O’Regan et al. (1) report stimulation of growth of a human estrogen receptor-positive endometrial tumor in athymic mice by two “antiestrogens” and to a greater degree by estrogen. On the basis of these observations, they (1) suggest, “toremifene, like tamoxifen, may be associated with an increased incidence of endometrial cancer,” presumably less so than estrogen, based on their model. This suggestion, however, ignores a published report of a side-by-side trial of the two drugs in which endometrial cancer occurred in two of 565 women receiving tamoxifen and in none of 592 women receiving toremifene (2). Various reasons for the apparent nonconcordance can be adduced, but one consideration is that the carcinogenicity of tamoxifen in humans may be a consequence of DNA alkylation in the endometrium (3) together with enhanced cell proliferation (4), a combination known to greatly increase the carcinogenic effects of other DNA-reactive carcinogens.

O’Regan et al. (1) take the position that the appearance of endometrial cancer in women after fewer than 2 years of treatment is not consistent with a DNA adduct mechanism and that tamoxifen is involved only in “activation and detection of pre-existing disease.” This theory, of course, would not apply to later occurring tumors and ignores possible associations with other cancers (5). Moreover, it is noteworthy that, in the induction of rat liver tumors by tamoxifen (6), for which the authors have also implicated a promoting effect, liver preneoplastic lesions occur within 2 weeks (7), undoubtedly as a consequence of DNA reactivity (6). In principle, neoplastic transformation by a mutagenic carcinogen such as tamoxifen can occur in the first division of an affected cell, and thus the carcinogenicity of DNA-reactive agents can be quite rapid.

Finally, O’Regan et al. (1) cite our paper (6) showing that toremifene has not been demonstrated to form DNA adducts in rat liver stating that “it was thought, therefore, that it would be less likely than tamoxifen to result in an increased risk for endometrial cancer.” No such statement was made in our paper. Nevertheless, I do believe that, on the basis of nonclinical toxicology (6, 7) and available clinical observations (2, 5), toremifene poses less of a potential cancer risk to patients than tamoxifen at most sites, including, so far, endometrium.

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REFERENCES


NOTE

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RESPONSE

Dr. Williams is to be congratulated for his persistence in pointing out the carcinogenicity of tamoxifen. This has stimulated critical laboratory research worldwide to show that the rat is a poor model to predict the risk of human liver cancer with tamoxifen. Originally, the animal data caused great concern, but the result in the laboratory was a paradox. After 20 years of clinical use around the world, there is no epidemic of hepatocellular carcinoma in women who took tamoxifen (1). We now know that rat liver cells activate tamoxifen to a DNA adduct as the first step in liver carcinogenesis but that human liver cells do not (2,3). This is why DNA adducts are not detected in liver samples from women taking tamoxifen (4). Nevertheless, members of the toxicology community suggested that it was not relevant that the human liver was unaffected by tamoxifen; the fact that endometrial cancer was increased was proof of principle. This position was predictable. Dr. Williams cites the work of Hemminki et al. (see above) as support for tamoxifen being an initiator of cancer in the human endometrium. However, Dr. Williams shares only one side of the story. Others have been unable to find adducts in human endometrium (5) but, most importantly, parallel studies using the same methods as those of Hemminki et al. have been unable to detect an adduct (6). Indeed, although there has been enormous progress in identifying adducts from tamoxifen in rat liver, no one has yet identified the “phantom” adduct in human uterus. Be that as it may, we are reassured there are no differences in genetic markers in uterus samples from control or tamoxifen-treated women (7). Therefore, if tamoxifen is not genotoxic in the human uterus, other mechanisms need to be considered to explain the increase in endometrial cancer associated with tamoxifen use in postmenopausal women.

We have chosen to take a practical, rather than a theoretical, approach to the safety of antiestrogens in the uterus. Both tamoxifen and toremifene have sufficient estrogenicity in the uterus to encourage the growth of a laboratory model of human endometrial cancer. The pure antiestrogen ICI 182,780, with no estrogenic properties, does not cause endometrial tumor growth. Since the model originally predicted the increase in the detection of endometrial cancer in postmenopausal women treated with tamoxifen, why should women and physicians not be apprised of the potential risk associated with toremifene use? This is not a large risk, even if the effects of toremifene and tamoxifen in the
uterus are found to be equivalent. However, until clinical data are available, we believe that physicians should assume that the risks from tamoxifen and toremifene are comparable.

Endometrial cancer is rare, so huge populations are necessary to establish an accurate association between toremifene and an elevated risk of the disease. At present, it is not possible to state that no association exists because the available clinical population for study, mentioned by Dr. Williams, is too small. Although toremifene has been studied for 15 years, its clinical drug development is at the point tamoxifen was in 1980—i.e., the use in advanced disease is approved in the United States, adjuvant clinical trials are ongoing, and no endometrial cancer has been reported. Only extensive clinical evidence of safety will provide a rationale for the expanded use of toremifene outside the treatment of advanced breast cancer.

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REFERENCES


