REVIEW

Libri Oncol., Vol. 42 (2014), No 1-3, 61 – 64

EFFECTS OF TAMOXIFEN ON THE FEMALE GENITAL TRACT

MARIO PULJIZ, DAMIR DANOLIĆ, ILIJA ALVIR and IVICA MAMIĆ

Department of Gynecologic Oncology, University Hospital for Tumors,
University Hospital Centre Sestre Milosrdnice, Zagreb, Croatia

Summary

Tamoxifen, a triphenylethyleneestrogen receptor modulator, is an effective treatment for estrogen receptor positive breast cancer patients. It acts as an estrogen antagonist in breast tissue and a week estrogen agonist in the female genital tract. Its estrogenagonist properties reflects on increased risk of gynaecologic pathologies and includes the development of endometrial cancer, endometrial hyperplasia, endometrial polyps, adenomyosis, leiomyomas, uterine sarcomas, cervical polyps and ovarian cysts. Breast cancer patients during tamoxifen treatment should be under close gynaecological and ultrasonographic surveillance.

KEY WORDS: *tamoxifen, breast cancer, female genital tract, endometrial cancer*

UČINAK TAMOXIFEN NA ŽENSKI REPRODUKTIVNI SUSTAV

Sažetak

Tamoxifen, trifeniletilenski modulator estrogesnih receptora, se koristi u liječenju raka dojke s pozitvnim estrogenskim receptorima. U tkivu dojke i tumorskim stanica ima estrogen-antagonistički učinak, a u ženskom spolnom sustavu blagi agonistički učinak što se očituje povećanim rizikom od ginekoloških bolesti koje uključuju rak endometrija, hiperplaziju endometrija, polipe endometrija, adenomiozu, miome, sarkome, polipe vrata maternice i ciste jajnika. Bolesnice s rakom dojke koje se liječe tamoxifenom trebaju biti redovito ginekološki i ultrazvučno pregledavane.

KLJUČNE RIJEČI: *tamoxifen, rak dojke, ženski spolni sustav, rak endometrija*

INTRODUCTION

Tamoxifen, a triphenylethyleneestrogen receptor modulator, is an effective treatment for estrogen receptor (ER) positive breast cancer patients. It has been conclusively demonstrated to reduce the risk of breast cancer recurrence in women with ER positive breast cancer by binding to ERs and blocking tumor proliferation (1). Tamoxifen treatment for 5 years reduces the rate of recurrence during the treatment and throughout the first decade after diagnosis and reduces breast cancer mortality rate by a third throughout the first 15 years after diagnosis (2). Prophylactic use of tamoxifen reduces the incidence of ER-positive breast cancer in healthy women for 45 % (3).

The side effects of tamoxifen are diverse and related to its mechanism of action, with mixed agonistic/antagonistic effects on various tissues. Its oestrogen-agonist properties reflects on increased risk of gynaecologicpathologies and includes the development of endometrial cancer, endometrial hyperplasia, endometrial polyps, adenomyosis, leiomyomas, uterine sarcomas, cervical polyps and ovarian cysts (3,4).

Tamoxifen is listed as human carcinogen since 1996.

GYNAECOLOGICAL CHANGES IN PREMENOPAUSAL BREAST CANCER PATIENTS RECEIVING TAMOXIFEN

The tamoxifen effects on female genital tract varies with the serum estradiol (E2) concentration and hence menopausal status of the patient (5,6). Clinical data indicate that tamoxifen therapy do not increased risk of endometrial pathology in premenopausal patients (3). Premenopausal women with continued ovarian activity and therefore elevated serum E2 levels have a little, or no risk of tamoxifen causing uterine cancer (2,3). In prospective study Cheng et al. detected no differences in mean endometrial thickness and histopathologic findings in premenopausal symptomatic patients, regardless of tamoxifen ingestion and concluded that tamoxifen might be associated with premalignant or malignant changes of endometrium only in symptomatic postmenopausal women (7). In their study, in premenopausal women using tamoxifen endometrial thickness was not increased.Chang et al. reported that patients who became amenorrheic during long-term tamoxifen treatment with low serum E2 levels have increased endometrial thickness on ultrasound, increased frequency of endometrial pathology and may be at special risk of endometrial cancer (8). Tamoxifen, in amenorrheic women with low serum E2 levels, causes endometrial thickening and in women with elevated serum E2 levels has an opposite antiestrogenic effect (8). Chen et al. in their retrospective cohort study including 74,280 tamoxifen treated breast cancer patients concluded that tamoxifen use for more than three years and/or patients older than 35 years have significantly increased risk for developing endometrial cancer (9). This study obtained several unique findings that are not in accordance with previous studies. Increased endometrial cancer risk was usually reported after 5-year tamoxifen use (10,11) and in accordance with menopausal status as mentioned above (2,7,9). Pateinetage (>35 years) became an important risk factor for the development of endometrial cancer in tamoxifen treated breast cancer patients.

Formation of ovarian cysts in breast cancer patients during tamoxifen treatment has also been reported (3,12). Mourits et al. in cross-sectional study reported that ovarian cysts in tamoxifen treated breast cancer patients develop only if ovaries are able to respond to tamoxifen by E2 production (13). In premenopausal women tamoxifen disrupts menstrual cycle by increasing the level of gonadotropin releasing hormone which stimulates ovarian estrogens production resulting in elevated E2 levels (3). Patients with menstrual periods during tamoxifen treatment usually develop simple ovarian cysts, follicular cysts, luteinized follicular cysts and corpus luteum cystswith reported incidence of 40-81% (3,13). These cysts disappeared in time or after cessation of tamoxifen therapy requiring no surgical intervention if not complicated by torsion (13). Powles et al. in a placebo-controlled tamoxifen trial reported significant increase in hot flushes mostly in premenopausal women, vaginal discharge, menstrual irregularities and increased incidence of benign ovarian cysts (14).

GYNAECOLOGICAL CHANGES IN POSTMENOPAUSAL BREAST CANCER PATIENTS RECEIVING TAMOXIFEN

The increased risk of endometrial cancer and benign uterine alterations has been reported for postmenopausal women associated with long term tamoxifen treatment (3,9,15). Tamoxifen is an estrogen agonist in the female genital tract in postmenopausal women. Deligdisch et al. evaluated endometrial histopathologic findings from 700 breast cancer patients treated with tamoxifen and found endometrial polyps, hyperplasia and cancer in one-third of all patients (16). These side effects are related to tamoxifen ability to stimulate proliferation of endometrium (4). Endometrial polyps occur in 8-50% of breast cancer patients treated with tamoxifen (3,16-18). Such polyps differ histologically from endometrial polypsof healthy patients not receiving tamoxifen and have more often (10-20 fold) malignant changes (3). Deligdisch et al. found 15 of 33 endometrial cancers in endometrial polyps (16). Endometrial hyperplasia occurs in 16-50% of breast cancer patients treated with tamoxifen (3,16-18). If endometrial atypical hyperplasia or endometrial complex hyperplasia without atypia is present cessation of tamoxifen therapy is advisable and if not, hysterectomy may be an option (3).Tamoxifen use increases the risk of endometrial cancer by 2 to 4 fold with overall incidence of 1.6-3.0 per 1000 tamoxifen treated breast cancer patients (2,3,19).

Van Leeuwen et al (20) reported that women who had used tamoxifen for more than 2 years had greater risk of endometrial cancer than never users. There was a significant trend of increasing risk of endometrial cancer with duration of tamoxifen use and also with cumulative dose (20). There is no difference in histologic phenotypes or prognostic factors of endometrial cancers found in tamoxifen treated patients from those of patients not receiving tamoxifen.In breast cancer patient with planned tamoxifen therapy pre-treatment-transvaginal ultrasonography screening is recommended to reveal high-risk group of patients with endometrial thickening. Transvaginal ultrasonography is also used to triage tamoxifen treated breast cancer patients. Standard, accepted endometrial thickness cut-off point is 5 mm in postmenopausal women, but with low frequency of significant findings on hysteroscopy. Love et al. recommended endometrial thickness cut-off point of 8 mm in asymptomatic tamoxifen treated breast cancer patients (21). Seoud et al. found that all patients with an abnormal endometrium had abnormal vaginal bleeding with no correlation between endometrial thickness and endometrial pathology and concluded that the value of routine ultrasonography screening for endometrial pathology is controversial (22). Endometrial sampling should always be obtained in symptomatic patients.

In addition, tamoxifen treatment is significantly associated with appearance of uterine sarcoma (especially MMMTs), endometrial stromal sarcomas, adenofibromas, cervical polyps, development of endometriosis and with growth of leiomyomasin postmenopausal breast cancer patients (3). The relationship between tamoxifen use and cervical cancer and vaginal neoplasms has not been reported in literature (3). There is no consensus whether postmenopausal breast cancer tamoxifen users risk developing ovarian cancer. Regardless of tamoxifen treatment, these patients have increased risk to develop ovarian tumorsdue to genetic factors (23).

The benefits of tamoxifentherapy are still without debate, despite possible severe side effects of this drug.

CONCLUSION

Breast cancer patients during tamoxifen treatment should be under close gynecological andultrasonographic surveillance. It is recommended that all tamoxifen treated breast cancer patients (premenopausal and postmenopausal) should undergo gynaecological and transvaginal ultrasonographic examination every 4-6 months or at least annually. Endometrial sampling should be obtained when the endometrium is thickened or in the event of abnormal uterine bleeding or vaginal discharge.

REFERENCES

1. Dhingra K. Selective estrogen receptor modulation: the search for an ideal hormonal therapy for breast cancer. Cancer Invest. 2001;19:649-59.
2. Davies C, Pan H, Godwin J, Gray R, Arriagada R, Raina V, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381: 805-16.
3. Nasu K, Takai N, Nishida M, Narahara H. Tumorigenic effects of tamoxifen on the female genital tract. Clin Med Pathol. 2008;1:17-34.
4. Leão RB, Andrade L, Vassalo J, Antunes A Jr, Pinto-Neto A, Costa-Paiva L. Differences in estrogen and progesterone receptor expression in endometrial polyps and atrophic endometrium of postmenopausal women with and without exposure to tamoxifen. Mol Clin Oncol. 2013;1:1055-1060.
5. Kim HS, Jeon YT, Kim YB. The effect of adjuvant hormonal therapy on the endometrium and ovary of breast cancer patients. J Gynecol Oncol. 2008;19: 256-60.
6. Powles TJ, Jones AL, Ashley SE, O'rien MER, Tidy VA, Treleaven J, et al. The Royal Marsden Hospital pilot tamoxifen chemoprevention trial. Breast Cancer Res Treat. 1994;31:73–82
7. Cheng WF, Lin HH, Torng PL, Huang SC. Comparison of endometrial changes among symptomatic tamoxifen-treated and nontreated premenopausal and postmenopausal breast cancer patients. Gynecol Oncol. 1997;66:233-7.
8. Chang J, Powles TJ, Ashley SE, Iveson T, Gregory RK, Dowsett M. Variation in endometrial thickening in women with amenorrhea on tamoxifen. Breast Cancer Res Treat. 1998;48:81-5.
9. Chen JY, Kuo SJ, Liaw YP, Avital I, Stojadinovic A, Man YG, et al. Endometrial cancer incidence in breast cancer patients correlating with age and duration of tamoxifen use: a population based study. J Cancer. 2014;5:151-5.
10. Swerdlow AJ, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. J Natl Cancer Inst. 2005;97:375–384.

11. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. Lancet 2000;356:881–887.
12. Hochner-Celnikier D, Anteby E, Yagel S. Ovarian cysts in tamoxifen-treated premenopausal women with breast cancer--a management dilemma. Am J Obstet Gynecol. 1995;172:1323-4.
13. Mourits MJ, de Vries EG, Willemse PH, ten Hoor KA, Hollema H, Sluiter WJ, et al. Ovarian cysts in women receiving tamoxifen for breast cancer. Br J Cancer. 1999;79:1761-4.
14. Powles TJ, Jones AL, Ashley SE, O'rien MER, Tidy VA, Treleaven J, et al. The Royal Marsden Hospital pilot tamoxifen chemoprevention trial. Breast Cancer Res Treat. 1994;31:73–82.
15. Fisher B, Costantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst. 1994;86:527–53.
16. Deligdisch L, Kalir T, Cohen CJ, et al. Endometrial histopathology in 700 patients treated with tamoxifen for breast cancer. Gynecol Oncol. 2000;78:181–6
17. Gerber B, Krause A, Muller H, et al. Effects of adjuvant tamoxifen on the endometrium in postmenopausal women with breast cancer: a prospective long-term study using transvaginal ultrasound. J Clin Oncol. 2000;18:3464–70
18. Gal D, Kopel S, Bashevkin M, et al. Oncogenic potential of tamoxifen on endometria of postmenopausal women with breast cancer. Gynecol Oncol. 1991;42: 120–3.
19. Assikis VJ, Jordan VC. Gynecological effects of tamoxifen and the association with endometrial carcinoma. Int J Gynecol Obstet. 1995;49:241–57.
20. Van Leeuwen FE, Benraadt J, Coebergh JW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. Lancet 1994;343:448–452.
21. 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;17:2050-4.
22. Seoud M, Shamseddine A, Khalil A, Salem Z, Saghir N, Bikhazi K, et al. Tamoxifen and endometrial pathologies: A prospective study. Gynaecol Oncol. 1999; 75:15–9.
23. Cohen I, Beyth Y, Tepper R, Shapira J, Zalel Y, Figer A, et al. Ovarian tumors in postmenopausal breast cancer patients treated with tamoxifen. Gynecol Oncol. 1996; 60:54-8.

Author's address: Mario Puljiz, Department of Gynecologic Oncology, University Hospital for Tumors, University Hospital Center Sestre milosrdnice, Ilica 197, 10000 Zagreb, Croatia; e-mail: mario.puljiz@kbcsm.hr