Challenges in Monitoring the Breast Cancer Prevention Trial

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ABSTRACT

The Breast Cancer Prevention Trial (BCPT) was a double-masked, placebo-control, randomized clinical trial designed and conducted by the National Surgical Breast and Bowel Project (NSABP), a National Cancer Institute (NCI)-funded cancer cooperative group. The primary hypothesis tested was whether tamoxifen, a drug that is beneficial for treatment of breast cancer, was effective in preventing the occurrence of cancer in women at increased risk. The Endpoint Review, Safety Monitoring, and Advisory Committee (ERSMAC), the independent data monitoring committee for the BCPT, implemented an innovative monitoring strategy that combined traditional monitoring rules for individual diseases with a global monitoring index in order to weigh the beneficial effects of treatment with known and potential detrimental effects. In addition to developing a monitoring plan tailored for a prevention trial with multiple endpoints of interest, other concerns that were addressed included a reassessment of study sample size and power subsequent to a lengthy suspension of accrual during the trial and handling the occurrence of an unexpected ocular toxicity in association with tamoxifen. Although there were numerous issues that arose during its course, the trial progressed to completion of accrual and successful early termination following the fourth interim analysis, when there was reliable evidence that, not only did tamoxifen prevent breast cancer, but that the beneficial effect outweighed adverse effects of taking tamoxifen.

INTRODUCTION AND BACKGROUND

The BCPT was the first major multicenter randomized clinical trial designed to assess a therapeutic agent for the primary prevention of breast cancer. The therapeutic agent was tamoxifen citrate, a drug marketed under the name Nolvadex®, that had been extensively tested and found...
effective as a treatment in reducing the risk of recurrence and death among women with primary breast cancer. NCI funded the study and the pharmaceutical company, AstraZeneca, provided the medications (tamoxifen and placebo) used in the trial. To be eligible for participation, a woman had to be at least 35 years of age, have no history of an invasive breast cancer or ductal carcinoma in situ, and be at high risk for developing invasive breast cancer. A woman was considered at high risk for developing invasive breast cancer if she met at least one of the three following criteria: (1) was sixty years of age or older; (2) had a prior diagnosis of a lobular carcinoma in situ; or (3) had a five-year predicted risk of developing breast cancer of at least 1.66% as determined by the modified Gail model. Randomization was stratified by age, race, history of lobular carcinoma in situ, and level of predicted breast cancer risk. Women were treated for a planned duration of five years with either 20 mg bid tamoxifen or placebo.

Screening of women for eligibility to the BCPT began in April 1992 and the first participants were randomized in June. Accrual of the 13,388 women randomized to the BCPT occurred between June 1, 1992, and September 30, 1997, although the majority of participants were accrued during the first two years of recruitment. In March 1998, at the time of the fourth interim efficacy analysis, the independent Endpoint Review, Safety Monitoring and Advisory Committee (ERSMAC) for the BCPT recommended that the trial be stopped early due to evidence that tamoxifen was highly beneficial in reducing the incidence of invasive breast cancer. Within a matter of a few days, the trial results were announced by the NCI via the internet and subsequently all participants were unblinded. The formal publication of results in the Journal of the National Cancer Institute occurred a few weeks thereafter.

Throughout the course of the trial, from its initial inception until its early termination with a 45% observed reduction in invasive breast cancer among participants receiving tamoxifen, the BCPT provided many challenges to the study leadership, sponsors, and ERSMAC. The ERSMAC dealt effectively with numerous safety and ethical concerns, often in conjunction with intense public, media, and governmental scrutiny that surrounded the trial. The ERSMAC played a central role in preserving the integrity of the trial that ultimately resulted in determining the effectiveness of tamoxifen for primary prevention of breast cancer. In the discussion that follows, we focus on how the ERSMAC addressed several issues that exemplify the complexity and difficulties in monitoring a large prevention study. These are (1) how to handle an unanticipated ocular toxicity that was identified during the course of recruitment; (2) innovative development of a “global” monitoring strategy to assist in weighing multiple benefits and risks of tamoxifen; and (3) the application of this global monitoring strategy that led to the decision to stop the trial early because of a beneficial effect of tamoxifen therapy.