1. Early Breast Cancer Triallists' Collaborative Group E. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomized trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. *Lancet* 1992, **339**, 1–15.
2. Powles T, Hardy J, Ashley S, *et al.* A pilot trial to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer. *Br J Cancer* 1989, **60**, 126–131.
3. Jones A, Powles T, Treleaven J, *et al.* Haemostatic changes in thromboembolic risk during tamoxifen therapy in normal women. *Br J Cancer* 1992, **66**, 744–747.
4. Powles TJ, Hickish T, Kanis JA, Tidy A, Ashley S. Effect of tamoxifen on bone mineral density measured by dual energy X-ray absorptiometry in healthy pre-menopausal and post-menopausal women. *J Clin Oncol* 1996, **14**, 78–84.
5. Chang J, Powles T, Ashley S, Iveson T, Gregory R, Dowsett M. Variation in endometrial thickening in women with amenorrhoea on tamoxifen. *Breast Cancer Res and Treat* 1998, in press.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S18–S19, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00091-4

II.2 Tamoxifen and Benign Endometrial Lesions

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Benign endometrial lesions are common among breast cancer patients treated with tamoxifen but also among healthy women taking this drug in a breast cancer prevention trial. The most frequent lesion is glandulocystic atrophy which seems specific for this drug. Endometrial polyps are also very often seen but only a few of them could undergo malignant degeneration. Hyperplasia of the endometrium is more frequently reported among tamoxifen patients than among control patients. © **1998 Elsevier Science Ltd. All rights reserved.**

TAMOXIFEN IS a non-steroidal anti-oestrogen drug widely used as first-line endocrine therapy in breast cancer patients. However, this molecule has also some oestrogen agonist activity on the female genital tract. Our paper summarises the benign endometrial lesions related to tamoxifen use.

Endometrial atrophy remains the commonest histological finding in postmenopausal women receiving tamoxifen but endometrial proliferation, glandulocystic changes, hyperplasia, endometrial decidualisation and various sorts of polyps have all been described with the help of hysteroscopy, transvaginal ultrasound scan, saline infusion sonography, colour Doppler flow studies, Pipelle aspiration or Novak biopsy and curettage. The exact incidence of these lesions is difficult to assess precisely because most publications are describing very different and generally small groups of patients. Furthermore, various study designs are utilised and several instruments of investigation of the cavity have been used. Moreover, different parts of the same endometrium in an individual patient may display contrasting features.

Three benign endometrial lesions have been described among tamoxifen users, the first one being the most typical and specific of the effect of this drug upon the uterine cavity.

Glandulocystic atrophy [1]

Hysteroscopy shows a smooth, white but hypervascularised endometrial layer with many scattered protuberances. This pseudopolypoid glandulocystic mucosa represents an atrophic, thin epithelium overlying cystic dilatations of the endometrial glands in a dense, rich in collagen stroma containing large oedematous areas. In these cases, ultrasonography displays an irregularly thickened endometrium with Gruyère cheese pictures.

Endometrial polyps which frequently contain dilated cystic glands and sometimes also stromal decidualisation changes

Both hyperplastic and atrophic polyps have been reported but, according to Ismail [2], periglandular stromal condensation, epithelial metaplasias and proliferative activity, sometimes with various degrees of atypia, are typical for the histologic appearance of tamoxifen-induced endometrial polyps. Among these patients, ultrasonography will reveal a free-floating glandulocystic structure and hysteroscopy will confirm the diagnosis.

Endometrial hyperplasia: simple or complex, with or without atypia may be observed

Retrospective studies describing tamoxifen effects on the endometrium are numerous and of limited interest because of lack of uniform methodology. A few case–control studies did compare postmenopausal breast cancer patients treated by tamoxifen with similar breast cancer patients without this treatment. Neven [3] using hysteroscopy, Cohen [4] using endovaginal ultrasonography and Exacoustos [5] and Lahti [6] using both methods together, did report on 212 tamoxifen patients. In general they observed oestrogen-like activity (including glandulocystic atrophy) in 20–35% of tamoxifen-

treated patients compared to 5–15, 0–10 and 2–5%, respectively among non-treated women. A comparable case–control study was conducted among healthy women taking part in a breast cancer prevention trial. After 2 years [7], a proliferative endometrium was observed in 15% of tamoxifen patients, endometrial polyps in 8% and atypical hyperplasia in 16%. Placebo-treated women presented with 8, 2 and 0% of these lesions, respectively.

As breast cancer patients receiving tamoxifen most frequently have oestrogen receptor positive tumours, they are not totally comparable to patients with receptor negative tumours. In this sense, prospective cohort studies monitoring the uterine evolution during tamoxifen treatment are of great interest. Gal [8] followed 11 patients by Novak biopsies during 4–12 months and reported three endometrial hyperplasias. Achiron [9] observed that, among 45 patients with a normal endovaginal ultrasound, the endometrium of 25 remained atrophic after 12–36 months of tamoxifen. However, the mucosa of 12 became abnormally thick and 8 developed a polyp.

In our department, the uterine cavity of 57 postmenopausal breast cancer patients was regularly checked by means of hysteroscopy and endometrial biopsy before and during tamoxifen-treatment (12–144 months, mean 54). Endometrial atrophy was observed in 33.3%, glandulocystic atrophy in 26.3%, polyp in 35.5%, hyperplasia in 3.5% and carcinoma in 5.3%. Moreover, a polyp did appear in the cavity of 35.5%.

In conclusion, endometrial lesions are very frequent among asymptomatic breast cancer patients treated with tamoxifen. These women should be regularly evaluated for evidence of any intra-uterine anomaly. Moreover, it seems that endometrial polyps which are rare among untreated controls, are an important endometrial feature in these patients on tamoxifen. These polyps are often multiple and can be unusually large, occurring on a background of endometrial hyperplasia. These lesions should be resected and followed because of a possible pathogenetic relation between polypoid endometrial hyperplasia and malignancy.

1. Touraine Ph, Driguez P, Cartier I, *et al.* Lack of induction of endometrial hyperplasia with tamoxifen. *Lancet* 1995, **345**, 254–255.
2. Ismail S. Pathology of endometrium treated with tamoxifen. *J Clin Pathol* 1994, **47**, 827–833.
3. Neven P, De Muylder X, Van Belle Y, Vanderick G, De Muylder E. Tamoxifen and the uterus and the endometrium. *Lancet* 1989, **i**, 375.
4. Cohen I, Rosen D, Shapira J, *et al.* Endometrial changes with tamoxifen: comparison between tamoxifen-treated and non-treated asymptomatic, postmenopausal breast cancer patients. *Gynecol Oncol* 1994, **52**, 185–190.
5. Exacoustos C, Zupi E, Cangi B, Chiaretti M, Arduini D, Romanini C. Endometrial evaluation in postmenopausal breast cancer patients receiving tamoxifen: an ultrasound, color flow Doppler, hysteroscopic and histological study. *Ultrasound Obstet Gynaecol* 1995, **6**, 435–442.
6. Lahti E, Blanco G, Kauppila A, *et al.* Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen. *Obstet Gynaecol* 1993, **81**, 660–664.
7. Kedar R, Bourne T, Powles T, *et al.* Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. *Lancet* 1994, **343**, 1318–1321.
8. Gal D, Kopel S, Bashevkin M, *et al.* Oncogenic potential of tamoxifen on endometria of postmenopausal women with breast cancer—preliminary report. *Gynecol Oncol* 1991, **42**, 120–123.
9. Achiron R, Lipitz S, Sivan E, *et al.* Changes mimicking endometrial neoplasia in postmenopausal tamoxifen-treated women with breast cancer: a transvaginal Doppler study. *Ultrasound Obstet Gynecol* 1995, **6**, 116–120.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S19–S21, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00092-6

II.3 Tamoxifen and Uterine Fibroids

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Tamoxifen, an anti-estrogen widely used for breast cancer treatment, has variable agonistic effects on the uterus (mostly concerning endometrium but also myometrium). 14 cases of growing uterine fibroleiomyomas during tamoxifen treatment which required hysterectomy are described. No myometrial malignancy was observed. © **1998 Elsevier Science Ltd. All rights reserved.**

TAMOXIFEN—A non-steroidal triphenylethyl compound derivative from diethylstilboestrol—has clinically dual anti-oestrogenic and oestrogenic actions. Because of these paradoxical agonist properties for oestrogen-sensitive tissues, some detrimental side-effects may occur on the internal genital tract in (postmenopausal) women taking tamoxifen. Various uterine pathologies have been reported: endometrial hyperplasia and polyps, endometrial carcinoma, adenomyosis, growth of leiomyoma.

In our institution surgical exploration with total hysterectomy was performed in 14 patients receiving tamoxifen who demonstrated rapid or progressive overgrowth of uterine