The ongoing dilemma over the optimal duration of tamoxifen both in adjuvant and chemopreventive settings is perhaps an inevitable consequence of its identity as a cytostatic rather than a cytotoxic agent (1). Although early in vitro studies revealed tumoricidal effects of tamoxifen, subsequent in vivo data confirmed that short-term tamoxifen acted as a tumorstatic agent and suppressed mammary tumor promotion; growth was re-established upon cessation of tamoxifen. Moreover, continuous tamoxifen treatment for longer periods (>6 months) resulted in emergence of tamoxifen-dependent clones (2).

The most recent overview of adjuvant trials confirms the benefits of at least 5 years of tamoxifen relative to shorter durations with proportional improvements in rates of recurrence and overall survival at 10 years of 47% and 26%, respectively (3). Furthermore, serum levels of tamoxifen and its active metabolites (N-desmethyltamoxifen) remain stable over a period of up to 10 years of continual usage without development of metabolic intolerance (4). The survival benefits of tamoxifen continue beyond 5 years, although much of the effect on recurrence occurs before cessation of therapy. This “carryover effect” is clinically opportune and of particular importance in the context of the B-14 trial results that fail to reveal any benefit from more prolonged tamoxifen treatment.

Most patients do not appreciate this carryover effect and intuitively believe that continued prescription of tamoxifen is beneficial not only in terms of their primary breast cancer but also in terms of any second or contralateral tumor. Of interest, results from the B-14 study show no statistically significant reduction in contralateral tumors following the second randomization; previous adjuvant trials revealed that, for both control and tamoxifen-treated groups, contralateral cancers were more likely to be smaller (T1) ($P<.05$) and lymph node negative with a more favorable prognosis, despite a greater proportion of estrogen receptor-negative tumors in the tamoxifen group ($P = .05$) (5). A patient’s clinical fate is probably determined by the characteristics of the primary tumor and not of any subsequent contralateral lesion, consistent with the comparable survival figures for unilateral versus bilateral tumors. Arguments for broadening the spectrum of tamoxifen therapy should, therefore, not be based on reduction of a second breast cancer, for which there is a cumulative
risk of 2%-15% (depending on the age of the patient at diagnosis). Continued therapeutic intervention may not impart any overall survival gain with respect to either the primary breast cancer or any second or contralateral breast cancer, and indeed a net detrimental effect may ensue from adverse side effects, such as increased risk of thromboembolic phenomena or uterine malignancy. Further follow-up will indicate whether the non-significant trend toward reduced survival with more prolonged tamoxifen treatment will become statistically robust (1). Although the relative benefits of tamoxifen in premenopausal women were emphasized in the most recent overview (3), there are potential concerns regarding more prolonged treatment in this age subgroup. In animal models, supra-physiologic levels of circulating estradiol (in response to tamoxifen) can lead to reversal of the inhibitory action of tamoxifen on MCF-7 tumor xenografts (6). Despite increasing use of adjuvant chemotherapy in premenopausal women, resumption of ovarian function within the period of continued tamoxifen therapy may reduce the antitumor efficacy of more prolonged antiestrogen therapy. Ovarian suppression (e.g., gonadotropin-releasing-hormone agonists) may be a more appropriate strategy for sustained hormonal manipulation in premenopausal patients, for whom there is a 50% chance of response to oophorectomy following tamoxifen failure in advanced disease (7).

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REFERENCES


NOTE

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