We have evaluated the effects of two new anti-oestrogens, toremifene and ICI 182,780, on the growth of endometrial cancer in athymic mice. Two models were employed: a tamoxifen-stimulated model, where the mice were implanted with human endometrial tumours (EnCa101) previously passaged in mice treated with tamoxifen and an oestrogen-stimulated model, where the endometrial tumours were previously exposed to oestrogen.

In the tamoxifen-stimulated model, toremifene at doses of 0.5, 1.5 and 5 mg daily administered by mouth stimulated endometrial cancer growth in an identical manner to tamoxifen (data not shown).

In the oestrogen-stimulated model, neither tamoxifen or toremifene at doses of 0.5 mg and 1.5 mg daily significantly stimulated tumour growth compared with untreated animals (Figure 1).

ICI 182,780 inhibited tumour growth, both in the presence and absence of postmenopausal levels of oestrogen, in the tamoxifen-stimulated model (Figure 2).

These animal data suggest not only that toremifene is capable of stimulating pre-existent endometrial cancer similar to tamoxifen but that it too may be associated with an increased incidence of endometrial cancer. In contrast, ICI 182,780 should not be associated with endometrial cancer.

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V.4 Toremifene and the Uterus

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TOREMIFENE IS an interesting new anti-oestrogen. It is a triphenylethylene analogue, which is chemically and pharmacologically related to tamoxifen. A 60 mg dose of toremifene has been shown to be equivalent to 20 mg of tamoxifen for antitumour efficacy in breast cancer [1, 2]. At equimolar doses toremifene is less oestrogenic than tamoxifen in the rat uterus. Ten times more toremifene is needed than tamoxifen to obtain a similar anti-oestrogenic effect. In rodent uterine weight tests, toremifene has roughly 40 times less intrinsic oestrogenic activity than tamoxifen, but the maximal oestrogenic effect is the same [3].

Both drugs exhibit a paradoxical species- and tissue-specific pharmacology. They act like oestrogen in the mouse uterus, partially like oestrogen with anti-oestrogenic properties in the rat and as an anti-oestrogen with some oestrogen-like properties in humans.

In a prospective randomised study we compared the effects of 60 mg/day toremifene ($n = 15$) and 20 mg/day tamoxifen ($n = 16$) as an adjuvant therapy on the uterus and vagina of 31 gynaecological asymptomatic postmenopausal breast cancer patients. All the patients were examined with vaginal ultrasonography, vaginal and endometrial cytology, hysteroscopy and endometrial biopsy.

The endometrial thickness increased significantly during the 12 months of treatment with both toremifene and tamoxifen, with no significant differences between the groups. In the toremifene group, the endometrial thickness (median, range) before treatment, at 6 and 12 months of treatment was 3.9 (2.0–7.2), 6.0 (2.7–11.0) and 7.0 (3.6–10.4) mm, respectively. Similarly, in the tamoxifen group it was 3.6 (1.6–11.9), 5.6 (3.3–13.5) and 6.0 (2.8–10) mm.

During the 1 year study period comparing both treatments, the mean increase in uterine volume was not significant. However, in 6 of the toremifene and 7 of the tamoxifen patients the increase in uterine volume was more than 20% of the initial volume.

Before anti-oestrogen treatment, 3 of 12 toremifene and 6 of 15 tamoxifen patients showed oestrogenic changes in the endometrium. At the end of the follow-up study after 1 year of treatment, 2 of 10 (20%) patients in the toremifene and 8 of 14 (57%) patients in the tamoxifen group had marked endometrial oestrogenic changes.

None of the patients had proliferative changes in the endometrium at the beginning of the study, whereas after 1 year of treatment 2 patients in the toremifene and 2 in the tamoxifen group showed proliferative changes in the histological evaluation. Oestrogenic changes in the Pap smear were observed in all patients during treatment with both drugs. At 6 months, the proportion of superficial cells of the total cell count had increased by 12% in the toremifene and 15% in the tamoxifen group when compared to the initial values. At 12 months, the increase was 11% in both groups compared to the initial values.

During the 1 year treatment, new endometrial polyps were detected with hysteroscopy in 1 patient in the toremifene and 2 in the tamoxifen group [4].

In our study we demonstrated that toremifene and tamoxifen induced comparable oestrogenic effects on the endometrium and on the vaginal epithelium of postmenopausal breast cancer patients. The endometrial thickness increased significantly in both groups during the treatment. The oestrogenic changes in both groups were more common in the vaginal epithelium than in the endometrium. We demonstrated that unwanted side-effects such as endometrium thickening and development of intrauterine polyps were associated with both toremifene and tamoxifen treatment. Although toremifene and tamoxifen seem to have similar oestrogenic effects in the endometrium, toremifene has not been associated with endometrial carcinoma so far. During one year of treatment with tamoxifen or toremifene we did not find any hyperplasia or endometrial cancer. An interesting finding was that 2 patients in the toremifene group with endometrial atrophy before treatment showed clear oestrogenic changes at 6 months, but only a slight oestrogenic effect at 12 months of treatment. This suggests that the oestrogen-like effects of toremifene in the uterus may diminish during the treatment after an initial period of stimulation.

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