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Editorial

Tamoxifen and the Uterus

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TAMOXIFEN IS without any doubt one of the most useful drugs in the treatment of breast cancer. After the publication of Fornander and colleagues [1] suggesting an association of tamoxifen with endometrial cancer, many clinicians have continued to debate the advantages and disadvantages of the drug on the uterus, breast, bone and cardiovascular system. These controversies prompted the Flemish Gynaecologic Oncology Group and the Sint-Jan Hospital of Brussels to organise an international meeting on 12–13 December 1997. The meeting gathered the experts on most topics from all over the world and was attended by almost 300 participants. In this supplement of the *European Journal of Cancer* each presentation is summarised as a short communication. In this editorial we will discuss the following topics:

(1) What are the oestrogenic and anti-oestrogenic effects of tamoxifen?
(2) Is tamoxifen a proven carcinogenic drug and if so how does it induce cancer?
(3) Should we and if so how should we screen for endometrial cancer during tamoxifen treatment?
(4) Is there a possibility to prevent uterine lesions? What about newer anti-oestrogens?

WHAT ARE THE OESTROGENIC AND ANTI-OESTROGENIC EFFECTS OF TAMOXIFEN?

Mainly oestrogenic in the breast, various anti-oestrogenic effects of tamoxifen on cholesterol, clotting factors, bone mineral density (BMD) and the uterus have been observed. In a chemopreventive trial for breast cancer the reduction in total cholesterol was mainly due to a fall in the low density lipoprotein cholesterol with no obvious reduction in high density lipoprotein cholesterol, suggesting a cardioprotective effect of tamoxifen [2]. On the other hand only marginal oestrogenic effects on clotting factors involved in haemostasis were observed. Furthermore tamoxifen induced an increase in BMD in postmenopausal but a decrease in premenopausal patients.

The use of tamoxifen has been associated with extensive senile cystic endometrial atrophia, hyperplasia, endometrial polyps [3, 4] and uterine fibroids [5]. The polyps can be unusually large and often multiple and are observed in up to 50% of the patients using tamoxifen [3, 6]. Ismael [4] suggested that tamoxifen-associated polyps show a combination of mitotic activity, epithelial metaplasia and patchy periglandular stromal condensation and suggested that the epithelial metaplasia observed in tamoxifen-treated patients might be linked to endometrial neoplasia. The association between tamoxifen and endometrial carcinoma will be discussed further in this text.

Recently an increased risk of ovarian cyst formation has been observed during tamoxifen treatment [7, 8]. There is some controversy as to whether this increased incidence of ovarian cysts is only present in premenopausal patients [7] or also in all postmenopausal patients [8]. Tamoxifen induces an oestrogen-like effect on the vaginal epithelium, but is not associated with an increased risk of vaginal or cervical malignancy [8].

It is postulated that the oestrogen-like effect of tamoxifen on the endometrium may be mediated through changes in the steroid receptors with a decrease in stromal oestrogen receptors and an increase in glandular cell progesterone receptors [9]. However, Dallenbach-Hellweg and Schmidt [10] suggest that tamoxifen has a progesterone-like and not an oestrogen-like effect on the endometrium. In this hypothesis tamoxifen induces a proliferation of the endocervical glands and reserve cells with endocervical-type atypical metaplasia in the resting or atrophic endometrium as a result. These metaplasias might be the precursors of endometrial endocervical-type hyperplasias and carcinomas. Indeed, according to these authors, all tamoxifen-associated endometrial carcinomas are mucinous (endocervical type), clear cell or serous papillary carcinomas and not of the usual endometrioid type.

IS TAMOXIFEN A PROVEN CARCINOGENIC DRUG, AND IF SO HOW DOES IT INDUCE CANCER?

Over the past decade evidence has emerged that tamoxifen is associated with an increased risk of endometrial carcinoma [11]. The excess risk was observed in four reports on randomised controlled trials. In addition in one cohort study as well as in four out of five case–control studies an increased

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incidence of endometrial carcinoma was observed [12–15]. In the studies the risk of endometrial cancer among tamoxifen-treated women is estimated to be 2- to 7-fold increased as compared to the risk in non-users with breast cancer. In the seven studies that examined the effect of duration of tamoxifen treatment, a significantly positive trend was observed in five, a non-significant positive trend in one and a non-significant negative trend in one study [13, 14]. There is, however, evidence that some endometrial cancers reported in patients on tamoxifen had been present before the women started taking the drug and that patients receiving tamoxifen treatment might have been examined gynaecologically more often than the control patients (ascertainment and surveillance bias) [16, 17]. There is general agreement that the benefits of adjuvant tamoxifen treatment in breast cancer in reducing both recurrence and the development of contralateral breast carcinoma far outweigh the risk of developing an endometrial carcinoma.

Some authors have suggested that endometrial carcinomas associated with tamoxifen use may behave more aggressively and carry a worse prognosis than endometrial carcinoma developing in the general population [18, 19]. However, five other large studies showed that tamoxifen is not associated with the development of high-risk endometrial carcinoma and that these tumours have the same prognosis as in patients not receiving the drug [15, 20]. Moreover, in recurrent endometrial carcinoma, tamoxifen has even been shown to be an effective drug [21].

It is now generally accepted that tamoxifen is a genotoxic, mutagenic liver carcinogen in the rat. Debate has centred upon whether tamoxifen is genotoxic to human tissues, as is the case in the rat where it is metabolised to a reactive metabolite (α-hydroxy-tamoxifen) which gives rise to high levels of DNA adducts in the liver (a genotoxic event) [22]. In one study five out of seven endometrial samples from patients treated with tamoxifen, low levels of DNA adducts were observed [23]. However, two other studies in humans showed no convincing evidence for tamoxifen-derived DNA adducts in human endometrium [22, 24] making us conclude that at this time point there is no convincing evidence that tamoxifen is metabolised in women to electrophiles that bind to DNA in the endometrium in sufficient quantity to implicate a genotoxic mechanism for carcinogenicity. In addition, the metabolism of α-hydroxy-tamoxifen to a sulphate ester in rat hepatocytes, which is a highly important process for the production of DNA adducts in rat liver cells, does not occur in humans [25]. Other local non-genotoxic mechanisms have been suggested for tamoxifen such as the upregulation of the mitogen insulin-like growth factor I (IGF-I) or down-regulation of IGF binding proteins [26, 27] or of transforming growth factor-beta (TGF-β) [28]. The most prevalent chromosome changes found in endometrial polyps associated with or without tamoxifen have been shown to be the same [29]. Most endometrial carcinomas associated with tamoxifen use are diploid [30].

SHOULD WE AND IF SO HOW SHOULD WE SCREEN FOR ENDOMETRIAL CANCER DURING TAMOXIFEN TREATMENT?

The main purpose of a screening programme to detect endometrial cancer in tamoxifen users—decreasing the number of deaths in tamoxifen users—is unlikely to be proven in the future. Those who do screen women on tamoxifen for endometrial lesions should realise that blind endometrial procedures such as repeat endometrial biopsies are of no use. Because of the proliferative effect of tamoxifen on the endometrial stroma transvaginal sonography (TVS) will not accurately detect endometrial epithelial changes. TVS will also detect the benign polyps which are observed very frequently in patients treated with tamoxifen. However, the finding of a thin endometrial strip of 5 mm or less with TVS has a high predictive value. About two-thirds of the patients being screened with TVS will require further testing with saline infusion sonography (SIS) [6, 31, 32] or office hysteroscopy [33]. In experienced hands SIS and office hysteroscopy are equally good, but in the only prospective randomised study, significantly more patients preferred SIS to outpatient hysteroscopy [6]. The exact role of endometrial cytology should be further studied [34]. Because tamoxifen-related uterine changes show specific magnetic resonance (MR) features, this technique might also be helpful in some difficult cases [35].

In woman with a normal uterus at the start of the tamoxifen treatment endometrial hyperplasia or cancer is unlikely to be found during the first 2 years [36]. Those who advocate screening should start with a pretreatment uterine assessment with TVS or office hysteroscopy. Symptom-free women can be screened annually with TVS starting after 2 years tamoxifen [6, 31, 33, 37]. SIS or hysteroscopy will be required if there is endometrial thickening on TVS.

IS THERE A POSSIBILITY TO PREVENT UTERINE LESIONS? WHAT ABOUT NEWER ANTI-OESTROGENS?

In the study by Whitehead [38] 100 patients on tamoxifen were randomised to receive either 6 months of oestrogen replacement therapy or not. The use of oestrogen replacement therapy in addition to tamoxifen did not reduce the endometrial thickness nor the uterine vascular resistance. These findings indicate that the activity of tamoxifen might be independent of and more potent than that of oestradiol valerate. Whether the use of a progesterone-loaded intrauterine device at the start of tamoxifen treatment will protect the endometrium against stimulation is currently under investigation [39].

Toremifene is a new anti-oestrogen, which is clinically and pharmacologically related to tamoxifen. In a prospective randomised trial toremifene and tamoxifen had a similar oestrogenic effect on the endometrium and the vaginal epithelium. In another study toremifene, like tamoxifen, stimulated endometrial cancer growth in athymic mice [41]. Based on these observations it is probable that also toremifene will be associated with endometrial carcinoma, but up to now the number of patients treated with toremifene has been too small to come to any conclusion. The newer pure anti-oestrogen, ICI 182,780 did not, however, stimulate endometrial cancer tumour growth in athymic mice [41]. Furthermore ICI 182,780 induced uterine involution and was associated with suppression of uterine IGF-I expression [26]. Also another anti-oestrogen, with the profile of a selective oestrogen receptor modulator, raloxifene does not stimulate the human endometrium in a 2 year randomised placebo-controlled trial using raloxifene to prevent osteoporosis [42]. There are no clinical data available that would indicate equivalent clinical efficacy of raloxifene to tamoxifen in the treatment of breast cancer.

1. Fornander T, Rutqvist LE, Cedermark B, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989, 1, 117–120.
2. Powles TJ. Tamoxifen's oestrogen-like effects in a breast cancer chemoprevention trial. *Eur J Cancer* 1998, **34**(Suppl. 4), S17–S18.
3. De Muylder X, Neven P, Van Belle Y. Tamoxifen and benign endometrial lesions. *Eur J Cancer* 1998, **34**(Suppl. 4), S18–S19.
4. Ismail SM. Significance of benign uterine pathology on tamoxifen. *Eur J Cancer* 1998, **34**(Suppl. 4), S26–S27.
5. Le Bouedec G, De Latour M, Dauplat J. Tamoxifen and uterine fibroids. *Eur J Cancer* 1998, **34**(Suppl. 4), S19–S21.
6. Timmerman D, Deprest J, Bourne T, Van den Berghe I, Collins WP, Vergote I. Saline infusion sonography (SIS) or office hysteroscopy: which one is the best? A prospective randomised study. *Eur J Cancer* 1998, **34**(Suppl. 4), S32–S33.
7. Mourits MJE, de Vries EGE, Willemse PHB, *et al.* Is ovarian cyst formation related to tamoxifen use? *Eur J Cancer* 1998, **34**(Suppl. 4), S21–S22.
8. Cohen I. Tamoxifen and other genital tissues: vagina, cervix and ovaries. *Eur J Cancer* 1998, **34**(Suppl. 4), S22–S23.
9. Schwartz L. Alterations in steroid hormone receptors in the tamoxifen-treated endometrium. *Eur J Cancer* 1998, **34**(Suppl. 4), S23–S24.
10. Dallenbach-Hellweg G, Schmidt D. The progestin-like activity of tamoxifen on the endometrium. *Eur J Cancer* 1998, **34**(Suppl. 4), S24–S25.
11. International Agency for Research on Cancer. *IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 66. Some pharmaceutical drugs.* Lyon, International Agency for Research on Cancer, 1996.
12. Sasco AJ. Tamoxifen, a human carcinogen or the share of common risk factors? *Eur J Cancer* 1998, **34**(Suppl. 4), S43–S44.
13. Van Leeuwen F, Bergman L, Benraadt J. Does risk of endometrial cancer increase with longer duration of tamoxifen use? *Eur J Cancer* 1998, **34**(Suppl. 4), S44–S45.
14. Bernstein L, Cerhan J, Schwartz S, Liff J, Perlman J, Ford L. The combined effects of ERT, obesity and tamoxifen therapy for breast cancer on endometrial cancer risk. *Eur J Cancer* 1998, **34**(Suppl. 4), S46.
15. Mignotte H, Lasset C, Bonadona V. Iatrogenic risks of endometrial carcinoma after treatment for breast cancer in a large French case–control study. *Eur J Cancer* 1998, **34**(Suppl. 4), S46–S47.
16. Jordan VC. Tamoxifen and uterine cancer: confounding variables. *Eur J Cancer* 1998, **34**(Suppl. 4), S50–S51.
17. Baum M. Tamoxifen and the breast. *Eur J Cancer* 1998, **34**(Suppl. 4), S7–S8.
18. Magriples U, Naftolin F, Schwartz PE, *et al.* High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients. *J Clin Oncol* 1993, **11**, 485–490.
19. Van Hooff I. High grade endometrial cancer associated with tamoxifen use. *Eur J Cancer* 1998, **34**(Suppl. 4), S48–S49.
20. Barakat R. Tamoxifen and endometrial cancer: most cancers are early stage and highly curable. *Eur J Cancer* 1998, **34**(Suppl. 4), S49–S50.
21. Bonte J. Tamoxifen to treat endometrial cancer. *Eur J Cancer* 1998, **34**(Suppl. 4), S51–S52.
22. Martin EA, White INH, Turteltau KW, Smith LL. Identification of tamoxifen-DNA adducts. *Eur J Cancer* 1998, **34**(Suppl. 4), S65–S66.
23. Hemminki K, Rajaniemi H. Tamoxifen-DNA adducts in breast cancer patients. *Eur J Cancer* 1998, **34**(Suppl. 4), S66.
24. Carmichael PL, Sardar S, Neven P, *et al.* Detection of DNA adducts in the human endometrium: a lack of evidence. *Eur J Cancer* 1998, **34**(Suppl. 4), S66–S67.
25. Phillips DH, Davis W, Venitt S, Glatt H. Tamoxifen metabolism and activation: the reason for interspecies differences. *Eur J Cancer* 1998, **34**(Suppl. 4), S13–S14.
26. Pollak M. Effects of anti-oestrogens on insulin-like growth factor (IGF-I) physiology systemically and in the uterus. *Eur J Cancer* 1998, **34**(Suppl. 4), S11–S12.
27. Tomás E. Does the human uterus agree with existing models? Experiences with insulin-like growth factor (IGF). *Eur J Cancer* 1998, **34**(Suppl. 4), S12–S13.
28. Carmichael PL, Mills JJ, Neven P. An epigenetic mechanism for tamoxifen-associated uterine carcinogenesis? *Eur J Cancer* 1998, **34**(Suppl. 4), S10–S11.
29. Van Den Berghe H. Cytogenetic changes in endometrial polyps from tamoxifen users. *Eur J Cancer* 1998, **34**(Suppl. 4), S63.
30. Moberger B, Fornander T, Hellström AC. DNA content in tamoxifen-induced endometrial carcinoma. *Eur J Cancer* 1998, **34**(Suppl. 4), S64.
31. Franchi D, Colombo NN, Bocciolone L, Maggioni A, Costa A, Sacchini V. Tamoxifen and the uterus: potential uterine risks of anti-oestrogens. The approach of the European Institute of Oncology. *Eur J Cancer* 1998, **34**(Suppl. 4), S34–S35.
32. Neele SJM, van Baal WM, van der Mooren MJ, Kenemans P, Netelenbos JC. Saline infusion sonography is a good approach for additional assessment of the endometrium. *Eur J Cancer* 1998, **34**(Suppl. 4), S35–S36.
33. Van Belle Y, Campo R, Neven P, De Muylder X, Vanderick G. Tamoxifen and the uterus—the hysteroscopic approach. *Eur J Cancer* 1998, **34**(Suppl. 4), S31–S32.
34. Mathelin C, Walter P, Gharbi M, Viville B, Gairar B, Brettes JP. Is endometrial cytology of any use? *Eur J Cancer* 1998, **34**(Suppl. 4), S38–S39.
35. Van Hoe L, Gryspeerdt S, Bloemen H, *et al.* Tamoxifen-induced changes of the uterus: MRI features. *Eur J Cancer* 1998, **34**(Suppl. 4), S36–S37.
36. Neven P, De Muylder X, Van Belle Y, Van Hooff I, Vanderick G. Longitudinal hysteroscopic follow-up during tamoxifen treatment. *Lancet* 1998, **1**, 351:36.
37. Vosse M, Renard F, Hertens D, Grivegnée AR, Coibion M. Tamoxifen and endometrium: preliminary results of a follow-up study. *Eur J Cancer* 1998, **34**(Suppl. 4), S33–S34.
38. Whitehead M. A randomised pilot study of hormone replacement therapy (HRT) in breast cancer patients: the combined effects of tamoxifen and HRT on the endometrium. *Eur J Cancer* 1998, **34**(Suppl. 4), S55.
39. Van Liedekerke D, Gevers R, De Sutter Ph, Bourgain C, Amy JJ. Use of levonorgestrel intrauterine device for prevention of endometrial changes induced by tamoxifen. *Eur J Cancer* 1998, **34**(Suppl. 4), S55–S56.
40. Tomás E. Toremifene and the uterus. *Eur J Cancer* 1998, **34**(Suppl. 4), S58.
41. O'Regan R, Cisneros A, Jordan VC. Is there life after tamoxifen? New anti-oestrogens. *Eur J Cancer* 1998, **34**(Suppl. 4), S57–S58.
42. Delmas PD, Bjarnsson NH, Mitlak BH, *et al.* Effects of raloxifene on bone mineral density, serum cholesterol concentrations and uterine endometrium in postmenopausal women. *N Engl J Med* 1997, **337**, 1641–1647.

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