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Prevention in the Balance

VICTOR G. VOGEL

Many clinicians and investigators with experience in managing the risk of breast cancer [1] would report a more balanced presentation of the current status of breast cancer chemoprevention than that represented by Dr. Trevor Powles in the last issue of The Oncologist [2].

The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (P-1 study) has been criticized because it did not report a reduction in breast cancer mortality among women taking tamoxifen. In his description of the P-1 trial, however, Dr. Powles is not accurate in saying that, “….mortality from breast cancer was a part of the primary objective of this trial…” The authors of the study clearly indicate that the primary aim of the P-1 trial was to determine whether tamoxifen administered for 5 years prevented invasive breast cancer in women at increased risk. Secondary aims of the trial were to determine whether tamoxifen would lower the incidence of fatal and nonfatal myocardial infarction or reduce the incidence of bone fractures. Breast cancer mortality was listed as an “additional” objective and was not one of the primary aims of the study [3]. The absence of a mortality benefit does not diminish the significant reduction in the risk of breast cancer incidence achieved by tamoxifen in the P-1 trial.

Dr. Powles believes that the magnitude of the effect of tamoxifen on premenopausal women has not been reported, but this statement is in error. If one looks at the published results of the P-1 trial, the risk ratio for women less than 49 years of age was shown to be 0.56 with a 95% confidence interval of 0.37-0.85 in Table 3 of the report [3].

Some investigators, including Dr. Powles, have used the Royal Marsden Hospital trial in an attempt to refute the NSABP P-1 trial results. It is erroneous to say, however, that the Royal Marsden trial had a 90% chance of detecting a 50% reduction in breast cancer incidence by 1998, the year the P-1 results were published. The actual power of the Royal Marsden trial has been calculated by reviewers outside the trial as being closer to 35%-40% rather than 90% [4]. This fact, rather than “tamoxifen resistance” or “the low number of events,” is the explanation for the negative results of the Royal Marsden Hospital trial. Dr. Powles should provide substantiation for his statement that the Royal Marsden participants were a “relatively tamoxifen resistant group of participants.” This questionable assertion further complicates the evaluation of the overall long-term clinical benefits of tamoxifen in the risk reduction setting. The low statistical power of the Royal Marsden Hospital trial to demonstrate the benefit of tamoxifen for reducing breast cancer incidence does not equate to tamoxifen resistance as Dr. Powles would have us believe. He provides no data to suggest that the women in the Royal Marsden Hospital trial were any different from those in the P-1 trial, nor does he define “tamoxifen resistance.” It would seem that the real difference is that there were only 2,494 women in the Royal Marsden trial compared to 13,388 in the P-1 trial. The problem with the Royal Marsden trial is one of statistical power, and neither design nor differences among the patient populations explain the Royal Marsden’s results when compared with the NSABP P-1 trial.

Postmenopausal women in the Royal Marsden Hospital trial were permitted to take replacement estrogen therapy. Although Dr. Powles may believe there is no evidence of any negative interaction between hormone replacement therapy and tamoxifen, this possibility still exists [4] and may explain the negative results of the Royal Marsden Hospital trial.

It is also inaccurate to say that it is not clear from the results of the P-1 trial that the observed reduction in early metastatic breast cancer was achieved. Although there was no effect on the rate of breast cancer mortality, the reduction in breast cancer incidence was statistically significant, with a relative risk of 0.56 and a 95% confidence interval of 0.37-0.85 [3].

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incidence of breast cancer is of clinical benefit. Dr. Powles fails to cite the very important publication by Gail and his colleagues that weighs the risks and benefits of tamoxifen treatment for preventing breast cancer [5]. There is substantial net benefit in all premenopausal women whose 5-year risk of developing breast cancer is greater than 1.7%, and in all postmenopausal women whose 5-year risk of developing breast cancer is 2.0%-2.5% and higher, especially among those women who have had a hysterectomy. Dr. Powles fails to acknowledge these demonstrated net benefits, and his unwillingness to recognize the value of tamoxifen reveals a bias in his stated conclusions.

By ignoring the available risk-benefit models, Dr. Powles weakens his contention, “It is not clear from the results of the P-1 trial that the observed reduction in the early incidence of breast cancer is of clinical benefit because of the uncertainty that the treatment of the cancers in women on placebo would have been as effective and safe, the results of toxicity of all 6,681 women randomized to tamoxifen for five years.” This statement ignores the calculations performed by Gail and his colleagues [5] and may discourage the use of tamoxifen for reducing breast cancer risk where it is indicated. It also implies that, for some investigators, prevention is simply not worth the effort. Prevention does, in fact, “save the labor of being sick.”

Dr. Powles does not properly characterize chemoprevention trials that are currently in progress. It is not accurate to say, for example, as Dr. Powles contends, that the primary objective of the STAR Trial (the NSABP’s Study of Tamoxifen and Raloxifene that he mentions neither by name nor by its P-2 designation) is to show equivalence in efficacy between raloxifene and tamoxifen. The published objective of the STAR Trial is to determine whether raloxifene is superior to tamoxifen in reducing breast cancer incidence, whether tamoxifen is superior to raloxifene, or whether they are equivalent. The trial also has primary cardiovascular and bone outcomes that are neither mentioned nor described by Dr. Powles.

Furthermore, Dr. Powles does not reflect published medical opinion about the design of the P-2 trial. Commentary by recognized experts indicates that it is no longer possible to design a breast cancer chemoprevention trial with a placebo arm precisely because of the dramatic results of the P-1 study [6]. Dietary prevention trials, as proposed by Dr. Powles, are already ongoing in low- to average-risk women in studies such as the Women’s Health Initiative [7]. Dr. Powles should provide substantiation and preliminary data to support a trial of the isoflavone extract from red clover that he favors.

Dr. Powles suggests that “…because of the low number of events which are likely to occur in clinical [i.e., chemoprevention] trials, it is essential that any proposed long term medication is of the highest established safety.” Dr. Powles confuses sample size and power with “low number of events.” He also raises the specter of “toxicity that may remain latent for many years.” It is not evident to which toxicity Dr. Powles is referring. The toxicities associated with both tamoxifen and raloxifene are well known, particularly that for tamoxifen [5, 8]. He should enlighten all of us in regard to what those latent toxicities might be. The likelihood that some unknown but delayed toxicity will emerge in future trials would seem to be quite small based on the available millions of women-years of experience with tamoxifen in both the treatment and risk-reduction settings.

Reducing the risk of breast cancer through chemoprevention is now a clinical reality. Ongoing trials and most completed studies are being or have been conducted by accepted rules of clinical investigation. The completed and properly conducted trials have shown us that reducing the risk of invasive breast cancer by using effective chemopreventive interventions is an achievable goal. Tamoxifen is far from the perfect drug, and the search for safer, more effective agents should continue through a process of continual, rigorous peer-reviewed research that is held to the highest possible ethical standards. The data, and not simply personal opinion, should guide both our conclusions and our decisions about chemoprevention in the clinic. Patients, physicians, and the scientific community will all benefit from this approach.

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REFERENCES


