Modification of ultrasonographically measured endometrial thickness after discontinuation of adjuvant therapy with tamoxifen in postmenopausal breast cancer patients

M. Valenzano Menada, *M.D.*; **A. Papadia,** *M.D.*; **P. Lorenzi,** *M.D.*; **S. Costantini,** *M.D.*; **G.F. Bertelli**[1], *M.D.*; **N. Ragni,** *M.D.*

Department of Obstetrics and Gynecology, University of Genoa
[1]Medical Oncology S. Croce General Hospital, Cuneo (Italy)

Summary

Introduction: The aim of this study was to evaluate endometrial changes after five years of tamoxifen treatment by measuring endometrial thickness with transvaginal ultrasonography.

Materials and Methods: Fifty-five asymptomatic postmenopausal women who had assumed tamoxifen, 20 mg daily, for five years were controlled six months after discontinuation of the therapy. Of these 42 were followed-up at 12 months.

Statistical analysis was performed using the analysis of variance for repeated measures and the Anova test; $p < 0.05$ was considered statistically significant.

Results: We found a significant reduction in endometrial thickness at six months ($p = 0.0046$) and at 12 months ($p = 0.0003$) but not between six and 12 months ($p = 0.06$).

Conclusion: A statistically significant reduction in endometrial thickness after discontinuation of tamoxifen therapy was found. This can probably be attributed to the cessation of the estrogenic side-effects of tamoxifen therapy.

Key words: Endometrial thickness; Tamoxifen; Ultrasonography.

Introduction

Tamoxifen is considered a very effective drug in the adjuvant treatment of hormone sensitive invasive and non-invasive breast cancer [1-6].

Tamoxifen however exerts estrogenic side-effects in different organs [7]. Most studies report an increased incidence of benign endometrial changes such as polyps, hyperplasia, stromal edema [8, 9], but malignant changes are reported as well and in particular the risk of developing endometrial cancer seems to be up to four times higher in patients assuming this drug than in postmenopausal women not assuming tamoxifen [3, 7, 10-12]. For this reason some authors suggest routine transvaginal ultrasonography to measure endometrial thickness as a screening for endometrial pathologies [13-17].

Even though many data have been published on the best way to screen these women for endometrial changes, not everybody agrees on the best method to use, moreover not everybody believes that these patients should be screened at all [18-22].

Vice versa, little has been published on endometrial changes after adjuvant therapy when tamoxifen is concluded [17, 23].

The aim of this study was to evaluate endometrial changes after five years of tamoxifen treatment by measuring endometrial thickness with transvaginal ultrasonography.

Revised manuscript accepted for publication October 26, 2003

Materials and Methods

Between 1993 and 2001 the endometrial thickness of 310 women receiving tamoxifen, 20 mg daily, as adjuvant therapy for breast cancer was measured by transvaginal ultrasound (SSD 680 Aloka Japan; SSA 340 Toshiba Japan).

One hundred and fifty women completed therapy (five years) and in 66 endometrial thickness was measured at the end of the therapy (T0), 6 (T1) and 12 (T2) months after adjuvant therapy was completed. Of these, 55 were asymptomatic and in menopause and thus evaluable for this study. Fifty-five women were controlled at six months and 42 at 12 months.

Endometrial thickness at the end of the treatment was < 5 mm in eight patients (14.5%) and in the other cases hysteroscopy was suggested: three patients refused the exam. Hysteroscopy revealed simple hyperplasia in two cases (5%), polyps in 19 cases (43%), atrophic endometrium in 12 cases (27%), cystic atrophic endometrium in three cases (7%) and submucosal myoma in eight cases (18%). No malignant lesion was detected.

After hysteroscopic examination transvaginal ultrasound was repeated and this measure was considered the starting measure (T0).

We evaluated whether there was a significant reduction of the ultrasonographic endometrial thickness after discontinuation of the adjuvant treatment and if different values of ultrasonographic endometrial thickness at T0 behave in a different way. We divided these women into two groups using a cut-off of 8 mm: group 1 < 8 mm; group 2 ≥ 8 mm.

This cut off was set arbitrarily and it corresponds to a cut-off used in screening programs in postmenopausal women receiving adjuvant therapy with tamoxifen with a positive predictive value of 100% for the detection of an abnormal pathology of the endometrium [13, 25].

Statistical analysis was performed using the analysis of variance for repeated measures (Anova test); $p < 0.05$ was considered statistically significant.

Results

Mean endometrial thickness measurerd by transvaginal ultrasound at T0 was 11.3 mm (standard deviation: 5.5 mm), at T1 (6 months) 9.6 mm (SD: ± 5.3 mm) and at T2 (12 months) 8.8 mm (SD: ± 5.6 mm).

We found a significant reduction in endometrial thickness between T0 and T1 (p = 0.0046) and T0 and T2 (p = 0.0003) but not between T1 and T2 (p = 0.06), even though mean endometrial thickness continued to be reduced.

At T0 25% of the women (14/55) had an ultrasonographic endometrial thickness < 8 mm; this proportion reached 34% (19/55) at T1 and 55% (23/42) at T2 (Figure 1).

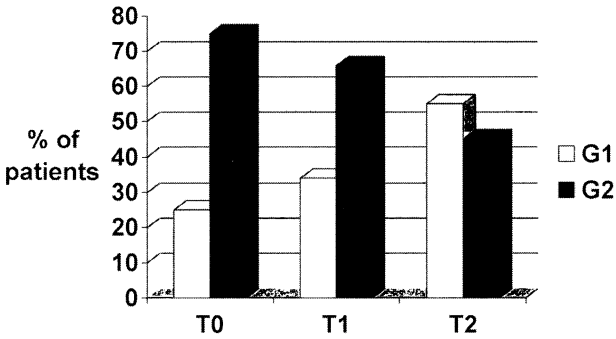

Figure 1. — Distribution of patients in groups 1 and 2 at T0, T1 and T2.

Mean endometrial thickness modification was significantly different between the two groups in the first 12 months (p = 0.0012): -1.328 mm for group 2 , + 0.083 mm for group 1.

Modification of endometrial thickness was significantly different between the two groups in the first six months (p = 0.0283): -2.317 mm in group 2; + 0.143 in group 1 (Table 1).

Table 1. — *Modification of endometrial thickness expressed in millimeters between G1 and G2 in the first six months.*

	No. of patients	Mean modification	Standard Deviation
G1	14	+ 0.143 mm	± 2.179
G2	41	– 2.314 mm	± 3.863

Modification of endometrial thickness expressed as percentage of the starting measure (T0) was significantly different for the two groups both at T1 (p = 0.0333; -16.6% for group 2, +1.2 for group 1) and at T2 (p = 0.0027; -25% for group 2. + 1.7% for group 1) (Tables 2 and 3).

Discussion

We found a statistically significant reduction in endometrial thickness after discontinuation of tamoxifen therapy. In contrast with Cohen *et al's.* results [23], this reduction continued up to 12 months after discontinuation of the therapy, even though the difference between

Table 2. — *Mean modification of endometrial thickness expressed in percentage of the starting value between T0 and T1.*

	No. of patients	Mean modification	Standard Deviation
G1	14	+ 1.198%	± 33.369
G2	41	– 16.579%	± 23.512

Table 3. — *Mean modification of endometrial thickness expressed in percentage of the starting value between T0 and T2.*

	No. of patients	Mean modification	Standard Deviation
G1	12	+ 1.667%	± 24.652
G2	30	– 24.952%	± 24.276

T1 and T2 was not statistically significant. Since in this case (modification between T1 and T2) p is 0.06 (p < 0.05 is considered statistically significant) we wonder what would have happened if all patients had continued follow-up to 12 months.

We have also demonstrated that this reduction was greater in women whose endometrium was thicker at the time of discontinuation of the therapy.

These findings can probably be attributed to the cessation of the estrogenic side-effects of the tamoxifen therapy as already suggested by Cohen *et al.* [23].

There is not always a strong correlation between endometrial thickness and hysteroscopic and histologic findings [8, 9, 24, 25].

Changes in the stroma have the same ultrasonographic appearance as changes in the endometrium and can therefore be considered the cause of this discrepancy.

Still, all these are changes which can be attributed to tamoxifen therapy. Whatever is the cause (epithelial or stromal) of the modification of the ultrasonographic measure, this appears to be strictly correlated to the estrogen side-effects of treatment with tamoxifen and to its cessation at the end of the therapy.

Acknowledgments

We acknowledge Prof. Domenico Risso and Prof. Pasquale Lantieri of the Department of Health Sciences of the University of Genova for statistical analysis.

References

[1] Jordan V.C.: "Tamoxifen: the herald of a new era of preventive therapeutics [editorial]". *J. Natl. Cancer Inst.*, 1997, *89,* 747.

[2] Early Breast Cancer Trialists' Collaborative Group: "Tamoxifen for early breast cancer: an overview of the randomised trials". *Lancet,* 1998, *351,* 1451.

[3] ACOG Committee Opinion: "Tamoxifen and endometrial cancer". *Int. J. Gyn. Obst.,* 2001, *73,* 77.

[4] Osborne C.K.: "Tamoxifen in the treatment of breast cancer". *N. Engl. J. Med.*, 1998, *339,* 1609.

[5] Fisher B., Dignam J., Wolmark N. *et al.*: "Tamoxifen in treatment of intraductal breast cancer: National Surgical Adjuvant Breast and Bowel Project B- 24 randomised controlled trial". *Lancet,* 1999, *353,* 1993.

[6] Fisher B., Costantino J.P., Wickerham D.L. *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.

[7] Mourits M.J.E., De Vries E.G.E., Willense P.H.B. *et al.*: "Tamoxifen treatment and gynecologic side effects: A review". *Obstet. Gynecol.*, 2001, *97* (5 part 2), 855.
[8] Marchesoni D., Driul L., Fabiani G. *et al.*: "Endometrial histologic changes in post-menopausal breast cancer patients using Tamoxifen". *Int. J. Gynecol. Obstet.,* 2001, *75* (3), 257.
[9] Mourits M.J.E., Van der Zee A.G.J., Willanse P.H.B. *et al.*: "Discrepancy between ultrasonography and hysteroscopy and histology of endometrium in postmenopausal breast cancer patients using Tamoxifen". *Gynecol. Oncol.,* 1999, *73,* 21.
[10] Bernstein L., Deapen D., Cerhan J.R. *et al.*: "Tamoxifen therapy for breast cancer and endometrial cancer risk". *J. Natl. Cancer Inst.,* 1999, *91* (19), 1654.
[11] Bergman L., Beelen M.L.R., Gallee M.P.W. *et al.*: "Risk and prognosis of endometrial cancer after Tamoxifen for breast cancer". *Lancet,* 2000, *356,* 881.
[12] Pukkala E., Kyyronen P., Sankila R. *et al.*: "Tamoxifen and Toremifene treatment of breast cancer and risk of subsequent endometrial cancer: a population – based case control study". *Int. J. Cancer*, 2002, *100* (3), 337.
[13] Kedar R.P., Bourne T.H., Powels T.J. *et al.*: "Effects of Tamoxifen on uterus and ovaries of post-menopausal women in a randomised breast cancer prevention trial". *Lancet,* 1994, *343*, 1318.
[14] Cohen I., Rosen D.J.D., Shapira J. et al.: "Endometrial changes with Tamoxifen: comparison between Tamoxifen treated and non-treated asymptomatic, post-menopausal breast cancer patients". *Gynecol. Oncol.,* 1994, *52,* 185.
[15] Cohen I., Azaria R., Shapira J. *et al.*: "Significance of secondary ultrasonographic endometrial thickening in postmenopausal Tamoxifen treated women". *Cancer,* 2002, *94* (12), 3101.
[16] Cohen I., Beyth Y., Tepper R.: "The role of ultrasound in the detection of endometrial pathologies in asymptomatic postmenopausal breast cancer patients with Tamoxifen treatment". *Obstet. Gynecol. Surv.,* 1998, *53* (7), 429.
[17] Gerber B., Krause A., Müller 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* (20), 3464.
[18] Juneja M., Jose R., Kekre A.N. *et al.*: "Tamoxifen induced endometrial changes in postmenopausal women with breast carcinoma". *Int. J. Gynecol. Obstet.*, 2002, *76* (3), 279.
[19] Seoud M., Shamseddle A., Khalil A. *et al.*: "Tamoxifen and endometrial pathologies: a prospective study". *Gynecol. Oncol.,* 1999, *75,* 15.
[20] Barakat R.R., Gilewski T.A., Almadrones L. *et al.*: "Effect of adjuvant Tamoxifen on the endometrium in women with breast cancer: a prospective study using office endometrial biopsy". *J. Clin. Oncol.*, 2000, *18* (20), 3459.
[21] Love C.D.B., Muir B.B., Scrimgeour J.B. *et al.*: "Investigation of endometrial abnormalities in asymptomatic women treated with Tamoxifen and an evaluation of the role of endometrial screening". *J. Clin. Oncol.*, 1999, *17* (7), 2050.
[22] Tabor A., Watt H.C., Wald N.J.: "Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding". *Obstet. Gynecol.,* 2002, *99* (4), 663.
[23] Cohen I., Beyth Y., Azzaria R. *et al.*: "Ultrasonographic measurement of endometrial changes following discontinuation of Tamoxifen treatment in postmenopausal breast cancer patients". *Br. J. Obstet. Gynecol.*, 2000, *107*, 1083.
[24] Gonçalves M.A.G., Gonçalves W.J., Matias M.M. *et al.*: "Hysteroscopic evaluation of the endometrium of post-menopausal patients with breast cancer before and after Tamoxifen use". *Int. J. Gynecol. Obstet.,* 1999, *66* (3), 273.
[25] Liedman R., Lindahl B., Andolf E. *et al.*: "Disaccordance between estimation of endometrial thickness as measured by transvaginal ultrasound compared with hysteroscopy and directed biopsy in breast cancer patients treated with Tamoxifen". *Anticancer Res.,* 2000, *20*, 4889.

Address reprint requests to:
M. VALENZANO MENADA, M.D.
Largo R. Benzi, 1
San Martino Hospital
Genova (Italy)