated by hysteroscopy, uterine ultrasonography and if remains ulcer biopsy should be done. In postmenopausal women treated with tamoxifen, any vaginal bleeding should be pursued with biopsy and close follow-up.[22,23] Postmenopausal women using tamoxifen with abnormal vaginal bleeding who have endometrial hyperplasia (especially atypical form) are candidates for hysterectomy. Moreover, evidence recommends dividing postmenopausal women into low- and high-risk groups for developing atypical hyperplasia based on the presence of benign endometrial polyps before therapy.[24] In this case, pretreatment screening with TVUS is recommended.[19]

There are no evidence-based recommendations for uterine malignancy screening for patients on tamoxifen. Current recommendations are annual gynecologic examination and evaluation of any abnormal vaginal bleeding.[20] The value of transvaginal ultrasound in asymptomatic patients on limited tamoxifen treatment (less than 5 years) is unproven. The abnormal endometrial thickness > 9 mm is acceptable in the studies, but further invasive investigations, such as dilation and curettage (D&C), are not recommended in the absence of vaginal bleeding.[25] Some studies recommend using hysteroscopic biopsy because D&C does not seem accurate enough to detect intrauterine pathologies in patients on tamoxifen.[26] New methods of screening are also introduced. Elastosonography, which measures endometrial tissue strain, was recently used to assess the endometrium in patients on tamoxifen.[27] Also, MRI can be used to assess endometrium and myometrium and their related pathologies when the TVUS findings are equivocal and hysterosonography is not possible to perform.[28,29]

Other alternatives to tamoxifen, such as anastrozole, were also studied. Trials showed the equivalency of anastrozole to tamoxifen in efficacy and tolerability in postmenopausal women with hormone-positive advanced breast cancer. Moreover, endometrial thickening was not observed

Multidisciplinary team (MDT) recommendation

As a conclusion, the use of tamoxifen for at least 5 years after diagnosis is a reasonable option for the prevention of breast cancer or its recurrence in high-risk patients. For premenopausal women taking tamoxifen, irregular vaginal bleeding should be evaluated via hysteroscopy or uterine ultrasonography, and, if the etiology remains unclear, a biopsy should be done. There are no evidence-based recommendations for uterine malignancy screening in patients who take tamoxifen. Current recommendations are annual gynecologic examination and evaluation of any abnormal vaginal bleeding.

Ethical Consideration

Medical ethics considerations were fully observed according to the protocol delivered by the ethics committee of the Department of Surgery at Tehran University of Medical Sciences (TUMS).

Conflict of Interest

None

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