

Tamoxifen Associated With Benefit Years After Discontinuation of Therapy

Follow-up reports from two major phase III cancer prevention trials reported in the February 21 issue of the *Journal of the National Cancer Institute* show that tamoxifen continues to protect women from estrogen receptor-positive breast cancer even after they have discontinued active treatment with it. The first International Breast Cancer Intervention Study (IBIS-1), a double-blind, placebo-controlled trial of women at elevated risk of breast cancer begun in 1992, randomized 7,154 women (35–70 years old) to tamoxifen or placebo. The results reported in 2002 showed that tamoxifen was associated with a 26% decrease in the incidence of estrogen receptor-positive breast cancer. Follow-up continued until April 2006 (median 96 months), and during year 5 and beyond, the time when treatment was discontinued, it was found that the rate of estrogen receptor-positive breast cancer was 44% lower among women who had received tamoxifen. During active treatment, tamoxifen was associated with a 2- to 3-fold increase in thromboembolic events and endometrial cancer, in addition to higher rates of vasomotor and gynecologic side effects. Twenty-year follow-up data from the Royal Marsden study was also reported. This study randomized 2,471 women at high risk of developing breast cancer to 8 years of tamoxifen treatment or placebo. The 1998 first interim analysis showed no discernible difference in outcome between the groups. However, the second analysis, 20 years after the trial's initiation (median 13 years of follow-up), showed that patients receiving tamoxifen were 39% less prone to developing invasive estrogen receptor-positive breast cancer than those receiving placebo ($P=.005$). As in the IBIS-1 trial, side effects did not persist after discontinuation of therapy.

Use of Historical Data in Many Phase II Trials Flawed

New research suggests that many phase II trials of cancer agents that use historical data may be using poorly chosen target response rates. The research, led by Dr. Andrew J. Vickers and published in the February 1 issue of *Clinical Cancer Research*, showed that historical data are used to establish null response rates without citing a source for the historical data or providing a single clear historical estimate. Because phase II trial design relies heavily on

establishment of a target rate of response, Dr. Vickers argued, "Poorly chosen targets reduce the ability of phase II [trials] to determine which agents or approaches should be considered for definitive phase III trials." The researchers systematically reviewed phase II trials that appeared in the *Journal of Clinical Oncology* or *Cancer* between June 1, 2002, and June 1, 2005. It was found that of 134 trials, 70 (52%) required historical data for their design, and 32 (46%) did not cite a source for the historical data used. Furthermore, only 9 (13%) of the trials provided a single historical estimate as the basis for the null rate of response used in the trial. The researchers found that a failure to properly cite historical data was strongly associated with a finding that the agent under investigation was active (82% vs 33%; $P=.005$). It was also found that the studies did not compensate for potential inaccuracies by employing statistical methods to account for errors, differences among cases, or differences between the historical controls and the study cohort. It is believed that proper use of historical data, including citation, will avoid unnecessary phase III trials of ineffective agents or early termination of research for drugs that may actually be beneficial.

CT-PET Finds Otherwise Undetected Metastases in Esophageal Cancer

Computed tomography (CT) combined with positron emission tomography (PET) is an important method of detecting distant metastases that can contraindicate resection in patients with esophageal cancer who have received neoadjuvant therapy. CT-PET can detect new metastatic disease in this setting, both during and after chemoradiotherapy, which would not be detected by other, standard methods of screening. Results of research regarding this combination screening method in esophageal cancer were published in the January issue of *Cancer*. The retrospective study included 86 patients with potentially resectable esophageal carcinoma who received neoadjuvant therapy. The patients underwent CT-PET before and after completion of therapy in order to evaluate treatment response. In this regard, the screening method was imperfect. CT-PET was unable to predict response in the primary tumor or locoregional lymph nodes, but it was able to identify the appearance of unexpected metastases in 8% of patients. Therefore, the authors believe CT-PET should become part of routine clinical assessment of patients with esophageal cancer in order to ensure that patients who receive resection are free from occult metastases.