EDITORIALS

Estrogen Receptor-Mediated Direct and Indirect Antitumor Effects of Tamoxifen

*V. Craig Jordan**

Tamoxifen is a nonsteroidal antiestrogen that has been successfully developed to treat all stages of breast cancer (*1*). An encouraging clinical finding is the observation that two years of adjuvant therapy with tamoxifen is able to provide a survival advantage in node positive postmenopausal women (*2*). However, tamoxifen is also known to be a reversible inhibitor of tumorigenesis in laboratory models of mammary cancer. Therefore, long-term adjuvant therapy is predicted to be an optimal strategy to suppress the recurrence of breast cancer (*3*). This strategy is being evaluated in randomized clinical trials.

The vast majority of laboratory and clinical evidence supports the view that tamoxifen produces its biological effects by competitive inhibition of estradiol binding to estrogen receptors (ERs) at the level of the tumor cell. Nevertheless, there is a growing body of laboratory evidence demonstrating that tamoxifen can affect non-ER mediated events (e.g., inhibition of protein kinase C, calmodulin, binding to "antiestrogen binding sites," blocking histamine receptors). These events individually or collectively (*4*) could facilitate the antitumor actions of tamoxifen and have, in fact, raised the possibility that a non-ER-regulated antitumor mechanism could be important. Indeed some clinical trials (*5,6*) report a high proportion of ER-negative patients that respond to adjuvant tamoxifen.

The article by Pollak and coworkers (*7*), which demonstrates a decrease in circulating insulin-like growth factor (IGF-1) during tamoxifen therapy, builds upon an earlier report (*8*) to modify our view of the endocrinological control of breast cancer growth. The release of growth hormone (GH) by the pituitary gland is under steroid control. The release of GH, in turn, causes an increase in circulating IGF-1, a known stimulatory growth factor. Pearson and colleagues (*9*) have demonstrated that some breast cancer patients who fail tamoxifen therapy improve following hypophysectomy. They speculate (*9*) that the ability to control both GH release and block ER in the tumor may prove to be an optimal therapeutic strategy to treat advanced disease.

The fact that tamoxifen not only blocks ERs at the level of the tumor but also reduces the level of circulating IGF-1, presumably by blocking ERs at the hypothalamopituitary axis, provides an interesting model for the endocrine control of hormone-dependent breast cancer. This model of the direct and indirect control of estrogen-regulated tumor growth may be used to explain the controversial clinical effect of tamoxifen therapy in patients with ER negative cancers.

There appears to be a correlation between the number of ER and IGF-1 receptors present in human breast tumors, although ER-negative tumors do have IGF-1 receptors (*10*) and ER-negative breast cancer cell lines will grow in response to IGF-1 in culture (*11*). Clearly, if some ER-negative tumors are responsive to IGF-1 for growth, and tamoxifen reduces the circulating level of IGF-1, then these facts provide a reasonable explanation of why some trials with adjuvant tamoxifen monotherapy produce improvement in patients with ER-negative tumors (*5,6*). The results by Pollak and coworkers (*7*) open up exciting future possibilities for the study of tamoxifen resistance in patients whose IGF-1 serum level may be refractory to reduction during adjuvant therapy. Perhaps the serum concentration of IGF-1 should be tested in the clinic to complement the measurement of ER levels in the tumor. If the time period required for tamoxifen to lower serum IGF-1 levels can be defined in patients, then measurement of IGF-1 levels before and during tamoxifen therapy may predict the responsiveness of the tumor to tamoxifen. In fact, monitoring patients during adjuvant therapy may be valuable as a predictive test of impending resistance to tamoxifen. Alternatively, the view can be taken that an ER-negative tumor may respond to tamoxifen therapy if it is IGF-1 receptor positive. Determination of IGF-1 receptors may be beneficial as a complementary test to steroid receptor assays.

In light of this modified view of hormone-dependent growth, it may be reasonable and realistic to treat *all* breast cancer patients (node negative and node positive) who are currently receiving no therapy to control their disease. This enormous population of patients is usually ignored until advanced disease is demonstrated. Clearly, the newly discovered indirect endocrine effect of tamoxifen, together with the well-established direct (ER) effect, provides sufficient evidence to require an evaluation of the need for tamoxifen *maintenance* in all women with a diagnosis of breast cancer. The possibility that some women with previously ER-negative tumors may derive some benefit from tamoxifen should make long-term tamoxifen maintenance an attractive therapeutic possibility. Indeed, the weak estrogen-like effects of tamoxifen on bone (*12*) and circulating lipids (*13*) may also make tamoxifen maintenance of value to node-negative postmenopausal women as a hormone replacement therapy.

Unfortunately, the estrogen-like qualities of tamoxifen may impair the full potential of this so-called "antiestrogen" to block GH release from the pituitary gland. The recently described (*14*) pure antiestrogens may provide optimal control

Received October 2, 1990; accepted October 3, 1990.

**Correspondence to:* V. Craig Jordan, PhD, DSc, Department of Human Oncology and Pharmacology, University of Wisconsin Clinical Cancer Center, K4/666, 600 Highland Ave, Madison, WI 53792.

of circulating IGF-1 and completely block tumor growth. The new antiestrogens, should they become available in the clinic, may facilitate the survival of node-positive patients and be useful to maintain the control of tumor growth in advanced breast cancer. Regrettably, the physiological side-effects that could be associated with the long-term treatment of node negative disease (i.e., atherosclerosis and osteoporosis) may preclude an application in these patients.

The concept of a dual ER-mediated control mechanism for regulating breast tumor growth will provide new opportunities to block endocrine-dependent growth completely. The possibility that tamoxifen and other less estrogenic antiestrogens may retard the growth of some ER-negative tumors heralds the broader application of an effective anticancer agent. Indeed, the beneficial therapeutic effect of tamoxifen in patients with a wide range of malignancies (i.e., melanoma, pancreatic carcinoma), cited in numerous anecdotal reports, may be a consequence of reduced serum IGF-1 levels. Pharmacological methods to lower markedly or to eliminate serum IGF-1 levels may prove to be a valuable therapeutic strategy to control a variety of malignancies. Perhaps phase I clinical studies with pure antiestrogens will demonstrate antitumor effects in cancers other than breast cancer via an IGF-1 mediated mechanism.

References

(1) LERNER LJ, JORDAN VC: Development of antiestrogens and their use in breast cancer: Eighth Cain memorial award lecture. Cancer Res 50:4177–4189, 1990

(2) Early Breast Cancer Trialists' Collaborative Group: Effects of adjuvant tamoxifen and of cytotoxic therapy on mortality in early breast cancer. An overview of 61 randomized trials among 28,896 women. N Engl J Med 319:1681–1692, 1988

(3) JORDAN VC: Long-term adjuvant tamoxifen therapy for breast cancer: Prelude to prevention. Cancer Treat Rev. In press

(4) JORDAN VC, MURPHY CS: Endocrine pharmacology of antiestrogens as antitumor agents. Endocr Rev. In press

(5) Nolvadex Adjuvant Trial Organisation: Controlled trial of tamoxifen as single adjuvant agent in management of early breast cancer. Analysis at six years. Lancet 1:836–840, 1985

(6) Breast Cancer Trials Committee, Scottish Cancer Trials Office (MRC) Edinburgh: Adjuvant tamoxifen in the management of operable breast cancer: The Scottish trial. Lancet 2:171–175, 1987

(7) POLLAK M, CONSTANTINO J, POLYCHRONAKOS C, ET AL: Effect of tamoxifen on serum insulinlike growth factor I levels of stage I breast cancer patients. J Natl Cancer Inst 82:1693–1697, 1990

(8) COLLETTI RB, ROBERTS JD, DEVLIN JT, ET AL: Effect of tamoxifen on plasma insulin-like growth factor I in patients with breast cancer. Cancer Res 49:1882–1884, 1989

(9) MANNI A, ARAFRAH B, PEARSON OH: Changes in endocrine status following antioestrogen administration to premenopausal and postmenopausal women. *In* Non-steroidal Antioestrogens (Sutherland RL, Jordan VC, eds). Sydney: Academic Press, 1981, pp 435–452

(10) PEYRAT JP, BONNETERRE J, BEUSCART R, ET AL: Insulin-like growth factor I receptors in human breast cancer and their relation to estradiol and progesterone receptors. Cancer Res 48:6429–6433, 1988

(11) ARTEAGA CL, OSBORNE CK: Growth inhibition of human breast cancer cells in vitro with an antibody against the type I somatomedin receptor. Cancer Res 49:6237–6241, 1989

(12) TURKEN S, SIRIS E, SELDIN E, ET AL: Effects of tamoxifen on spinal bone density in women with breast cancer. J Natl Cancer Inst 81:1086–1088, 1989

(13) LOVE RR, NEWCOMB PA, WIEBE DA, ET AL: Effects of tamoxifen therapy on lipid and lipoprotein levels in postmenopausal patients with node-negative breast cancer. J Natl Cancer Inst 82:1327–1332, 1990

(14) WAKELING AE, BOWLER J: Steroidal pure antioestrogens. J Endocrinol 112:R7–R10, 1987

Implications of Potential Positive Correlation Between Autologous Tumor-Cell-Killing Activity and Prognosis in Lung Cancer

John R. Ortaldo, Robert H. Wiltrout*

Patients with cancer have traditionally been treated with some combination of surgery, chemotherapeutic drugs, and radiation. While some cancers have responded in varying degrees to these treatment modalities, others have been relatively unresponsive.

Immunotherapy has been proposed as a fourth modality of cancer treatment, and numerous clinical trials have been performed to test its efficacy against different tumor types. A variety of biological response modifiers (BRMs) have been extensively studied in phase I and II clinical trials; these agents include recombinant cytokines and adoptively transferred (propagated and reinfused) cytotoxic effector cells. Immunotherapy studies have often demonstrated response rates of 10% to 25%, depending on the agent used, the type of cancer treated, and the institution performing the study. To date, the response rates for most protocols have not been markedly increased by alterations in doses and schedules of treatment. Thus, it remains unclear why a subset of patients responds to a given BRM, while the majority remain unresponsive.

Many basic scientists and clinicians are currently searching for some immunological parameter or tumor characteristic that could be used prospectively either to predict patient response to a given BRM or to provide definitive answers regarding the mechanisms by which a BRM actually induces an antitumor response. The report by Uchida and colleagues (*1*) in this issue of the Journal may indirectly address both of these issues. This report puts forth the possibility that the presence of peripheral blood lymphocytes with autologous tumor-cell-killing (ATK) activity in patients with lung cancer may predict long-term survival of such patients treated by a variety of conventional approaches.

The data reported by Uchida et al (*1*) are consistent with the hypothesis that the immune system may play a beneficial role in the eventual rejection of at least some tumors in some