CORRESPONDENCE

Re: Effects of the Antiestrogens Tamoxifen, Toremifene, and ICI 182,780 on Endometrial Cancer Growth

On the basis of their study conducted in nude mice, O’Regan et al. (1) concluded that toremifene, like tamoxifen, is likely to be associated with an increased incidence of endometrial cancer. It is, however, controversial to draw conclusions about human carcinogenicity on the basis of studies in rodents. The mouse is a problematic species to use in this respect, because both drugs are more estrogenic in mice than in humans (2), even if one takes into account that O’Regan et al. studied human tumor xenografts in nude mice. Moreover, as shown in the article, the main metabolite of toremifene in mice is the 4-OH derivative, which comprised 67% of the total serum concentration of toremifene and its metabolites at 8 hours after toremifene administration (1). The concentration of this estrogenic metabolite was up to 30 times higher than the concentration of the corresponding metabolite of tamoxifen. In humans given therapeutic doses of toremifene, this metabolite is not seen (3).

However, because the above article raised a concern about the possible carcinogenic effect of toremifene on human endometrium, we checked the endometrial carcinomas reported in patients who received toremifene. As of September 30, 1998, the total cumulative clinical exposure to toremifene was more than 100,000 patient-years, and the drug had been administered to 3402 breast cancer patients in clinical trials (Table 1). Adjuvant treatment trials in breast cancer were initiated in 1992, and more than 1100 patients have now been given toremifene, with a median treatment duration of 30 months.

It is interesting that no cases of endometrial carcinoma have thus far been reported in the marketed use of toremifene. In the clinical trials since 1982, a total of seven nonfatal endometrial carcinomas have been reported worldwide in patients receiving toremifene. Six of these patients participated in trials for breast cancer (three patients had advanced cancer, the other three received adjuvant therapy), and one was given toremifene for a desmoid tumor. The doses of toremifene ranged from 40 mg/day (two patients) to 60 mg/day (three patients) and 200 mg/day (one patient) to 240 mg/day (one patient). Of the seven patients, five had received toremifene for less than 1 year before the diagnosis of endometrial cancer (1, 4, 5, 6, and 9 months, respectively). Two patients had been treated with toremifene for approximately 2 years, and one of these was the patient with the desmoid tumor. The patient with the desmoid tumor, and another patient who had received toremifene for only 4 months had previously been on long-term tamoxifen (for 3 years).

Even if one assumes that the six reported cases of concomitant breast and endometrial cancers are linked to toremifene (which is in fact unlikely), the annual hazard rate (per 1000 patient-years) of developing endometrial carcinoma in postmenopausal breast cancer patients exposed to toremifene is only 0.96. It is noteworthy that the hazard rate is almost the same, or 1.08, for patients participating in adjuvant treatment trials, although these patients had received toremifene for a median of 30 months. In comparison, the hazard rates, as calculated from the literature, are 2.0 and 0.4 for patients exposed in adjuvant trials to tamoxifen and placebo, respectively (4–6).

In conclusion, the findings of O’Regan et al. (1) should be interpreted with caution because toremifene (and tamoxifen) are significantly more estrogenic in mice than in humans. We do agree that toremifene may unmask pre-existing endometrial tumors through its partial estrogen agonist activity (7). However, no clinical data exist to support the view that toremifene would increase the risk of endometrial cancer in postmenopausal women with breast cancer.

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REFERENCES


NOTES

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Table 1. Annual hazard rate (per 1000 patient-years) of developing endometrial cancer in postmenopausal patients with breast cancer treated with toremifene

<table>
<thead>
<tr>
<th>Dose, mg/day</th>
<th>Adjuvant trials</th>
<th>All trials*</th>
<th>Cumulative total exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>40–60</td>
<td>20–300</td>
<td>3402</td>
</tr>
<tr>
<td>No. of patient-years</td>
<td>2768</td>
<td>6270</td>
<td>111,635</td>
</tr>
<tr>
<td>No. of events</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Annual hazard rate (95% confidence interval)</td>
<td>1.08 (0.37–3.19)</td>
<td>0.96 (0.44–2.09)</td>
<td>0.05 (0.02–0.12)</td>
</tr>
</tbody>
</table>

*Trials for treatment of advanced cancer and as adjuvant therapy, combined.
**Response**

We thank Mäenpää and colleagues for their informative letter. Although it is well known that the triphenylethylene-type antiestrogens have estrogen-like pharmacology and are converted to hydroxymetabolites in the mouse, the two events are not connected. The athymic mouse with heterotransplants of human tumors has been an important model for identifying the target-site-specific effects of antiestrogens. We found that an estrogen receptor–drug complex is interpreted as an estrogenic signal in the mouse uterus or transplanted human uterine tumor, but it is interpreted as an antiestrogenic signal in a human breast tumor transplanted into the same athymic mouse (1,2). We demonstrated that the spectrum of metabolites was the same in the target tissues, so we concluded that tamoxifen-like compounds were selectively antiestrogenic (2). The concept is now known as selective estrogen receptor modulation. In addition, a tamoxifen-stimulated tumor will grow equally well in an athymic rat (3), where the circulating metabolites are almost identical to those found in humans (4). Thus, the tissue, not the environment or metabolites, seems to be the factor that governs the biologic activity of tamoxifen-like drugs.

That being the case, we believe (as do Mäenpää et al.) that toremifene can probably stimulate the growth of pre-existing endometrial cancer. It is known that the level of occult endometrial cancer harbored in the uterus is five times that found clinically (5). So it is no surprise that tamoxifen use can increase the detection of endometrial cancer up to fourfold in postmenopausal women. Mäenpää et al. state that not a single case of endometrial cancer has been reported in patients treated with toremifene, outside a clinical trial, since its release for advanced breast cancer a few years ago. However, there were also no reports of endometrial cancer in women taking tamoxifen for more than 10 years after the drug was first available for the treatment of advanced breast cancer.

Mäenpää et al. show that an early adjuvant study with toremifene has, up to now, shown no increase in the reporting of endometrial cancer. The adjuvant result with toremifene is encouraging, but the same was said about tamoxifen 7 years ago (6). At present, there is only one adjuvant trial of toremifene ongoing, but it is important to remember that three adjuvant trials from Britain all initially reported no association between endometrial cancer incidence and tamoxifen [reviewed in (7)]. We do not believe that tamoxifen causes endometrial cancer, but we contend that if tamoxifen and toremifene have the same estrogen-like effects in the uterus, then there is the same potential risk for an increased incidence of endometrial cancer. Only large, well-documented clinical studies will prove otherwise.

**Ruth O'Regan**  
V. Craig Jordan

**References**


**Editor’s Note**

V. C. Jordan is a member of the speaker’s bureau for Zeneca Pharmaceuticals, the maker of tamoxifen, but he holds no stock in the company nor is he conducting research sponsored by Zeneca.

**Notes**

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