Original article

Annals of Oncology 16: 70–74, 2005
doi:10.1093/annonc/mdi021

Third generation aromatase inhibitors may prevent endometrial growth and reverse tamoxifen-induced uterine changes in postmenopausal breast cancer patients

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Received 26 April 2004; revised 31 August 2004; accepted 2 September 2004

Background: Tamoxifen may induce uterine abnormalities of clinical concern. Our aim was to compare early uterine changes occurring in postmenopausal breast cancer patients treated in first-line with tamoxifen or third generation aromatase inhibitors. We also assessed the effect of aromatase inhibitors on tamoxifen-induced uterine changes.

Patients and methods: Seventy-seven consecutive postmenopausal breast cancer patients scheduled to start endocrine treatment were included in this prospective study. Transvaginal ultrasonography (TVUS) was carried out before and after 3 months of therapy. No interventions were done on pre-existing asymptomatic uterine abnormalities seen on baseline sonography.

Results: After 3 months of therapy, tamoxifen significantly increased endometrial thickness and uterine volume. Additionally, tamoxifen induced endometrial cysts and polyps, and increased the size of pre-existing fibroids. In contrast, aromatase inhibitors did not stimulate endometrial growth and were not associated with endometrial pathologies seen under tamoxifen. Furthermore, aromatase inhibitors decreased endometrial thickness and uterine volume in patients previously treated with tamoxifen.

Conclusions: Our study demonstrates that tamoxifen induces uterine abnormalities from as early as 3 months of therapy. In contrast, these abnormalities are not seen in patients on aromatase inhibitors. Furthermore, our data indicate that tamoxifen therapy followed by an aromatase inhibitor may lead to a reduction in endometrial pathologies associated with tamoxifen.

Key words: aromatase inhibitors, breast cancer, endometrial thickness, SERM, tamoxifen, uterine changes

Introduction

Tamoxifen is a selective estrogen receptor modulator with a proven benefit in all stages of breast cancer. Its uterine effect increases the risk of endometrial hyperplasia, polyps [1, 2] and cancer [3]. The benefit of screening is controversial since most of these uterine changes are benign [4, 5]; however, many women undergo interventions to exclude malignant disease. Strategies to protect the endometrium from tamoxifen-induced changes using progestagens have been evaluated [6, 7]. However, the potential detrimental effect of such agents on the breast remains a matter of concern [8, 9]. Nowadays, third-generation non-steroidal aromatase inhibitors such as anastrozole and letrozole, and the steroidal type exemestane are increasingly being used in the management of breast cancer [10, 11]. These agents suppress estrogen synthesis by inhibiting aromatase, blocking the conversion of androgens to estrogens in postmenopausal women to almost undetectable circulating levels [12–14]. In the adjuvant ATAC trial, anastrozole when compared to tamoxifen was associated with less uterine abnormalities [15], while the uterine effects of letrozole and exemestane have not yet been fully documented. Our aim was to compare early changes in double endometrial thickness (DET) and uterine volume (UV) occurring in postmenopausal breast cancer patients receiving either tamoxifen or aromatase inhibitor in first-line. We also assessed the uterine effects of aromatase inhibitors in patients previously exposed to tamoxifen.

Patients and methods

We conducted a prospective single-center study in all fit non-hysterectomised postmenopausal breast cancer patients scheduled to start endocrine

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treatment. Postmenopausal status was defined as cessation of menses for more than 1 year. In case of doubt, follicle stimulating hormone and estradiol levels were assessed and had to be in the postmenopausal range. Women on hormone replacement therapy while being diagnosed with breast cancer had stopped therapy for at least 1 month before the start of this study. Two investigators (DT and MLK), who were blinded on the hormonal treatment patients were receiving, carried out transvaginal ultrasonography (TVUS) before the start of endocrine treatment and after 3 months of therapy. The uterus was completely assessed in sagittal and coronal planes with uterine size recorded in three diameters (D_1, $_2$, $_3$). The volume (ml) was estimated as ($D_1 \times D_2 \times D_3 \times 3.14$)/6. DET was measured in the sagittal plane, from one endometrial–myometrial interface to another excluding intracavitary fluid. Endometrial abnormalities such as internal cysts and polyps were recorded. The presence of internal cysts was defined by visualization of more than one anechogenic area greater than 2 mm. No interventions were done on pre-existing asymptomatic uterine abnormalities seen on baseline sonography. The study was conducted according to the guidelines for clinical studies described in the Declaration of Helsinki (as revised by the World Medical Association, http://www.wma.net). The protocol was approved by the Ethical Committee for Clinical Studies and all participants provided written informed consent.

Statistical analysis was done with SAS (Version 8). ANOVA was used to determine differences in mean DET and UV between the different treatment groups. If significant differences were detected, appropriate post-hoc comparisons were done. Multiple regression analysis was carried out to detect variables influencing DET. Table 1 shows the six different treatment groups. Groups 1 to 4 comprised patients receiving adjuvant therapy with either tamoxifen, letrozole, anastrozole, or a blinded treatment with either tamoxifen or letrozole (randomized FEMTA trial with equal chances of receiving either treatment). Group 5 patients received exemestane after tamoxifen. Group 6 patients received exemestane after letrozole.

Results

The 77 women included in this study had a mean age of 60 years, were on average 10 years postmenopausal, and had a mean BMI of 25 kg/m^2. Fifty-nine patients (77%) received adjuvant hormonal treatment whereas the remaining patients were treated for advanced disease. Table 1 shows that at baseline, a significantly higher mean DET of 9.89 mm was recorded in patients previously treated with tamoxifen ($P < 0.0001$) while no significant difference in the baseline DET and UV was seen between the other groups. Three months on tamoxifen led to a 65% increase in mean DET and a 38% increase in UV ($P < 0.0001$ and $P = 0.0062$, respectively). Patients on first-line letrozole or anastrozole and patients on exemestane after exposure to letrozole did not have significant changes in both parameters. In contrast, crossing-over to exemestane because of breast cancer progression under tamoxifen resulted in a 37% decrease in mean DET and a 26% decrease in UV. Compared with the tamoxifen group, this change from baseline mean DET and UV for patients on exemestane was significant ($P < 0.0001$ and $P = 0.0035$, respectively). The mean DET and UV observed at 3 months in the FEMTA group was in agreement with the results expected from a 50/50 mixture of patients on tamoxifen or letrozole. In five patients not belonging to any of the previously described six groups, formal statistical analysis was not done due to the limited number. Two of them crossed-over from tamoxifen to letrozole, which induced mean DET and UV decreases of 3.35 mm and 12 cm^3, respectively, after 3 months. The last three patients who were therapy naive received adjuvant exemestane. TVUS was done after 3 months therapy (one patient) and was postponed to 6 months (two patients) for patients' convenience. In all three patients, adjuvant exemestane induced further uterine atrophy with a 1.23 mm mean decrease in DET and an 8 cm^3 decrease in UV. The change in DET from baseline to 3 months treatment of each individual patient is illustrated in Figure 1.

Apart from the above mentioned DET and UV changes, other sonographic findings after 3 months are shown in Table 2. Those on tamoxifen developed internal cysts (40%), endometrial polyps (15%) and an increase in size of

Table 1. Transvaginal sonographic changes of the uterus from baseline to 3 months of treatment

	No prior treatment				Prior treatment with	
					Tamoxifen	Letrozole
Group	1	2	3	4	5	6
Treatment	Tamoxifen	FEMTA	Letrozole	Anastrozole	Exemestane	Exemestane
No. of patients	20	21	9	6	9	5
DET (mm)						
Baseline	3.82 (2.35)	3.78 (1.91)	2.54 (1.15)	3.25 (0.42)	9.89 (7.33)	4.82 (3.53)
3 months	6.30 (3.46)	3.87 (2.37)	2.28 (0.78)	2.93 (1.47)	6.27 (4.57)	4.36 (3.28)
Difference	2.48 (2.20)	0.08 (1.76)	−0.26 (1.43)	−0.32 (1.34)	−3.62 (6.27)	−0.46 (0.47)
UV (cm^3)						
Baseline	61 (60)	42 (21)	34 (20)	39 (25)	58 (30)	57 (18)
3 months	84 (70)	50 (26)	34 (15)	32 (20)	43 (27)	54 (18)
Difference	23 (38)	8 (14)	0 (9)	−7 (8)	−15 (23)	−3 (5)

Values are shown as mean (SD). Abbreviations: FEMTA, randomized double blind trial comparing adjuvant tamoxifen versus letrozole; DET, double endometrial thickness in millimeters; UV, uterine volume in cubic centimeters.

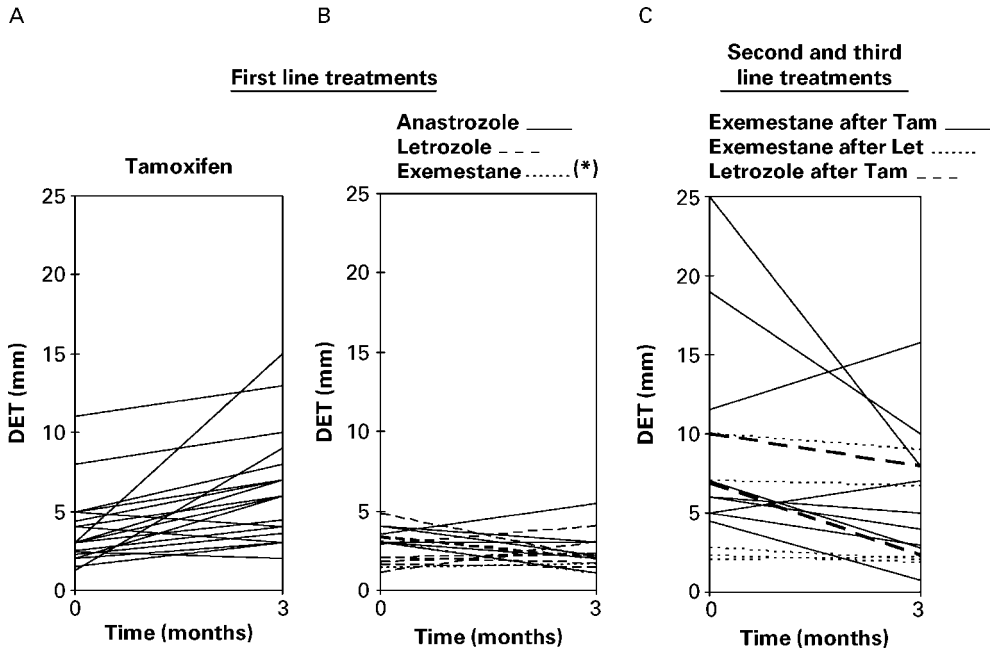


Figure 1. Changes in DET from baseline to 3 months of treatment. Each line represents each individual patient. (A) First-line treatment; solid line, tamoxifen. (B) First-line treatment; solid line, anastrozole; dashed line, letrozole; dotted line, exemestane. Second TVUS was done after 6 months in two patients receiving first-line exemestane. (C) Second- and third-line treatments; solid line, exemestane after tamoxifen; dotted line, exemestane after letrozole; dashed line, letrozole after tamoxifen. Abbreviations: DET, double endometrial thickness.

pre-existing fibroids (25%), whereas those receiving aromatase inhibitors did not develop internal cysts or polyps and 28% had a decrease in the size of pre-existing polyps or fibroids. On multiple regression analysis, the presence of internal cysts and polyps significantly correlated with DET ($P = 0.0051$ and $P = 0.0164$, respectively). There were two patients in whom DET could not be measured after 3 months: one developed a symptomatic endometrial polyp diagnosed at 8 weeks of tamoxifen use and one had a hysterectomy and bilateral salpingo-oophorectomy for an ovarian tumor discovered on baseline TVUS (mucinous cystadenoma on histopathology).

Discussion and conclusions

Our study demonstrates that tamoxifen significantly increases endometrial thickness and uterine volume after only 3 months of therapy. Likewise, very early uterine abnormalities induced by tamoxifen, such as endometrial cysts, polyps and an increase in size of pre-existing fibroids, are already evident. In contrast, steroidal and non-steroidal aromatase inhibitors induce uterine atrophy and are not associated with uterine pathologies seen under tamoxifen. Furthermore, an important finding is that aromatase inhibitors can decrease endometrial thickness and uterine volume in patients treated with tamoxifen.

To date, the early uterine effect of tamoxifen after only 3 months of therapy has not been assessed. Furthermore, studies on the uterine effects of aromatase inhibitors, particularly their effects on tamoxifen-associated abnormalities, are limited. The lack of endometrial effect of anastrozole, a non-steroidal aromatase inhibitor has recently been reported [16]. Letrozole was shown to reverse tamoxifen-induced endometrial thickening in a preliminary report of 24 patients [17]. However, this study did not mention the effect of letrozole on other tamoxifen-associated abnormalities such as polyps and fibroids. While the atrophic effect of letrozole may be anticipated from what is known with the other non-steroidal aromatase inhibitor, anastrozole, the observation on exemestane patients is novel. Since exemestane belongs to another category of aromatase inhibitors, being steroidal in structure, its uterine effects cannot be presumed to be identical to non-steroidal aromatase inhibitors. It is devoid of total cross-resistance with non-steroidal aromatase inhibitors [18] and displays a different action (possibly androgen-mediated) on organ systems such as serum lipids [19–23] and the bone [13, 24]. However, our data on the favorable effect of exemestane on tamoxifen-induced endometrial abnormalities have to be confirmed in larger studies with a longer follow-up period, such as the endometrial substudy of the Intergroup Exemestane Study [25].

TVUS is a relatively non-invasive procedure which enabled us to demonstrate the distinct uterine effects of tamoxifen and aromatase inhibitors early in the course of therapy. A study such as this with a detailed systematic pre-treatment uterine evaluation allowed us to attribute accurately the uterine changes observed after 3 months to a particular treatment. Although routine screening is not recommended in asymptomatic women receiving tamoxifen, the application of TVUS in clinical trials looking at endometrial safety of different endocrine treatments can be considered an adequate procedure, having shown equal accuracy and better acceptability than relatively more invasive procedures [26].

Table 2. Transvaginal sonographic abnormalities of the uterus at 3 months of treatment

	No prior treatment				Prior treatment with	
					Tamoxifen	Letrozole
Group	1	2	3	4	5	6
Treatment	Tamoxifen	FEMTA	Letrozole	Anastrozole	Exemestane	Exemestane
No. of patients	20	21	9	6	9	5
Internal cysts						
No change	0	0	0	0	3	1
Developed	8	0	0	0	0	0
Disappeared	0	1	0	0	1	1
Polyps						
No change	1	1	0	0	1	0
Increased size	1	0	0	0	0	0
Decreased size	0	0	0	0	0	0
Developed	3	0	0	0	0	0
Disappeared	0	1	0	0	3	1
Myomas						
No change	4	0	2	0	2	1
Increased size	5	2	0	0	0	0
Decreased size	0	0	0	1	2	1
Disappeared	0	1	0	1	0	0

Our results have some important clinical implications. First, steroidal and non-steroidal aromatase inhibitors seem safe from a gynecological point of view. They all induce uterine atrophy which fit with their putative mechanism of action of inhibiting estrogen synthesis. This is reassuring because these compounds are increasingly being used in the adjuvant and even in the preventive setting. Secondly, on the assumption that tamoxifen-induced endometrial thickening by TVUS is often a precursor or surrogate marker of endometrial pathologies [2], the reversal of such suggests that tamoxifen therapy followed by an aromatase inhibitor may not only be more effective as shown in the recent MA-17 trial [27] but may, in the end, lead to a reduction in endometrial pathologies associated with tamoxifen.

Although it is interesting to consider the possibility that a short treatment with aromatase inhibitors in patients with tamoxifen-induced uterine abnormalities could possibly reduce or obviate invasive procedures such as hysteroscopy or curettage, the validity and safety of such an approach warrants further evaluation. Future clinical trials looking at endometrial safety of endocrine treatments, particularly those trials involving sequential treatments with selective estrogen receptor modulators and aromatase inhibitors, should also take into account the potential effect on the uterus of a wash-out period after tamoxifen treatment. The studies will determine whether tamoxifen-induced changes would eventually resolve over time or whether aromatase inhibitors can offer a protective effect on the endometrium of patients treated with tamoxifen.

Acknowledgements

We thank all the women who took part in this study. The statistical analysis in connection with SVH and LA was supported by interdisciplinary research grants of the research council of the Katholieke Universiteit Leuven, Belgium (IDO/99/03 and IDO/02/09 projects), by the Belgian Programme on Interuniversity Poles of Attraction (IUAP PhaseV-22) and by the Concerted Action Project MEFSTO-666 of the Flemish Community.

References

1. Neven P, De Muylder X, Van Belle Y et al. Tamoxifen and the uterus and endometrium. Lancet 1989; i: 375.
2. Kedar RP, Bourne TH, Powles TJ et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. Lancet 1994; 343: 1318–1321.
3. 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.
4. Neven P, Vergote I. Should tamoxifen users be screened for endometrial lesions? Lancet 1998; 351: 155–157.
5. Goldstein S. Controversy about uterine effects and safety of SERMs: the saga continues. Menopause 2002; 9: 381–384.
6. Powles TJ, Bourne T, Athanasiou S et al. The effects of norethisterone on endometrial abnormalities identified by transvaginal ultrasound screening of healthy post-menopausal women on tamoxifen or placebo. Br J Cancer 1998; 78: 272–275.
7. Gardner FJE, Konje JC, Abrams KR et al. Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing

intrauterine system: a randomised controlled trial. Lancet 2000; 356: 1711–1717.
8. Rossouw J, Anderson G, Prentice R et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002; 288: 321–333.
9. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003; 362: 419–427.
10. Goss PE, Strasser K. Aromatase inhibitors in the treatment and prevention of breast cancer. J Clin Oncol 2001; 19: 881–894.
11. Lake D, Hudis C. Aromatase inhibitors in breast cancer: An update. Cancer Control 2002; 9: 490–498.
12. Paridaens R, Thomas J, Wildiers J et al. Safety, activity and estrogen inhibition by exemestane in postmenopausal women with advanced breast cancer: a phase I study. Anti-Cancer Drugs 1998; 9: 675–683.
13. Dowsett M, Jones A, Johnston SRD et al. In vivo measurement of aromatase inhibition by letrozole (CGS 20267) in postmenopausal patients with breast cancer. Clin Cancer Res 1995; 1: 1511–1515.
14. Geisler J, King N, Dowsett M et al. Influence of anastrozole (Arimidex), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in postmenopausal women with breast cancer. Br J Cancer 1996; 74: 1286–1291.
15. The ATAC (Arimidex Tamoxifen Alone or in Combination) Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002; 359: 2131–2139.
16. Duffy S, Jackson T. Fewer endometrial abnormalities with anastrozole than tamoxifen: Endometrial subprotocol results from the ATAC (Arimidex, Tamoxifen Alone or in Combination) early breast cancer trial in postmenopausal patients. Ann Oncol 2002; 13 (Suppl 5): 39 (Abstr 139).
17. Garrone O, Mezi S, Occelli M et al. Reversal of tamoxifen induced endometrial modifications by switching to letrozole in early breast cancer patients: A prospective TVUS study. Ann Oncol 2003; 14 (Suppl 4): iv7 (Abstr A22).
18. Lonning PE, Bajetta E, Murray R et al. Activity of exemestane in metastatic breast cancer after failure of non-steroidal aromatase inhibitors: a phase II trial. J Clin Oncol 2000; 18: 2234–2244.
19. Goss P. Anti-aromatase agents in the treatment and prevention of breast cancer. Cancer Control 2002; 9: 2–8.
20. Engan T, Krane J, Johannessen DG et al. Plasma changes in breast cancer patients during endocrine therapy—lipid measurements and nuclear magnetic resonance (NMR) spectroscopy. Breast Cancer Res Treat 1995; 36: 287–297.
21. Atalay G, Dirix L, Biganzoli L et al. The effect of exemestane on serum lipid profile in postmenopausal women with metastatic breast cancer: A companion study to EORTC Trial 10951, 'Randomized phase II study in first line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients'. Ann Oncol 2004; 15: 211–217.
22. Elisaf MS, Bairaktari ET, Nicolaides C et al. Effect of letrozole on the lipid profile in postmenopausal women with breast cancer. Eur J Cancer 2001; 37: 1510–1513.
23. Dewar J, Naboltz J, Bonneterre J et al. The effect of anastrozole (Arimidex) on serum lipids—data from a randomized comparison of anastrozole versus tamoxifen in postmenopausal women with advanced breast cancer. Breast Cancer Res Treat 2000; 64 (Suppl 51): 51 (Abstr 164).
24. Goss P, Thomsen T, Banke-Bochita J et al. A randomized, placebo-controlled, explorative study to investigate the effect of low estrogen plasma levels on markers of bone turnover in healthy postmenopausal women during the 12-week treatment with exemestane or letrozole. Breast Cancer Res Treat 2002; 76 (Suppl 76): 576 (Abstr 267).
25. Gibson L, Gianfilippo B, Hall E et al. Transvaginal ultrasound findings in patients participating in the Intergroup Exemestane Study. Proc Am Soc Clin Oncol 2002; 21: 486 (Abstr 2005).
26. Timmerman D, Deprest J, Bourne T et al. A randomized trial on the use of ultrasonography or office hysteroscopy for endometrial assessment in postmenopausal patients with breast cancer who were treated with tamoxifen. Am J Obstet Gynecol 1998; 179: 62–70.
27. Goss P, Ingle J, Martino S et al. A randomized trial of letrozole in postmenopausal women after 5 years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 2003; 349: 1–10.