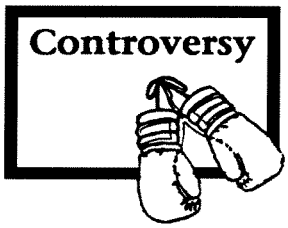

...a matter for doctor/ patient decision.

Tamoxifen: A caveat on the con side of the debate

Steven M Moser MD*

Having reviewed the recent literature on the anti-estrogen drug tamoxifen, I am concerned about the recently initiated National Cancer Institute (NCI) clinical trial to determine the worth of tamoxifen for preventing breast cancer in healthy women, the NSABP (National Surgical Adjuvant Breast and Bowel Project) Protocol P-1. This $60-million trial will enroll 16,000 women: half placebo controls, and the other half tamoxifen subjects. The latter group includes all women over the age of 60, and women between the ages of 35 to 59 whose minimum 5-year risk is at least that of a woman >60 (calculated by a composite mathematic model weighing family history, age of menarche, number of relatives with breast cancer and other factors).

While there does not appear to be a problem with enrolling women with the highest risk of developing breast cancer in such a trial (those with the diagnosis of lobular carcinoma in situ or those who have both a mother and a sister with breast cancer), the current study design of subjecting all 60-year-olds as well as younger, lower-risk women to prolonged tamoxifen exposure may not be warranted, based on several recent studies that have been released since the protocol was completed. This may be especially true for Hawaiian and oriental populations for reasons that will be explained.

Tamoxifen was chosen for this trial because it has been shown in several large studies[1-4] to reduce the recurrence of contralateral breast cancers in women who have had estrogen receptor-positive (hormone sensitive) primary breast cancer. These studies were all short-term, actuarial trials in nature, looking only at survival rates and disease-free intervals and did not routinely include biopsy or autopsy examinations of study and control groups. This may have led to an underestimation of new, non-metastatic malignancies that were either missed or mistaken for metastatic breast cancer.

This is an important consideration because of the animal and human studies that have demonstrated tamoxifen to be a cancer promoter in uterine, hepatic and estrogen receptor-negative breast cancers. In the Swedish study[3], there was an excess of nonfatal endometrial cancers in the test group (1.4% tamoxifen group vs 0.2% control group). There are several case reports of uterine cancer in women taking tamoxifen[5-7]. When combined with the new evidence that tamoxifen is a teratogen in the developing female genital tract, with strong similarities to diethylstilbesterol[8], these studies predict a danger to both postmenopausal and premenopausal women that is not sufficiently addressed in the current NSABP P-1 Protocol and its informed consent form (1/24/92 version).

Postmenopausal women who have not had hysterectomies are required by the protocol to have pelvic examinations at initiation of the study and every 12 months thereafter. The study protocol states that in the case of menstrual irregularities which persist in the face of normal pelvic exams, the patient should undergo further testing such as hysteroscopy or dilatation and curettage (D&C). These expensive procedures, as are all office exams, lab tests and procedures, are charged to the patient, which might prove to be a deterrent to careful follow up for uninsured or indigent patients. The possibility that endometrial carcinoma may develop in patients without obvious menstrual irregularities until late in the course of their cancer is not addressed. Untreated uterine carcinoma is a major cause of morbidity in women who have it.

Premenopausal women in the study are advised on the one hand not to become pregnant, as tamoxifen is a human teratogen, and on the other hand, they are told not to use birth control pills because estrogens will interfere with the action of tamoxifen. It is well-known that barrier methods of birth control have a high failure rate [9], as does the rhythm method. The consent form also discourages the use of IUDs because they promote menstrual irregularities. These factors, when coupled with the clomiphene-like propensity of tamoxifen to increase fertility, may increase the likelihood that premenopausal women may indeed find themselves pregnant while taking tamoxifen. At this point, the protocol and the informed consent form also fail to provide funding or moral and legal support for the abortion which would presumably be indicated.

Tamoxifen is a known liver carcinogen in rats. At doses of 35 mg/kg/day, it caused hepatocellular carcinomas at between 31 and 37 weeks of use[10]. Other studies have shown carcinogenicity at lower doses. At an average of 40 kg to 60 kg weight for an average 60-year-old woman in the study, the margin of safety is somewhat less than a factor of 100, which is the accepted standard of protection for humans in the face of a known carcinogen. The half-life of tamoxifen is longer in humans than in rats, which may further compromise this safety factor. The tumors in rats are highly malignant, perhaps explained by the finding of the induction of covalent DNA adducts with tamoxifen, with mutations occurring within a few days of starting the drug [11].

(Continued) ➤

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Submitted for publication October 27, 1992

TAMOXIFEN: A CAVEAT ON THE CON SIDE OF THE DEBATE

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The Swedish tamoxifen trial[3] found 2 liver carcinomas in its study population, which was several-fold higher than the average incidence of this tumor. As mentioned before, other studies have either not looked for it or may have mistaken it for metastatic breast cancer. Very few healthy women have taken tamoxifen for more than 5 years, and therefore very little adequate human data have been obtained to conclude that tamoxifen is or is not hepatotoxic in humans[12]. The NSABP P-1 protocol does not call for specific liver function testing but mentions only "chemistry tests" to be done every 6 months.

In other work published this year and not referenced by the study protocol is a work by Zimnisky et al in which tamoxifen was found to promote growth of dimethylbenzanthracene-induced, hormone-independent tumors in the rat mammary gland. While growth of hormone-dependent tumors was, as expected, decreased significantly in the tamoxifen group, hormone-independent mammary tumors developed during tamoxifen administration and displayed "...extremely rapid growth"[13]. These tumors grew 3 times faster than similar hormone-independent tumors in control animals, as well as significantly faster than hormone-dependent tumors. In the discussion of this paper, the authors point out that tamoxifen has been shown in other studies merely to delay the onset of hormone-sensitive tumors.

Fentiman, of the Royal Marsden Hospital in London, points out that tumors in younger women are likely to be receptor-negative, and goes on to say, "If, however, the malignant phenotype ie receptor-positive is inhibited for say 2 to 5 years, with subsequent emergence of a more aggressive hormone-independent variant, the prognosis might be worse if no tamoxifen had been given"[14].

In Hawaii, this consideration of induction of estrogen receptor-negative malignancy carries greater significance because of the greater prevalence of estrogen receptor-negative disease that our Japanese population exhibits[15].

Other considerations involve the significant incidence of ocular toxicity and thrombophlebitis in women receiving tamoxifen. In a prospective study of 63 women receiving low dose (20 mg/d), long-term tamoxifen, 6.3% of the subjects developed retinopathy and/or keratopathy from between 10 to 35 months of initiation of therapy[16]. Unfortunately, the protocol and the informed consent do not mention the probability of ocular disease development at low doses of tamoxifen to either the investigators or to the prospective study enrollees, and does not recommend or provide for either routine ophthalmological exams or slit-lamps, both of which should be mandated based on this and other information.

In the NSABP B-14 Trial, 3 of 1,414 women in the control group and 18 of the 1,403 women in the tamoxifen group developed deep venous thromboses or embolism. Two deaths occurred from pulmonary embolus[1]. If this incidence is extrapolated to 8,000 healthy women, some of whom have an increased statistical risk of developing breast cancer, we can expect approximately 80 of them to develop deep venous thrombosis or an embolic event, and around 9 or 10 of them to die of massive pulmonary embolus.

In addition, there is ample evidence that tamoxifen causes significant side effects in those who take it over the long term. In a recent study of 140 patients receiving adjuvant tamoxifen therapy, 17% had moderate to severe vasomotor symptoms and gynecologic symptoms in 4%[17]. In their conclusions, the authors state, "...this study suggests that in a population of postmenopausal women with a history of axillary node negative breast cancer, almost half of the tamoxifen-treated women will report moderate or greater levels of symptoms." Premenopausal women may have an even higher incidence of side effects. How this will affect their compliance with a long-term, preventive tamoxifen trial remains to be seen.

In conclusion, while I do not have a problem with the use of tamoxifen for the prevention of breast cancer in the older, higher-risk patients, there is an obvious ethical problem when we submit healthy women of child-bearing age, who have a nil to slightly increased risk of breast cancer, to a known carcinogen which, in addition to increasing their fertility, is also a demonstrated teratogen. This is especially problematic when they are forbidden the most effective forms of birth control and are not advised to have routine endometrial exams. These risks are compounded by the possibility of an increased incidence of hepatocellular carcinoma and estrogen receptor-negative breast carcinoma, as well as a significant probability of developing ocular toxicity or thrombophlebitis.

Clinicians who are advising patients interested in enrolling in this study would do well to aquaint themselves with the availiable literature on the toxicity of tamoxifen, some of the most impressive of which has been published since the latest protocol was completed. In this way they may persuade both themselves and their patients that prudence in entering this trial is well-warranted.

ACKNOWLEDGEMENTS

I would like to express my appreciation to Hazel Cunningham for making me aware of the recent literature regarding tamoxifen, and to Ann Kelminski for supplying me with the NSABP Protocol.

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