MINIREVIEW

The Tamoxifen Controversy—Clinical Chemopreventive Agent and Experimental Carcinogen (43846A)

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While dramatic decreases in the mortality of heart disease, the major fatal disease in the United States, have occurred since 1950, there has been a slight but measurable increase in the cancer mortality rate since 1950 in this country. The reasons for the former precipitous decline in death from heart disease are a balanced combination of prevention and early detection of risk factors combined with improved treatment modalities. While improved treatment modalities of neoplasia have led to significant decreases in certain cancers such as that of testis, Hodgkin's disease, acute lymphatic leukemia in children, and several other cancers, mortality rates from the major cancers, namely lung, breast, prostate, and colon, have either increased or not changed during this period (1). Since the treatment arm of cancer control has not exhibited the dramatic successes seen in, for example, heart disease therapy, many have and are advocating the importance of cancer prevention.

Cancer prevention may be designated as either active or passive (2) in one context or as primary and secondary prevention (3) in another. Avoiding potential carcinogens by quitting smoking, altering diet, and decreasing sunlight exposure are examples of passive or primary prevention. Active or secondary prevention requires patient intervention such as screening, other diagnostic methods for early precancer, or the active administration of agents which inhibit the development of the neoplastic process. This latter field has been termed chemoprevention, a word originally coined by Sporn and Newton in reference to the effect of retinoids in preventing experimental neoplasia (4). Since that time the application of chemoprevention has been extended to a number of human clinical trials using a variety of agents for the chemoprevention of a number of different types of neoplasms (5). One of the most recent and certainly the most highly publicized chemoprevention trials involves the use of the antiestrogen, tamoxifen, for the prevention of breast cancer in patients at risk for developing the disease but who are clinically free of the disease. The extensive clinical experience with tamoxifen as an adjuvant therapy for the prevention of the recurrence of breast cancer in patients treated for the disease was a major factor in the development of this trial (6). In addition, the extensive evidence that tamoxifen prevents carcinogenesis in the experimental animal (7) offered a model on which to base such therapy. Tamoxifen therapy has been beneficial in non-neoplastic conditions as a potential prevention for osteoporosis (8, 9) and decreases the risk of cardiovascular disease by lowering low-density lipoprotein cholesterol levels in postmenopausal women (10, 11).

As with any therapy there is always a related risk. However, the question has arisen as to whether the evaluation of risk should be different for disease prevention than for cancer therapy. This question of increased risk of inducing disease by tamoxifen is based primarily but not exclusively on animal experimentation. Tamoxifen may be a risk factor for thromboembolic events, as has been implicated from studies of the use of this antiestrogen in the therapy of advanced

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breast cancer (12). In the ongoing trials, women with a history of clotting disorders are excluded, thus largely obviating this potential risk factor. However, recent findings by Fisher and his colleagues (13) indicate that there is an increased risk of endometrial cancer following tamoxifen therapy. In rodents, especially rats, tamoxifen is a tumor promotor for hepatocarcinogenesis (14). Chronic high doses of tamoxifen given by gavage for periods of 12 months or more induce hepatocellular carcinomas in rats (15, 16). In addition, tamoxifen administration induces the appearance of DNA adducts whose structure is as yet unknown (16, 17). Recently, our laboratory demonstrated that the administration of a single dose of tamoxifen (0.3–35 mg/kg) by gavage 24 h after a 70% partial hepatectomy induced a very high rate of aneuploidy and chromosomal disruption in hepatocytes cultured 24 h following tamoxifen administration (18). Thus, at very high doses, tamoxifen is hepatocarcinogenic in the rat with the formation of DNA adducts and, at doses used pharmacologically in the human, is clastogenic *in vivo*.

The following two articles, each written by an expert in the field, discuss both sides of this controversial question. The chemoprevention trial of tamoxifen is ongoing, involving thousands of women in the United States and Great Britain. While every undertaking of an individual or a population involves both a benefit and a risk, this ratio has significant implications in the tamoxifen and other chemoprevention trials.

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