REVIEW

THE EFFECT OF LONG-TERM TAMOXIFEN USAGE ON THE LOWER PART OF FEMALE GENITAL TRACT IN BREAST CANCER SURVIVORS: A REVIEW

Yusuf Yıldırım, Emrah Toz

Aegean Obstetrics and Gynecology Training and Research Hospital, Obstetrics and Gynecology Unit, Izmir, Turkey

ABSTRACT

Tamoxifen (TAM), an anti-estrogenic synthetic drug, is widely used in the treatment of breast cancer. Due to its partial agonistic effect, long-term TAM usage may give rise to both pre-malignant and malignant uterine corpus lesions and functioning ovarian cysts. However, there are little data in the literature on the association between TAM usage and female lower genital tract lesions, such as cervical polyp and intraepithelial neoplasia (CIN), in breast cancer survivors. The present 'review' provides a current update on this topic.

Keywords: Tamoxifen, Breast cancer, Female lower genital tract

MEME KANSERİNDE UZUN SÜRELİ TAMOKSİFEN KULLANIMININ KADIN AŞAĞI GENİTAL TRAKTUS ÜZERİNE ETKİSİ

ÖZET

Sentetik anti-östrojenik bir ilaç olan Tamoksifen (TAM) meme kanseri tedavisinde yaygın olarak kullanılmaktadır. Uzun süreli TAM kullanımı parsiyel agonistik etkisine bağlı olarak pre-malign ve malign uterin korpus lezyonları ve fonksiyonel ovaryen kistlere yol açabilir. Bununla birlikte, meme kanseri öyküsü olan hastalarda TAM kullanımı ile aşağı kadın genital sistemi lezyonları, örneğin servikal polip ve servikal intra-epitelyal neoplazi (CIN), arasındaki ilişki hakkında literatürde çok az veri vardır. Mevcut 'review' bu konu hakkında güncel bir derleme sunmaktadır.

Anahtar Kelimeler: Tamoksifen, Meme kanseri, Kadın aşağı genital sistemi

INTRODUCTION

A synthetic drug Tamoxifen (TAM) originally developed by Imperial Chemical Industries (ICI, England) in 1966 has been widely used in the adjuvant treatment of breast cancer[1]. 'The National Surgical Adjuvant Breast and Bowel Project' (NSABP) has also recommended it as a chemopreventive drug in high risk population for breast cancer[2].

In spite of many years of investigations, there are still many controversies regarding the magnitude of risk of the genital pathologies, the optimal diagnostic methods of these pathologies and the value of active surveillance in TAM treated breast cancer patients[3-8].

An ambivalent drug 'TAM' has both antagonist and agonist effects. Its effects on the female genital tract depend on the ambient estradiol concentration and the menopausal status of the woman[9]. In postmenopausal women the agonistic effects

İletişim Bilgileri:
Emrah Toz, M.D.
Aegean Obstetrics and Gynecology Training and Research Hospital,
Obstetrics and Gynecology, Izmir, Turkey
e-mail: dremrah212@hotmail.com

Marmara Medical Journal 2007;20(3);196-201
Yusuf Yıldırım et al
The effect of long-term tamoxifen usage on the lower part of female genital tract in breast cancer survivors: a review

are more prominent. Additionally, some TAM metabolites such as Met-E have agonistic activity, too, but their relevance to the overall agonistic effect of the drug on the human female genital tract is debatable[10].

Depending on its weak estrogenic effect, TAM can give rise to various epithelial and non-epithelial uterine corpus lesions, such as endometrial polyp, hyperplasia, and cancer and uterine sarcoma[11,12]. Our previous study also demonstrated that a substantial rate of TAM-treated women with breast cancer (17.6%) have developed functioning ovarian cysts some of which require surgical intervention[13]. Apart from TAM's these apparent effects on the upper part of the female genital tract, it may also affect other parts of the female genital tract such as the cervical and vaginal squamous epithelium, due to the presence of estrogen receptors (ERs) in these structures[14]. However, there are few data on TAM-related female lower genital lesions in English scientific literature.

The present review has focused on presenting and discussing current knowledge on the relationship between female lower genital tract changes and long term TAM usage in breast cancer survivors. Relevant literature was traced using Medline by entering the following words and word groups 'Tamoxifen', 'lower part of female genital tract', 'abnormal cervical cytology', 'cervix uteri', 'vagina', 'cervical and vaginal squamous epithelium', 'female urethra', 'pelvic floor', 'sexual dysfunction'.

UTERINE CERVIX AND CERVICOVAGINAL SMEARS

With its weak estrogenic effect on local tissues, it is reported that TAM increases the incidence of cervical polyps as well as endometrial polyps[9,10,15,16]. Fotiou et al compared the histopathologic features of curettage and laparotomy specimens of 56 TAM-treated patients who presented with abnormal bleeding. All patients were under TAM treatment (10-40 mg daily) for a period ranging from 5 months to 15 years. Cervical and endometrial polyps were the most common findings in the curettage material (44%)[17].

In 1977, the first cytological observations regarding TAM showed that TAM-treated postmenopausal women had estrogenised rather than atrophic smears[18]. The use of TAM is associated with an increased karyopycnotic and maturation indices of cervicovaginal smears. These are related to the estrogen-like effect of TAM on the vaginal and cervical epithelium[14,19-21]. However, there is some evidence that the effects of TAM on cervicovaginal squamous epithelium change with the duration of TAM usage. Yokosuka et al reported that in contrast to increasing intermediate squamous cells (IMT), superficial cells (ST) decreased during TAM administration for up to 4 years; but when the TAM therapy was continued for longer than 4 years, IMT showed a gradual decrease and ST increased gradually. The caryopicnotic index values also showed similar changes[22].

Long-term TAM therapy is not found in relation to an increased risk of cervical inflammation[23]. On the cervical smears of these women, however, a high incidence (from 19% to 40%) of 'small blue cells', which have fine hyperchromatic chromatin and small nucleoli, is observed without other coexisting pathologies such as neuro-endocrine malignancy[20-24]. These cells are currently considered to represent proliferative 'reserve cells' of the cervicovaginal epithelium, stimulated by the agonistic effect of TAM. But these cells are not observed in women under hormone replacement therapy (HRT), so an ER-independent mechanism of action for this observation may be considered most likely[20].

In the cervicovaginal smears of TAM-treated women there is a higher incidence of benign reactive atypia or atypical squamous cells of undetermined significance (ASCUS), without accompanying increase in the risk of cervical intraepithelial neoplasia (CIN) or invasive cervical cancer. In a retrospective study, Gill et al reported that atypical cells were seen more frequently in the women who received

Marmara Medical Journal 2007;20(3);196-201
Yusuf Yıldırım et al
The effect of long-term tamoxifen usage on the lower part of female genital tract in breast cancer survivors: a review

TAM (32 of 52 patients, 61%) compared with women who had no TAM therapy at the time of the smear (6 of 21 patients, 28%; P=0.05). Of the 19 patients who had a pap smear categorized as ASCUS, 13 had undergone a subsequent cervical biopsy. Varying degrees of reactive changes were noted, but none showed dysplasia or changes diagnostic of human papilloma virus (HPV) infection[14]. In a review of the effects of TAM on the female genital tract, Fornander et al showed no difference in the occurrence of cervical cancers in a group of breast cancer patients treated with TAM compared with controls[23].

VAGINA AND SEXUAL FUNCTION

Leucorrhea is a commonly reported side effect of selective estrogen receptor modulators (SERMs) such as TAM, but somewhat paradoxically it appears to worsen vaginal dryness. The etiology of the leucorrhea is unknown; a possible estrogenic stimulation of the vagina has been suggested[15,25,26].

A possible association between TAM and mesenchymal lesions in the lower part of the female genital tract, such as fibroepithelial stromal polyp, superficial vulvovaginal and cervicovaginal myofibroblastoma, and angiomyofibroblastoma has been suggested[15,16,27,28]. Since most of these neoplasms are ER positive, some investigators have suggested that TAM might play a key role in their development or growth due to its weak estrogenic effects[27,28].

While the psychological impact of breast cancer diagnosis and subsequent cytotoxic chemotherapy can cause profound changes in sexual function, TAM itself may increase the incidence of sexual dysfunction in breast cancer survivors. Some studies also indicate that TAM treatment is associated with decreased sexual desire and increased dysparonia rates[29-32]. In a study designed to specifically assess the effects of TAM on sexual function in women with breast cancer, 22 of 41 sexually active subjects (54%) experienced pain or discomfort during sexual intercourse, unrelated to previous chemotherapy[33]. Animal studies demonstrated

that the vaginal responses of increased blood flow and fluid transudate production are estrogen dependent[34-36]. In another animal study, Kim et al reported that TAM treatment significantly reduced vaginal blood flow and increased ER expression possibly reflecting a compensatory up regulation under conditions of ER antagonism[37]. There is also some evidence that TAM treatment may possibly be associated with decreasing arginase activity in the vaginal epithelium. Arginase has been shown to modulate vascular responses in female genital tissue by decreasing intracellular arginine pools and inhibiting nitric oxide (NO) synthesis through substrate competition. The decrease in arginase activity in TAM infused rats may be reflective of a compensatory down regulation in the local vasculature to maintain vaginal perfusion. Alternatively, since arginase has been shown in other tissues to be critical for regulating cell growth via the polyamine synthesis pathway[38,39]; the lower arginase activity may be an early physiological change that eventually results in vaginal atrophy with prolonged TAM treatment.

URETHRA AND PELVIC FLOOR TISSUE

The female urinary tract has a complex control system which depends on the adequate interaction between several nervous system centers and the anatomic integrity of the bladder, urethra, and pelvic floor. Based on the importance of urethral vessels for continence[40,41]. Faria et al studied and reported that TAM led to periurethral blood flow changes measured by Doppler velocimetry (decreased pulsatility and resistance indices) and an increasing number of periurethral vessels, but they concluded that the clinical relevance of these findings was not clear[42].

Hypoestrogenism is generally considered an important causal factor for pelvic floor dysfunction including urinary incontinence, anal incontinence and pelvic organ prolapse[43,44]; although a certain beneficial role of HRT in improving the function of the pelvic floor has recently been questioned[45].

Marmara Medical Journal 2007;20(3);196-201
Yusuf Yıldırım et al
The effect of long-term tamoxifen usage on the lower part of female genital tract in breast cancer survivors: a review

TAM, as a member of the SERMs family, is known to exert estrogen-like effects on the lower genital tract; but its effect on pelvic organ prolapse and incontinence is controversial[46,47]. Vardy et al investigated short term urogenital effects in a double blind study involving 57 healthy postmenopausal women randomized to raloxifene, TAM, conjugated equine estrogen (CEE), and placebo for 20 weeks. Both raloxifene and TAM appeared to worsen prolapse and the difference was statistically significant compared with CEE and placebo. In particular, prolapse was worsened in 60% of the patients on TAM, compared with only 18% of the patients in the placebo group and 22% of the patients in the CEE group, 33% of patients on TAM complained of incontinence[46]. In contrast to this study, clinical experience with long-term TAM usage in breast cancer survivors has not supported an increased incidence of urinary incontinence[47].

CONCLUSION

Although there are relatively little data about the pathologic effects of TAM on the lower part of female genital tract, long-term TAM usage seems to be associated with not only uterine corpus and ovarian pathologies but also cervical, vaginal, urinary and pelvic floor pathologies some of which could potentially affect quality of life (Table I). The physicians interested in both gynecology and breast diseases should be aware of these pathologic effects. We recommend that all TAM users should be followed up with annual pelvic examination and cervicovaginal Pap smear, even if they have not experienced any gynecologic symptoms. We also address that carrying out new clinical trials regarding the possible relationship between the use of new anti-hormonal agents, such as aromatase inhibitors, and the development of benign and malignant lower genital tract lesions could be interesting.

Table I. TAM-related lower genital tract lesions in women with breast cancer

---

I. Cervical polyps
II. Abnormal cervico-vaginal cytological findings;
    -Increased karyopycnotic and maturation indecies
    -Benign atypical changes and ASCUS
    -The presence of 'small blue cells'
III. Fibroepithelial tumors such as fibroblastoma
IV. Vaginal atrophy resulting in dysparonia and sexual dysfunction
V. Leucorrhea
VI. Urogenital prolapse

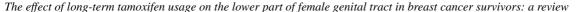ASCUS: Atypical squamous cells of undetermined significance

REFERENCES

1. Ugwumadu AH, Carmichael PL, Neven P. Tamoxifen and the female genital tract. Int J Gynecol Cancer 1998; 8: 6-15.
2. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998; 90 : 1371-1388.
3. Committee on Gynecologic Practice, The American College of Obstetricians and Gynecologists. ACOG committee opinion: Tamoxifen and endometrial cancer. Int J Gynaecol Obstet 2001; 73: 77-79 .
4. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. J Clin Oncol 1999; 17: 2050-2054.
5. Neven P, Vernaeve H. Guidelines for monitoring patients taking tamoxifen treatment. Drug Saf 2000; 22: 1-11.
6. Senkus-Konefka E, Konefka T, Jassem J. The effects of tamoxifen on the female genital tract. Cancer Treat Rev 2004; 30: 291-301.

Marmara Medical Journal 2007;20(3);196-201
Yusuf Yıldırım et al
The effect of long-term tamoxifen usage on the lower part of female genital tract in breast cancer survivors: a review

7. Neven P, Vergote I. Tamoxifen, screening and new oestrogen receptor modulators. Best Pract Res Clin Obstet Gynaecol 2001; 15: 365-380.

8. Lhomme C, Pautier P, Zagame L, et al. Endometrial surveillance of women on tamoxifen. Gynecol Obstet Fertil 2003; 31: 647-656.

9. Cohen I. Benign gynecologic conditions in tamoxifen treated patients. Am J Obstet Gynecol 2006; 194: 1204-1205 .

10. Katzenellenbogen BS, Norman MJ, Eckert RL, Peltz SW, Mangel WF. Bioactivities, estrogen receptor interactions, and plasminogen activator-inducing activities of tamoxifen and hydroxy-tamoxifen isomers in MCF-7 human breast cancer cells. Cancer Res 1984; 44: 112-119.

11. Le Donne M, Lentini M, De Meo L, Benedetto V, Mesiti M. Uterine pathologies in patients undergoing tamoxifen therapy for breast cancer: ultrasonographic, hysteroscopic and histological findings. Eur J Gynaecol Oncol 2005; 26: 623-626.

12. Yildirim Y, Inal MM, Sanci M, Yildirim YK, Mit T, Polat M, et al. Development of uterine sarcoma after tamoxifen treatment for breast cancer: report of four cases. Int J Gynecol Cancer 2005; 15: 1239-1242.

13. Inal MM, Incebiyik A, Sanci M, Yildirim Y, Polat M, Pilanci B, et al. Ovarian cysts in tamoxifen-treated women with breast cancer. Eur J Obstet Gynecol Reprod Biol 2005; 120: 104-106.

14. Gill BL, Simpson JF, Somlo G, McGonigle KF, Wilczynski SP. Effects of tamoxifen on the cytology of the uterine cervix in breast cancer patients. Diagn Cytopathol 1998; 19: 417-422.

15. Varras M, Polyzos D, Akrivis CH. Effects of tamoxifen on the human female genital tract: review of the literature. Eur J Gynaecol Oncol 2003; 24: 258-268.

16. Nucci MR, Young RH, Fletcher CDM. Cellular pseudosarcomatous fibroepithelial stromal polyps of the lower female genital tract: an unrecognized lesion often misdiagnosed as sarcoma. Am J Surg Pathol 2000; 24: 231-240.

17. Fotiou S, Tserkezoglou A, Hadjieleftheriou G, Apostolikas N, Karydas I, Stravolemos K. Tamoxifen associated uterine pathology in breast cancer patients with abnormal bleeding. Anticancer Resb 1998; 18: 625-629.

18. Ferrazzi E, Cartei G, Mattarazzo R, Fiorentino M. Oestrogen-like effect of tamoxifen on vaginal epithelium. BMJ 1977; 1: 1351-1352.

19. Daniel Y, Inbar M, Bar-Am A, Peyser MR, Lessing JB. The effects of tamoxifen treatment on the endometrium. Fertil Steril 1996; 65: 1083-1089.

20. Yang YJ, Trapkin LK, Demoski RK, Bellerdine J, Powers CN. The small blue cell dilemma associated with tamoxifen therapy. Arch Pathol Lab Med 2001; 125: 1047-1050.

21. Friedrich M, Mink D, Villena-Heinsen C, Woll Hermann A, Schmidt W. Tamoxifen and proliferation of vaginal and cervical epithelium in postmenopausal women with breast cancer. Eur J Obstet Gynecol Reprod Biol 1998; 80: 221-225.

22. Yokosuka K, Teshima H, Katase K, Fujimoto I, Yamauchi K, Hasumi K, et al. Effects of long-term administration of tamoxifen on vaginal epithelium and complications of endometrial lesions in breast cancer patients. Nippon Sanka Fujinka Gakkai Zasshi 1995; 47: 125-132.

23. Fornander T, Rutqvist LE, Wilking N. Effects of tamoxifen on the female genital tract. Ann NYAcad Sci 1991; 622: 469-476.

24. Opjorden SL, Caudill JL, Humphrey SK, Salomao DR. Small cells in cervical vaginal smears of patients treated with tamoxifen. Cancer 2001; 93: 23-28.

25. Silfen SL, Ciaccia AV, Bryant HU. Selective estrogen receptor modulators: tissue specificity and differential uterine effects. Climacteric 1999; 2: 268-283.

26. Chalas E, Costantino JP, Wickerham DL, Wolmark N, Lewis GC, Bergman C, et al. Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. Am J Obstet Gynecol 2005; 192: 1230-1237.

27. Ganesan R, McCluggage WG, Hirschowitz L, Rollason TP. Superficial myofibroblastoma of the lower female genital tract: report of a series including tumours with a vulva location. Histopathology 2005; 46: 137-143.

28. Varras M, Akrivis C, Demou A, Kitsiou E, Antoniou N. Angiomyofibroblastoma of the vagina in a postmenopausal breast cancer patient treated with tamoxifen: clinicopathologic analysis of a case and review of the literature. Int J Gynecol Cancer 2006; 16: 581-585.

29. Mourits MJ, De Vries EG, Willemse PH, Ten Hoor KA, Hollema H, Van der Zee AG. Tamoxifen treatment and gynecologic side effects: a review. Obstet Gynecol 2001; 97: 855-866.

30. Marttunen MB, Cacciatore B, Hietanen P, Pyrhönen S, Tiitinen A, Wahlström T, et al. Prospective study on gynaecological effects of two antioestrogens tamoxifen and toremifene in postmenopausal women. Br J Cancer 2001; 84: 897-902

31. Morales L, Neven P, Timmerman D, Christiaens MR, Vergote I, Van Limbergen E, et al. Acute effects of tamoxifen and third generation aromatase inhibitors on menopausal symptoms of breast cancer patients. Anticancer Drugs 2004; 15: 753-760.

32. Mourits MJ, Bockermann I, de Vries EG, van der Zee AG, ten Hoor KA, van der Graaf WT, et al. Tamoxifen effects on subjective and psychosexual wellbeing in a randomized breast cancer study comparing high-dose and standard-dose chemotherapy. Br J Cancer 2002; 86: 1546-1550.

33. Mortimer JE, Boucher L, Baty J, Knapp DL, Ryan E, Rowland JH. Effect of tamoxifen on sexual functioning in patients with breast cancer. J Clin Oncol 1999; 17: 1488-1492.

34. Park K, Ahn K, Lee S, Ryu S, Park Y, Azadzoi KM. Decreased circulating levels of estrogen alter vaginal and clitoral blood flow and structure in the rabbit. Int J Impot Res 2001; 13: 116-124.

35. Min K, Munarriz R, Kim NN, Goldstein I, Traish A. Effects of ovariectomy and estrogen and androgen treatment on sildenafil mediated changes in female genital blood flow and vaginal lubrication in the animal model. Am J Obstet Gynecol 2002; 187: 1370-1376.

36. Min K, Munarriz R, Kim NN, Choi S, O'Connell L, Goldstein I, et al. Effects of ovariectomy and estrogen replacement on basal and pelvic nerve stimulated vaginal lubrication in an animal model. J Sex Marital Ther 2003; 29: 77-84.

37. Kim SW, Kim NN, Jeong SJ, Munarriz R, Goldstein I, Traish AM. Modulation of rat vaginal blood flow and estrogen receptor by estradiol. J Urol 2004; 172: 1538-1543.

38. Li H, Meininger CJ, Kelly KA, Hawker JR, Morris SM, Wu G. Activities of arginase I and II are limiting for endothelial cell proliferation. Am J Physiol 2002; 282: 64-69.

39. Morris SM Jr. Recent advances in arginine metabolism. Curr Opin Clin Nutr Metab Care 2004; 7: 45-51.

40. Raz S, Caine M, Zeigler M. The vascular component in the production of intraurethral pressure. J Urol 1972; 108: 93-96.

41. Rud T, Andersson KE, Asmussen M, Hunting A, Ulmsten U. Factors maintaining the intraurethral pressure in women. Invest Urol 1980; 17: 343-347.

42. Faria CA, Sartori MG, Baracat EC, de Lima GR, Girao MJ. Effects of tamoxifen on Doppler velocimetry parameters of periurethral vessels in postmenopausal women. Int Urogynecol J Pelvic Floor Dysfunct 2005; 16: 56-59.

43. Albertazzi P, Sharma S. Urogenital effects of selective estrogen receptor modulators: a systematic review. Climacteric 2005; 8: 214-220.

44. Rekers H, Drogendijk AC, Valkenburg HA, Riphagen F. The menopause, urinary incontinence and other symptoms of the genito-urinary tract. Maturitas 1992; 15: 101-111.

45. Grodstein F, Lifford K, Resnick NM, Curhan GC. Post menopausal hormone therapy and risk of developing urinary incontinence. Obstet Gynecol 2004; 103: 254-260.

46. Vardy MD, Lindsay R, Scotti RJ, Mikhail M, Richart RM, Nieves J, et al. Short term urogenital effects of raloxifene, tamoxifen, and estrogen. Am J Obstet Gynecol 2003; 189: 81-88.

47. Ganz PA, Desmond KA, Leedham B, Rowland JH, Meyerowitz BE, Belin TR. Quality of life in long-term, disease-free survivors of breast cancer: a follow-up study. J Natl Cancer Inst 2002; 94: 39-49.