

Tamoxifen Treatment and Risk of Endometrial Cancer: An Overview

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Abstract: For several decades, tamoxifen has proven effective in reducing recurrence and mortality for early and metastatic breast cancer with positive estrogen receptors, and has been proven to be beneficial in preventing breast cancer in high-risk women. However, tamoxifen has been associated with an increased risk of endometrial cancer by its agonist effects on the endometrium in postmenopausal women. The purpose of this article, through an exhaustive summary of literature, is to provide a better understanding of this relationship and its impact on managed care on patients.

Key words: Tamoxifen, endometrial cancer, screening.

1. Introduction

Tamoxifen is a nonsteroidal antiestrogen discovered in 1960 during research on contraception, but the Food and Drug Administration approved it in 1978 for the treatment of patients with breast cancer with hormone receptor positive [1].

He has since been the subject of hundreds of scientific publications.

A large trial interesting 75,000 patients have demonstrated that tamoxifen improves disease-free survival as well as overall survival in patients with breast cancer with hormone receptor positive regardless of their menopausal status [2].

The clinical trial findings B14 reported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) included 2,644 women with breast cancer without lymph node involvement and estrogen receptor positive [3]. They received 20 mg of tamoxifen for 5 years. After 4 years, there was a significant prolongation of disease-free survival among women treated with tamoxifen, as compared with those receiving placebo (83% versus 77%), but

without significant benefit in overall survival. Multivariate analysis confirms the benefit regardless of age.

Several studies have shown that tamoxifen reduces also the incidence of occurrence of contralateral breast cancer [1, 4, 5]. This has prompted investigations to seek the interest of tamoxifen for prevention of breast cancer among high-risk women [6-8].

Endometrial cancer is the most common female genital cancer in Europe and North America with 54,870 new cases per year [9]. However, in developing countries, it is much less common than carcinoma of the cervix. In Morocco, it's the third gynecological cancer (after breast cancer and cervical cancer) and it concerns 2.7% of all cancers [10].

The large majority of patients are diagnosed at early stage of International Federation of Gynecology and Obstetrics [FIGO] with an overall survival of 95%. The identified risk factors for endometrial cancer are numerous. Among the most important, obesity, diabetes, hypertensionand tamoxifen which is associated with small, but real, increased risk of endometrial cancer [11].

The first cases of endometrial cancer related to tamoxifen use were reported by Killackey in 1985 and

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since this association was the subject of several studies [12]. Currently, tamoxifen is considered as a risk factor of endometrial cancer.

In a study of the NSABP, the incidence of endometrial cancer in patients treated with tamoxifen 20 mg per day was 1.6 per 1,000 per year versus 0.2 per 1,000 per year in patients in the control arm and the relative risk of endometrial cancer for the latter versus the former group was 7.5 [13]. However, net benefit greatly outweighs risk with a disease-free survival in the randomized tamoxifen group was 38% less than that in the placebo group.

The purpose of this article is to provide a better understanding of this relationship, and its impact on the care of patients. Our research was based on the articles and journals in English from the Medline, Cochrane library, Central, and Web of Science, with the following keywords alone or in combination: tamoxifen, cancer of the endometrium, hormone therapy.

2. Pathophysiology

Tamoxifen behaves as an estrogen antagonist or agonist depending on the target tissue and menopausal status of the patients [14, 15]. While acting as an estrogen antagonist in the breast, it has estrogen agonist activity in other tissues; In the liver, its estrogenic actions predominates, reducing serum cholesterol levels with a favorable effect on the ratio of high density lipoprotein (HDL) versus low-density lipoprotein (LDL) cholesterol and a decrease in explaining its favorable cardiovascular effects. On bone, in premenopausal, tamoxifen has anti-estrogenic actions while in postmenopausal, it has estrogenic action that promotes bone mineralization.

Finally, tamoxifen has an agonist effect on the endometrium that can stimulate proliferation, which increases the risk of polyps, hyperplasia, and endometrial cancer in postmenopausal patients.

Tamoxifen is metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 to

active metabolites such as the 4-hydroxy and N-desmethyl-4-hydroxy (endoxifen) which have a much higher affinity to estrogen receptor than tamoxifen. These metabolites have the ability to form proteins or adducts, causing DNA damage [16]. Therefore, it was suggested that tamoxifen causes malignant tumors by genotoxicity.

The mechanism of action of tamoxifen is very complex. The ligand binding induces conformational change of the receptor that differs between oestrogen and tamoxifen [17]. The tissue-dependent mode of effect of tamoxifen can then be explained by the differential recruitment of co-factors in different tissues [18].

In breast cells, tamoxifen recruits the co-repressors: co-repressors nuclear receptor co-repressor (NCoR) and silencing mediator for retinoid and thyroid hormone receptors (SMRT) to the Estrogen Receptor (ER)-tamoxifen complex. However, in the endometrium the co-activators steroid receptor co-activator-1 (SRC-1), amplified in breast cancer-1 (AIB1) and CREB-binding protein (CBP) are recruited.

Few studies comparing the gene expression profiles of tamoxifen-associated and sporadic endometrial cancers [19, 20].

In a study by Ferguson et al, there was no difference between the gene-expression profile for tamoxifen-induced cancers and non-tamoxifen-associated endometrial cancer [19]. However, other studies have shown the opposite [20].

In vitro, tamoxifen induces endometrial cells proliferation by the activation of several signaling pathways that promote cell proliferation, including activated protein kinase mitogen and growth factor related to insulin (IGF1) [21].

Similarly, *in vivo*, tamoxifen causes an increase of cell proliferation, which results in a high Ki67 proliferation index, and a stimulation of the anti-apoptotic pathway (Fas, FasL and Bcl2) [22]. Several recent studies have suggested that the UPR and mTOR signaling pathways are activated in

long-term tamoxifen exposure-induced endometrial cancer [20, 23, 24].

By knowing the mechanism of action of tamoxifen, many new drugs were recently tested to lower the risk of endometrial cancer for tamoxifen users as: ABT-737, a BH3 mimetic drug, targeting the Bcl-2 protein, Bcl-xL and Bcl-w. The combined administration of ABT-737 with tamoxifen to mice for 10 days reduced the increase in endometrial thickness, possibly by promoting apoptosis. However, the molecular mechanism of BH3 mimetics effect of tamoxifen in blocking effects requires further investigation [25].

2.1 The Impact of Duration of Tamoxifen Treatment

The risk of developing endometrial cancer in patients treated with tamoxifen is dose and duration dependent [26-30].

The analysis of the ATLAS experiment on the interest of extending the period of use of adjuvant tamoxifen 5 years to 10 years in 12,894 patients between 1996 to 2005 has shown that the extension of its use reduces the risk of recurrence breast cancer for women with a considerable risk of relapse after completing five years of adjuvant endocrinotherapy especially in node positive cases and younger women (617 recurrences among 3,428 patients versus 711 among 3,418 patients in the control arm, $P = 0.002$), mortality from breast cancer (331 deaths versus 397 deaths, $P = 0.01$), but increases risk of development of endometrial cancer (116 versus 63 with a $P: 0.0002$). Therefore the authors suggest the use of tamoxifen for 10 years increases the risk of developing endometrial cancer by 2% [29].

Similarly, ATTOM trial (Adjuvant Tamoxifen To offer more) including 6,953 patients in 176 centers in the UK to seek the benefit of extending the use of adjuvant tamoxifen to 10 years reported 102 cases of endometrial cancer versus 45 cases (RR = 2.20, $P < 0.0001$), and higher rates of endometrial cancer death (1.1% versus 0.6%, $P = 0.02$) [30].

ATAC trial suggests that tamoxifen treatment

causes a doubling of the risk of endometrial cancer after 1-2 years and a quadrupling after 5 years of therapy respectively [31].

2.2 The Characteristics and Prognosis of Endometrial Cancer Induced by Tamoxifen

Several studies have reported that the use of tamoxifen is associated with a higher incidence of uterine sarcomas and other high-risk histologies (papillary serous, clear cell, mixed mesodermal tumor) [1, 32-35].

In a review of all the NASBP trials (B-09, B-14, B-21, B-23, B-24, and P-1), the incidence of uterine sarcomas in patients treated with tamoxifen was 10 per 10,000 per year versus no patient in the control arm [36].

Anthony et al reported a case-control study that the risk of developing malignant mixed mullerian tumors and sarcomas in patients on tamoxifen (OR = 13.5, 95% CI = 4.1 to 44.5) was higher than the risk of adenocarcinoma (OR = 2.1, 95% CI = 1.6 to 2.7) [37].

However, other studies found no difference between endometrial cancers that develop after tamoxifen therapy and endometrial cancers occurring in the general population [38, 39].

In a study from the Memorial Sloan Kettering Cancer Center including 73 patients with breast cancer who developed endometrial cancer, no difference was found in terms of age, stage, histologic type of uterine cancer, or in survival in patients treated with tamoxifen compared with other patients [39].

Most authors suggest that the prognosis of tamoxifen endometrial cancer is often poorer than among non-users [40-42]. Hoogendoorn et al showed that the 3-year survival of specific endometrial cancer is lower compared to the control arm (82% versus 93%, $P = 0.001$) even after adjustment for age, histological type and stage [41].

A recent study by Institut Curie has analyzed patients treated for an endometrial carcinoma from 1994 to 2004: patients without breast cancer (Group

1), patients with breast cancer without tamoxifen (Group 2) and patients with breast cancer with tamoxifen (group 3). Overall survival at 5 years was respectively in 1, 2 and 3: 82%, 73.2% and 61% ($P = 0.0006$) [42].

2.3 The Value of Screening Endometrial Cancer Treated with Tamoxifen

2.3.1 The Transvaginal Ultrasonography

Transvaginal ultrasonography (TVS) is the initial examination for detection of endometrial abnormalities with a sensitivity of 90% and a specificity of 48% [43].

The definition of an abnormal endometrial stripe in the patient receiving tamoxifen for breast cancer remains unclear.

Jindal et al reported that the thickness of the endometrial lining more than 5 mm is sufficient to define an abnormal endometrial ultrasound scan [44].

Kedar et al reported that an endometrial thickness greater than 8 mm has a predictive value of 100% of the presence of endometrial abnormalities [45]. The thickness of the endometrial lining was greater than 5 mm.

A cohort study had as objective to determine the prevalence and significance of endometrial changes in patients using tamoxifen with a six-monthly TVS was done and fractional curettage was performed if endometrial thickness ≥ 15 mm [46]. Only 12 patients (11.6%) had endometrial thickness ≥ 15 mm. Two patients had suspected malignancy on biopsy curettage which one was an adenocarcinoma.

The conclusion of the study was that there's no evidence of the interest of a systematic screening of asymptomatic endometrial cancer in patients treated with tamoxifen and that the biopsy endometrial curettage must be reserved for patients with breakthrough bleeding or vaginal discharge.

3. Endometrial Biopsy

Barakat presented the results of a prospective study

on the value of screening for endometrial abnormalities by endometrial biopsy in patients with breast cancer under tamoxifen on the 35th Congress of the American Society of Medical Oncology [47].

One hundred fifty-nine patients with a median age of 51 years were included. Endometrial biopsies were performed every 6 months during the first two years and then every year for the next three years, with 635 endometrial biopsies (an average of 5.8 per patient). Three patients had a hysterectomy but only a patient had a leiomyosarcoma.

The authors concluded that there is no interest of routine biopsy for screening in tamoxifen-treated women.

A more recent Indian study was performed in 50 patients treated for breast cancer with tamoxifen [44]. A transvaginal ultrasound in the follow-up was performed in all patients. If endometrial thickness was more than 5 mm hysteroscopy and endometrial biopsy was done.

Eleven patients (22%) had an endometrial thickness between 5.1 to 10 mm and 2 patients (4%) had an endometrial thickness more than 20 mm. Hysteroscopy was performed in 11 patients. 3 patients had abnormal appearance but only one patient had an endometrial adenocarcinoma histologically confirmed.

However, other studies have proposed to classify patients into low risk and high risk groups of developing endometrial cancer based on the presence or absence of benign endometrial polyps before starting treatment with tamoxifen in patients with breast cancer [48].

In a study by So Berliereand colleagues, 264 postmenopausal breast cancer patients, candidates for treatment with tamoxifen were studied prospectively with pelvic ultrasonography. Forty-six women (17.4%) had asymptomatic endometrial lesions diagnosed before starting tamoxifen, which were resected. The incidence of atypical hyperplasia was significantly higher in patients with abnormal lesion before treatment than in those without.

Thus, as recommended by the National Comprehensive Cancer Network 2015, all patients taking tamoxifen treatment should have an annual gynecological exam. The trans-vaginal ultrasound with or without an endometrial samples should be reserved for patients who have vaginal bleeding [49].

The American College of Ostertricians and Gynecologists, the American Cancer Society and the Canadian Cancer Society also does not recommend routine screening of asymptomatic patients for endometrial cancer [50-52].

4. Conclusions

Although the risks of tamoxifen are greatly outweighed by its benefits, patients must be informed of the risk of hyperplasia and endometrial cancer and the necessity to alert their physician about any sign of abnormal vaginal bleeding.

There is no consensus for monitoring patients taking tamoxifen. Routine endometrial surveillance has not proved to be effective and can cause unnecessary intervention and anxiety.

5. Conflict of Interest

The authors declare that they have no competing interests.

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