Value of sonographic endometrial findings in patients with breast cancer under tamoxifen therapy

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Tamoxifen is utilized as adjuvant therapy in women diagnosed with breast cancer. In these patients, despite its positive risk/benefit ratio, tamoxifen may cause secondary effects on the endometrium, with increased risk of malignant diseases[1].

So, the first question to be answered is: "Does tamoxifen increase the incidence of endometrial abnormalities?"

The literature presents two meta-analysis-studies that have been developed with this objective[2,3]. Both have demonstrated that long-term use of tamoxifen in patients with breast cancer is associated with a higher incidence of uterine diseases: the studies developed by Tabor et al.[2] and Cohen[3] — 48 papers and 106 papers, respectively. The first one has demonstrated 330 women with endometrial cancer, and other 3,483 without cancer.

Tamoxifen may lead to a range of histological alterations in the endometrium, including cystic atrophy, endometrial polyp, hyperplasia, atypical hyperplasia, endometrial adenocarcinoma, and, also, sarcoma[4,5] and uterine serous carcinoma[6] in a pre-existing polyp. The increase in the risk for endometrial cancer developed in polyps is estimated between 2.5% and 10%[5], although, according to other authors, it is a little lower[1]. Aggressive endometrial carcinoma[7] and uterine metastasis from infiltrating ductal carcinoma of the breast[8] also have been described.

Other authors have not found alterations in the endometrial thickness[9,10] or increase in the rate of polyps[11,12] and hyperplasia[12,13]. The rate of active endometrium pre- and post-tamoxifen therapy has been estimated in 10%[11]. Estrogenic effect on the endometrium has been observed in a minority of patients, without the development of hyperplasia or malignancy[14].

The second question is: "Is the ultrasound screening of asymptomatic patients mandatory?"

For answering this question, it is necessary to know the endometrial thickness (ET) cut-off value considered as ideal in the screening for endometrial diseases in postmenopausal women. The higher is the ET cut-off value, the lower will be the sensitivity (higher number of false-negative cases), and specificity (lower number of false-positive cases).

At the Clinic of Gynecology of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, ET ≤ 4 mm is considered as normal in postmenopausal women. The same value is adopted by the Department of Gynecology at Escola Paulista de Medicina da Universidade Federal de São Paulo[11].

By means of a questionnaire applied in the United Kingdom, 23.6% of the physicians have considered as normal an ET ≤ 4 mm, and 47.8%, an ET ≤ 5 mm[15]. Garuti et al.[16] have adopted ET = 4 mm in the follow-up of these patients, with safe outcomes, without increasing the number of hysteroscopies, highlighting that 2.7% of patients present pre-tamoxifen-therapy endometrial atypias. Therefore, it is necessary to perform an ultrasound study before initiating the therapy, as well as to treat each and every pre-existing uterine disease[16]. Transvaginal ultrasound (TVUS) is useful in the screening for endometrial diseases in asymptomatic patients with ET > 4 mm[17], although the screening of these patients is not universally accepted because of the high number of false-positive results[1]. An ET 15 mm-cut-off value has been proposed for women under tamoxifen therapy for increasing the specificity (87.2%), in spite of the low sensitivity (37.9%)[18]. TVUS seems to be insufficient in the screening for endometrial alter-

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ations[19], particularly hyperplasia in patients under tamoxifen therapy[9]. Combined TVUS and hysterosonography (HSG)[20,21], and color Doppler[22] may be utilized to improve the specificity of the method, and reduce the number of unnecessary interventions. However, the rate of failures is high because of cervical canal stenosis (39.3%) or patient's intolerance (6%)[23]. HSG has presented 85.5% sensitivity, 83.3% specificity, 93.7% positive predictive value, and 66% negative predictive value for differentiation between normal and pathological endometrium, lower values when compared with hysteroscopy that has presented 100% sensitivity, 94.1% specificity, 97.8% positive predictive value, and 100% negative predictive value[23]. HSG improves the sensitivity for the diagnosis of endometrial polyps, when compared with endometrial biopsy[21,24]. In postmenopausal patients under tamoxifen therapy, with bleeding, the ET cut-off value ≤ 5 mm has shown 97% sensitivity and 35% specificity. A higher cut-off value (≤ 10 mm) has not improved the overall accuracy in the diagnosis of endometrial pathological involvement[25].

According to Garuti et al.[16], hysteroscopy would be indicated in the following situations: a) ET > 4 mm[16,17]; b) increase of at least 50% in the ET measured by hysteroscopy; c) metrorrhagia; d) previous findings of endometrial hyperplasia.

A detailed investigation of the endometrium by means of endometrial cytology[26,27], and hysteroscopy with directed biopsy[9,28] have been proposed for asymptomatic patients under tamoxifen therapy. Hysteroscopy seems to be more accurate in the detection of polyps, hyperplasia and neoplasms[17,28], so many authors postulate that asymptomatic patients under tamoxifen therapy should be evaluated as if they were symptomatic[17].

Postmenopausal bleeding in patients under tamoxifen therapy increases the risk for endometrial diseases[29,30].

Other aspects regarding ET and use of tamoxifen that should be taken into consideration are: a) the therapy duration seems not affecting the lesions severity[17]; b) the ET increases with the therapy duration, at a rate of 0.75 mm/years, with a mean ET of 12 mm (6–21 mm) after five years, and decreases at a rate of 1.27 mm/year[31].

A secondary increase of > 50% in the ET measured by TVUS in postmenopausal women under tamoxifen therapy is associated with high rates of endometrial diseases, including endometrial cancer[32].

Future studies should be focused on the different etiologies of endometrial carcinomas associated with the use of tamoxifen and development of new selective estrogen receptor modulator (SERM)[33].

Patients with breast cancer are predisposed to the development of endometrial diseases[34]. The significant role of genetics and patient's predisposition to develop diseases like cancer is unquestionable.

References

1. Machado F, Rodríguez JR, León JP, Rodríguez JR, Parrilla JJ, Abad L. Tamoxifen and endometrial cancer. Is screening necessary? A review of the literature. Eur J Gynaecol Oncol 2005; 26:257–265.
2. Tabor A, Watt HC, Wald NJ. Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. Obstet Gynecol 2002;99:663–670.
3. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol 2004;94:256–266.
4. Sesti F, Patrizi L, Ermini B, Palmieri G, Orlandi A, Piccione E. High-grade endometrial stromal sarcoma after tamoxifen therapy for breast cancer. Gynecol Obstet Invest 2005;60:117–120.
5. Mbatsogo BA, Le Bouëdec G, Michy T, Bourdel N, Fouilloux G, Dauplat J. Endometrial cancers arising in polyps associated with tamoxifen use. Gynecol Obstet Fertil 2005;33:975–979.
6. McCluggage WG, Sumathi VP, McManus DT. Uterine serous carcinoma and endometrial intraepithelial carcinoma arising in endometrial polyps: report of 5 cases, including 2 associated with tamoxifen therapy. Hum Pathol 2003;34:939–943.
7. Renard F, Vosse M, Scagnol I, Verhest A. Aggressive endometrial carcinoma in a breast cancer patient treated with tamoxifen with normal transvaginal ultrasonography. Case report. Eur J Gynaecol Oncol 2002;23:25–28.
8. Meydanli MM, Karadag N, Ataoglu O, Kafkasli A. Uterine metastasis from infiltrating ductal carcinoma of breast in a patient receiving tamoxifen. Breast 2002;11:353–356.
9. Gardner FJ, Konje JC, Brown L, et al. Uterine surveillance of asymptomatic postmenopausal women taking tamoxifen. Climacteric 1998;1:180–187.
10. Salazar EL, Paredes A, Calzada L. Endometrial thickness of postmenopausal breast cancer patients treated with tamoxifen. Gynecol Endocrinol 2005;21:312–316.
11. Gonçalves MAG, Gonçalves WJ, Matias MM, Nazário ACP, Rodrigues de Lima G, Baracat EC. Hysteroscopic evaluation of the endometrium of post-menopausal patients with breast cancer before and after tamoxifen use. Int J Gynecol Obstet 1999; 66:273–279.
12. Juneja M, Jose R, Kekre AN, Viswanathan F, Seshadri L. Tamoxifen-induced endometrial changes in postmenopausal women with breast carcinoma. Int J Gynaecol Obstet 2002;76:279–284.
13. McGonigle KF, Smith DD, Marx HF, et al. Uterine effects of tamoxifen: a prospective study. Int J Gynecol Cancer 2006;16: 814–820.
14. Leslie KK, Walter SA, Torkko K, Stephens JK, Thompson C, Singh M. Effect of tamoxifen on endometrial histology, hormone receptors, and cervical cytology: a prospective study

with follow-up. Appl Immunohistochem Mol Morphol 2007;15: 284–293.

15. Brockbank EC, Ghaem-Maghami S, Bridges JE. The gynaecological management of women on tamoxifen: a national questionnaire survey. J Obstet Gynaecol 2004;24:675–679.
16. Garuti G, Grossi F, Centinaio G, Sita G, Nalli G, Luerti M. Pretreatment and prospective assessment of endometrium in menopausal women taking tamoxifen for breast cancer. Eur J Obstet Gynecol Reprod Biol 2007;132:101–106.
17. 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.
18. Markovitch O, Tepper R, Fishman A, Shapira J, Aviram R, Cohen I. The value of transvaginal ultrasonography in the prediction of endometrial pathologies in asymptomatic postmenopausal breast cancer tamoxifen-treated patients. Gynecol Oncol 2004; 95:456–462.
19. Fung MF, Reid A, Faught W, et al. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. Gynecol Oncol 2003; 91:154–159.
20. Fong K, Causer P, Atri M, Lytwyn A, Kung R. Transvaginal US and hysterosonography in postmenopausal women with breast cancer receiving tamoxifen: correlation with hysteroscopy and pathologic study. RadioGraphics 2003;23:137–150.
21. Hann LE, Kim CM, Gonen M, Barakat R, Choi PH, Bach AM. Sonohysterography compared with endometrial biopsy for evaluation of the endometrium in tamoxifen-treated women. J Ultrasound Med 2003;22:1173–1179.
22. Alcázar JL, Castillo G, Mínguez JA, Galán MJ. Endometrial blood flow mapping using transvaginal power Doppler sonography in women with postmenopausal bleeding and thickened endometrium. Ultrasound Obstet Gynecol 2003;21:583–588.
23. Garuti G, Cellani F, Grossi F, Colonnelli M, Centinaio G, Luerti M. Saline infusion sonography and office hysteroscopy to assess endometrial morbidity associated with tamoxifen intake. Gynecol Oncol 2002;86:323–329.
24. Develioglu OH, Omak M, Bilgin T, Esmer A, Tüfekçi M. The endometrium in asymptomatic breast cancer patients on tamoxifen: value of transvaginal ultrasonography with saline infusion and Doppler flow. Gynecol Oncol 2004;93:328–335.
25. Weaver J, McHugo JM, Clark TJ. Accuracy of transvaginal ultrasound in diagnosing endometrial pathology in women with post-menopausal bleeding on tamoxifen. Br J Radiol 2005;78: 394–397.
26. Labi FL, Meggiorini ML, Nusiner MP, et al. Cytologic endometrial surveillance in tamoxifen-treated women. Eur J Gynaecol Oncol 2002;23:537–539.
27. Mathelin C, Youssef C, Annane K, Brettes JP, Bellocq JP, Walter P. Endometrial brush cytology in the surveillance of post-menopausal patients under tamoxifen: a prospective longitudinal study. Eur J Obstet Gynecol Reprod Biol 2007;132:126–128.
28. Giorda G, Crivellari D, Veronesi A, et al. Comparison of ultrasonography, hysteroscopy, and biopsy in the diagnosis of endometrial lesions in postmenopausal tamoxifen-treated patients. Acta Obstet Gynecol Scand 2002;81:975–980.
29. Mossa B, Marziani R, Hannuna K, Iuele T, Melluso J, Napolitano C. Antiestrogenic therapy in breast cancer and endometrial modifications. Eur J Gynaecol Oncol 2005;26:99–102.
30. Machtinger R, Korach J, Padoa A, et al. Transvaginal ultrasound and diagnostic hysteroscopy as a predictor of endometrial polyps: risk factors for premalignancy and malignancy. Int J Gynecol Cancer 2005;15:325–328.
31. Fishman M, Boda M, Sheiner E, Rotmensch J, Abramowicz J. Changes in the sonographic appearance of the uterus after discontinuation of tamoxifen therapy. J Ultrasound Med 2006;25: 469–473.
32. Cohen I, Azaria R, Shapira J, Yigael D, Tepper R. Significance of secondary ultrasonographic endometrial thickening in postmenopausal tamoxifen-treated women. Cancer 2002;94:3101–3106.
33. Singh MN, Stringfellow HF, Paraskevaidis E, Martin-Hirsch PL, Martin FL. Tamoxifen: important considerations of a multi-functional compound with organ-specific properties. Cancer Treat Rev 2007;33:91–100.
34. Garuti G, Cellani F, Centinaio G, Sita G, Nalli G, Luerti M. Baseline endometrial assessment before tamoxifen for breast cancer in asymptomatic menopausal women. Gynecol Oncol 2005; 98:63–67.