Tamoxifen Induction of Apoptosis in Estrogen Receptor-Negative Cancers: New Tricks for an Old Dog?

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Tamoxifen is one of the most widely used anticancer drugs in the world. It was first employed as an antiestrogen to treat metastatic hormone-responsive breast cancer. The therapeutic use of tamoxifen was later expanded to adjuvant therapy for early-stage breast cancer (1). When it was observed that patients with early-stage breast cancer who had been treated with tamoxifen subsequently had a decreased incidence of cancer in the contralateral breast, tamoxifen was then used in trials of breast cancer prevention in high-risk women (2-4). In the course of the last 25 years, tamoxifen has been given to hundreds of thousands of patients and the toxicity profile has been recorded in more than 1 million patient-years of therapy. It is a remarkably safe drug with predictable and generally well-tolerated side effects.

The triphenylethylene compound tamoxifen and its hydroxylated metabolites are potent antiestrogens that bind to the estrogen receptor and antagonize the activity of estrogen. For more than a decade, systemic treatment of breast cancer employed either chemotherapy or tamoxifen, but the two were rarely combined because it was thought that by inhibiting cell growth as a cytostatic agent, tamoxifen would antagonize the cytotoxic effects of chemotherapy that favored actively growing cells. Consistent with the concept that chemotherapy was more effective in actively cycling cells, several clinical trials attempted to stimulate advanced breast cancer with estrogen prior to the administration of chemotherapy. The trials of estrogen synchronization did make a significant impact on the response of breast cancer to combination chemotherapy regimens. However, clinical trials showed that tamoxifen combined with cytotoxic chemotherapy was superior to chemotherapy alone in the adjuvant therapy for breast cancer (5). The clinical data did not indicate the presence of cross-resistance and thus the use of tamoxifen in combination with chemotherapy was explored. This led to the concept that tamoxifen might be used to induce apoptosis in estrogen receptor-negative cancers by taking advantage of the cytotoxic activity of chemotherapy that is more effective in actively cycling cells.

Note

Dr. Cole is a consultant to Schering-Plough, Inc.: this company may be a competitor of the manufacturer of the hepatic arterial infusion device used in the studies that are the subject of the article from the Meta-Analysis Group In Cancer.

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References


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See “Notes” section following “References.”
not support the concept that by inducing cells to enter the cell cycle one could increase the clinical efficacy of cytotoxic chemotherapy.

The results of clinical trials that showed superiority of combined cytotoxic and hormonal therapy over chemotherapy alone preceded our current understanding of the mechanisms behind cancer cell killing by these agents. It is now accepted that both cytotoxic chemotherapy and hormone antagonists have the capacity to induce apoptosis or programmed cell death in sensitive cells (6). Moreover, estrogens can protect estrogen receptor (ER)-positive cells from apoptosis induced by chemotherapeutic agents (7). Since hormonal blockade and cytotoxic chemotherapy induce apoptosis via different pathways, it is logical to conclude that these therapies may in fact be additive. Therefore, there is now a theoretical framework for preclinical and clinical studies to explore induction of apoptosis simultaneously by a variety of agents. The clinical testing of these ideas that was inadvertently begun more than a decade ago by the National Surgical Adjuvant Breast and Bowel Project (5) is now under way in a number of diseases. For example, the randomized Radiation Therapy Oncology Group trial of radiation therapy with or without neoadjuvant androgen ablation for prostate cancer is testing the premise that the induction of apoptosis via different pathways—hormone withdrawal and DNA damage—can be additive in cancer therapy.

Induction of apoptosis is being employed as an end point by which the efficacy of new therapeutic agents can be assessed in preclinical studies. Since tamoxifen can potentially affect cellular functions by binding to calmodulin (8) or inhibiting protein kinase C (9,10), it has been studied for the ability to inhibit cell growth and induce apoptosis independently of the presence of ER. Tamoxifen binding to calmodulin appears to be linked to its binding to the ER and may be associated with its antiestrogenic functions (11). However, tamoxifen inhibition of protein kinase C at concentrations from 5 to 10 μM has been the focus of attention for investigators who have demonstrated effects of tamoxifen on ER-negative cells. For example, tamoxifen has been shown to inhibit cell growth and induce apoptosis in cultured glioma cells (12,13). These preclinical studies provided the impetus for clinical trials of tamoxifen in patients with malignant gliomas. Three phase II trials of tamoxifen in malignant gliomas have been performed and have resulted in a few documented regressions in patients who had failed radiation therapy and chemotherapy (14-16). Tamoxifen was also shown to augment cell killing by cisplatin (17,18). This led to a series of phase II studies that suggested that tamoxifen improved the response of metastatic melanoma to combination chemotherapy including carbustine, cisplatin, and dacarbazine (19). Many other investigators duplicated the phase II studies and reported response rates from 13% to 55%.

The true benefit of adding tamoxifen to single-agent (20) or combination (3,21,22) chemotherapy for metastatic melanoma was addressed by randomized phase III trials where the addition of tamoxifen was the only treatment variable. These studies showed that tamoxifen added therapeutic benefit to single-agent dacarbazine (28% versus 12% response rate). However, when added to combination chemotherapy regimens or to chemotherapy plus interferon alfa, tamoxifen could not be shown to improve the overall response rate. Interestingly, in the trial of dacarbazine versus dacarbazine plus tamoxifen, female patients benefited from tamoxifen, whereas among men, there was no demonstrated difference between the two treatment arms. The effect of tamoxifen on melanoma cells is not clearly understood. Whether some melanoma cells do express ER (23,24) or whether estrogen binding to tyrosine hydroxylase (25) explains the estrogen binding data with melanoma cell cytosol has not been resolved. But, regardless of the mechanism of action, there are data from a randomized therapeutic trial that tamoxifen may augment the response of melanoma to single-agent dacarbazine. It is not unreasonable to ask whether dacarbazine and tamoxifen are comparable in efficacy to potentially more toxic chemotherapy regimens with drugs such as cisplatin. There is now both the preclinical and the clinical trial rationale to support the conduct of such a trial.

The apparent efficacy of tamoxifen in glioma and melanoma justifies further investigation in other ER-negative malignancies. Last year, Perry et al. (26) showed that 1 μM tamoxifen, a clinically achievable concentration, could induce apoptosis in both ER-positive and ER-negative breast cancer cell lines. Tamoxifen induction of apoptosis could be blocked by estradiol in the ER-positive cells but not in the ER-negative cells. Therefore, tamoxifen was not acting through a hormone receptor mechanism in the ER-negative cells. Antiestrogen induction of apoptosis in ER-positive cells had also been reported by Warri et al. (27) using the new antiestrogen torimefene. Moreover, 10 nM tamoxifen had been shown to induce apoptosis of A549 lung carcinoma cells that do not express ER (28). The effect of tamoxifen on the lung cancer cells was also not blocked by estradiol. Therefore, there appears to be confirmatory data in breast cancer and other cell lines that tamoxifen can induce apoptosis by both ER-mediated and ER-independent mechanisms.

In this issue of the Journal, Kang et al. (29) extended the observations to show that the tamoxifen-induced apoptosis is mediated by c-myc expression, since myc antisense oligonucleotides (but not control c-myc nonsense oligonucleotides) given to the cells simultaneously with tamoxifen can block apoptosis. This work suggests that tamoxifen could be combined with other agents that may induce apoptosis via different pathways to augment treatment of breast cancer, regardless of ER status. For example, if it could be shown that radiation induced apoptosis in breast cancer cells via a different pathway from tamoxifen, there would be a rationale for simultaneous administration of tamoxifen during radiation therapy for breast cancer. The report by Kang et al. (29) in this issue of the Journal tells us about one step in tamoxifen induction of apoptosis. As has been shown in other cell lines (30-32), c-myc is not universally required for apoptosis. Based on the results of Kang et al., MDA-MB-231 cells could be exposed to radiation therapy or doxorubicin to elucidate the induction of apoptosis by these DNA-damaging agents in the absence and presence of tamoxifen.

The mechanism of ER-independent, tamoxifen-induced apoptosis may be the inhibition of protein kinase C. The IC50 of tamoxifen for protein kinase C inhibition is four to 10 times the concentration for ER inhibition. Therefore, the dose of
tamoxifen for treatment of ER-negative tumors would have to be increased substantially over the 20 mg per day used in patients with ER-positive breast cancer. Higher doses of tamoxifen might decrease the therapeutic index by increasing toxicity. Therefore, the development of tamoxifen analogues that are more potent antagonists of protein kinase C may be worthwhile, especially since similar structural alterations of the tamoxifen molecule enhance not only its ability to inactivate protein kinase C but also its binding to calmodulin (33). Calmodulin binding of tamoxifen correlates with its antiestrogenic effects (34).

Although clinical trials will ultimately determine the efficacy of tamoxifen in ER-negative cancers, studies of the mechanisms of tamoxifen interaction with other molecules have provided both a rationale for its application in these settings and a framework on which to construct potentially more active agents. Meanwhile, development of effective combinations of clinical therapeutics can benefit from the new paradigm of activating diverse pathways to achieve cellular apoptosis.

References


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Note

Dr. Gelmann is a consultant to Zencera Corporation, the manufacturer of tamoxifen, in a matter unrelated to the subject of this editorial.
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