Tamoxifen Therapy and Carcinogenic Risk

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It is quite remarkable that tamoxifen, a drug that is so effective in the treatment of breast cancer, should have so low a toxicity profile. Since 1971, tamoxifen has been used to treat many millions of patients for periods sometimes in excess of 10 years, in doses sometimes eightfold higher than the usual dose; yet the incidence of serious toxic effects from tamoxifen has been almost negligible. This perhaps fortuitous result, however, should not induce a sense of complacency, since tamoxifen’s use is now widespread and includes large numbers of patients with a high cure rate and very long life expectancy, as well as healthy women in chemoprevention trials. Within these settings, considerable caution is warranted in the design and evaluation of clinical trials and treatment schedules of tamoxifen.

Perhaps the deepest concern is the carcinogenic potential of tamoxifen, since it is a proven carcinogen in the rat (1,2). Tamoxifen itself is not genotoxic but is activated by cytochrome P450 drug-metabolizing enzymes to form reactive intermediates that bind covalently to DNA to create adducts (3) and carcinogenic risk (4-7). Local detoxifying mechanisms and DNA repair will limit the likely expression of clinical cancer, and the balance of all these factors will determine the risk in any organ, in any species. For example, in several strains of rat, tamoxifen can cause cancers in the liver, but not in other tissues, at blood levels similar to those in women being treated for breast cancer with this agent (2,8). At these doses, the carcinogenic potential in the liver varies according to the strain of rat (9); carcinogenicity has not been reported in other species.

Therefore, quantitative prediction from these experimental data of any human risk, in any tissue, is not possible. At this time, all we can say is that tamoxifen is potentially carcinogenic in any human tissue that has the capability to generate the reactive metabolites and that possesses the cellular characteristics needed for expression of the carcinogenic potential.

The prediction of carcinogenic risk is complicated further by the observed estrogenic effects of tamoxifen on various tissues, including the endometrium, a tissue in which estrogen will promote clinical cancer (10). The possible synergism of genotoxicity with estrogenic promotion by tamoxifen makes the uterus a prime site for potential carcinogenic risk in humans. Hormone promotion may also be important in other tissues, such as the ovary.

Other organs potentially at special risk in humans are those with a high cellular proliferation rate, such as bone marrow, and those tissues that may be exposed to high levels of the carcinogenic metabolites, such as the liver, stomach, and colon.

Surprisingly, the clinical data are unclear about carcinogenic risk, in spite of extensive tamoxifen use. This situation may exist, in part, because its early use was predominantly in women with poor-prognosis, relapsed disease. Since then, tamoxifen has been used in adjuvant trials; unfortunately, however, many of these trials have had inadequate surveillance for second tumors. This omission occurred because of the lack of awareness of carcinogenic risk; therefore, new primary cancers may not have been carefully distinguished from metastatic relapse or may not have been recorded as separate events. More accurate assessment is now under way; but, in the meantime, it is necessary to rely on retrospective assessment within individual clinical trials, data from case-control studies, and the evaluation of any surrogate events, all of which have serious limitations for accurate assessment of risk.

As yet, there are few intermediate markers of carcinogenic risk, although it is reassuring to note that, within a small clinical trial, there was no evidence of any increase in DNA adducts in the livers of women being treated with tamoxifen compared with those of control subjects (11). More extensive evaluation of other tissues from women taking tamoxifen is needed.

Retrospective review of clinical trials of tamoxifen has shown no increased risk of acute leukemia or other hematopoietic cancers (12-14). These malignancies are diagnostically well defined and occur early relative to solid cancers. The incidence of other malignancies has not been so clearly defined in these retrospective studies. The Swedish study (12), using a tamoxifen dose of 40 mg per day for 2-5 years with a median follow-up of 9 years, and two other Scandinavian trials, using a tamoxifen dose of 30 mg per day for 1 year (12), all indicated a dose-dependent, increased risk of endometrial cancer in postmenopausal women; this finding is in keeping with the reported increased incidence of endometrial cancer in the patients receiving tamoxifen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial (13). The estimated relative risk of twofold to

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threefold for postmenopausal women given a tamoxifen dose of 20 mg per day was similar to that from a case–control study from The Netherlands (15). In absolute terms, this risk is small because the tumor is rare and because, for the most part, the risk is confined to postmenopausal women.

With regard to tamoxifen therapy and its association with other cancers, retrospective assessment of the Swedish adjuvant trial using cancer registry data (12) has indicated an increased risk of gastrointestinal tumors but no evidence of an increased risk of other tumors including tumors of the ovary. There is a similar increased risk of stomach and colorectal cancers in the other Scandinavian trials, indicating a relative risk of twofold to threefold for these cancers (12). This risk, if real, is substantial in absolute terms because of the high base-line incidence of these tumors (and because the follow-up is early in the natural history of solid tumor carcinogenesis). Much doubt has been cast on the reliability of these data and analytical methods (16,17). This observation has not been confirmed in the NSABP B-14 trial (13).

In general terms, retrospective analyses of clinical trials are unreliable, and some of the problems with these analyses can be overcome by using case–control studies. For example, the Dutch study (15) probably more accurately determined the actual risk of endometrial cancer than the clinical trials.

In this issue of the Journal, Cook et al. (18) report on a case–control study involving Surveillance, Epidemiology, and End Results (SEER) data from Washington State; this study was undertaken to evaluate risks of ovarian, endometrial, and breast cancers among women who have received tamoxifen (20 mg per day) for a mean duration of less than 2 years. The number of events were small, which limits the value of the study. Although the data confirm a 50% reduction in risk of subsequent contralateral breast cancers, in keeping with the retrospective analyses of other clinical trials (19), they fail to indicate any increase in endometrial cancer risk. This null result may be due to the short duration of treatment. As the authors acknowledge, this study, therefore, contributes little to our knowledge of the risk of second cancer in women who have had tamoxifen for periods of 2 years or longer.

In summary, the carcinogenic risk of tamoxifen in humans has not as yet been adequately evaluated. Further experimental work designed to elucidate the metabolic and cellular mechanisms that account for tissue and species variations may make it possible to establish experimental models for accurately predicting human risk and also to identify surrogate markers of risk in human tissues. In the meantime, we have to rely on the retrospective analysis of clinical trials and on case–control studies using data from cancer registries until reliable data become available from current prospective trials using meta-analysis techniques.

With the toxicity data available at the present time, what are the clinical indications for use of tamoxifen? For adjuvant treatment of patients who have had primary breast cancers, the benefit of a 30% reduction in risk of relapse and a 40% reduction in risk of contralateral breast cancer (19) would encourage the use of 20 mg of tamoxifen per day for 2 years or more in most prognostic categories. Further evaluation of benefit should be available from the updated overview in Oxford later this year. For use of tamoxifen in chemoprevention of breast cancer in healthy women, the toxicity data are less reassuring and use should be restricted to high risk women within clinical trials such as the NSABP trial. In the Royal Marsden Hospital trial (20), we have restricted eligibility to those women with a significantly increased relative risk of three to four times the normal age-related risk. If tamoxifen proves to be effective in preventing breast cancer, evaluation of the general toxicity of non-genotoxic analogues of tamoxifen, such as toremifene, droloxifene, and idoxifene, will become a priority for chemoprevention.

References

(17) Simons R. Discovering the truth about tamoxifen: problems of multiplicity in statistical evaluation of biomedical data [editorial; see comment citation in Medline]. J Natl Cancer Inst 1995;87:1359-64.
New Epidemiology of Human Papillomavirus Infection and Cervical Neoplasia

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The prospective study of cervical intraepithelial neoplasia (CIN) reported by Ho et al. (1) in this issue of the Journal illustrates how the epidemiologic study of cervical neoplasia has evolved during the past 10-15 years. The epidemiologic interview studies of the 1960s and 1970s correctly identified the venereal nature of cervical neoplasia, but they could not pinpoint a specific etiologic agent. Now the primary exposure measurements are DNA tests for the types of human papillomaviruses (HPVs) proven during the past decade to cause the vast majority of all grades of cervical neoplasia (2).

The new epidemiologic model incorporating a central role for HPV infection has spawned many testable hypotheses regarding the natural history of HPV and carcinogenic cofactors. Thus, molecular epidemiology groups, similar to the group of Ho et al. can focus intensely on clarifying particular stages in the natural history of HPV-induced neoplasia. In this issue of the Journal, Ho et al. have demonstrated how persistent detection of HPV DNA (especially high levels of DNA) is linked to persistent HPV DNA (8-10). HPV-negative cervical neoplasia is a rare though non-negligible event (<10% of all cases).

In their careful prospective study, Ho et al. (1) focused on the determinants of persistence and progression versus regression of CIN in 100 women with lesions originally diagnosed as CIN 2. CIN 2 is a troublesome, borderline category to epidemiologists and clinicians hoping to dichotomize CIN as either low grade (the mild and usually transient cytologic effect of HPV) or high grade (the fixed cancer precursor requiring immediate treatment). Ho et al. demonstrated the biologic and/or diagnostic heterogeneity of CIN 2 when they observed one third of their 100 presumed cases to “regress” immediately to normalcy. Given such data and the common observation that some CIN 2 lesions contain HPV types not found alone in cancers (8,10), it may be that many cases of CIN 2 are low-risk lesions, while only severe CIN 2 lesions (perhaps marked by aneuploidy) should be conceptually joined with CIN 3 in the high-grade category (11).

By following their remaining 70 patients with repeated examinations up to 15 months, Ho et al. attempted to find determinants of later regression versus persistence and progression of CIN. As mentioned above, the key host factor influencing the natural history of CIN is probably cell-mediated immunity, which Ho et al. did not assess. Instead, their study examined viral factors as well as behavioral factors assessed by questionnaire. The repeated HPV test measurements were especially complete and proved informative. This group has promoted studying HPV and CIN at multiple “levels” of detection, starting which Ho et al. did not assess. Instead, their study examined viral factors as well as behavioral factors assessed by questionnaire. The repeated HPV test measurements were especially complete and proved informative. This group has promoted studying HPV and CIN at multiple “levels” of detection, starting

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