Novel Translational Model for Breast Cancer Chemoprevention Study: Accrual to a Presurgical Intervention with Tamoxifen and N-[4-Hydroxyphenyl] Retinamide

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Abstract

Surrogate end point biomarkers for risk assessment and efficacy of potential chemopreventive agents are needed to improve the efficiency and reduce the cost of chemoprevention trials. It is imperative to develop the best clinical breast model for translational surrogate end point biomarker studies, especially with respect to accrual feasibility. We have initiated a prospective study to develop biomarkers for tamoxifen and N-[4-hydroxyphenyl] retinamide by administering either a placebo or both drugs for 2–4 weeks to women with ductal carcinoma in situ or early invasive cancers in the interval between the initial diagnostic core biopsy and definitive surgery. The principle end point is pretreatment versus posttreatment tumor levels of Ki-67; a number of other exploratory markers will also be examined. The planned target sample size is 100 patients. Between February 1997 and February 2000, 4514 women who had either an abnormal mammogram or a diagnosed breast cancer were screened for the study. Of these 4514 screened patients, 52 (1%) were registered on the study. Major factors of nonparticipation in the remaining 4462 women were as follows: (a) no evidence of malignancy (2081 patients; 46%); (b) ineligible per protocol criteria (575 patients; 13%); (c) preoperative chemotherapy/tamoxifen (520 patients; 11%); (d) surgery scheduling conflict (360 patients; 8%); (e) outside needle biopsy (221 patients; 5%); (f) no residual disease after excisional biopsy (345 patients; 8%); and (g) second opinion only (123 patients; 3%). Other nonparticipation factors included fine needle aspiration only, refusal, tumor size > 2 cm, and estrogen replacement therapy (35 patients each; 2% each). The protocol was amended in midstudy to allow outside needle biopsy, tumor > 2 cm, and estrogen replacement therapy. Accrual to biomarker (nontherapeutic) protocols with delay in definitive cancer surgery is challenging but feasible. Although some accrual problems remain, we have nonetheless succeeded in recruiting 50% of our target sample size in a 3-year period.

Introduction

Although steady gains have been made in the early diagnosis and treatment of breast cancer, 30–50% of affected women still die of their disease. Attention has therefore turned to the significant potential of chemoprevention for decreasing breast cancer incidence and mortality. Chemoprevention refers to the administration of drugs to block or reverse carcinogenesis before the development of invasive cancer.

The promise of chemoprevention in breast cancer was raised by the results of clinical trials of tamoxifen in women with clinically detectable breast cancers. These studies showed a benefit from tamoxifen in reducing tumor recurrence, prolonging survival, and reducing the incidence of contralateral breast cancer, as compared with placebo (1–3). Another promising drug for the chemoprevention of breast cancer is 4-HPR. This synthetic retinoid has been shown to be more effective and less toxic than other retinoids for chemoprevention of mammary cancer in animals (4). 4-HPR was the subject of a recent 5-year clinical trial conducted to assess its usefulness in preventing contralateral breast cancer in a population of patients previously operated on for breast cancer (5). The combined administration of tamoxifen and 4-HPR has proven to be additive or synergistic in both the growth inhibition of the breast cancer cell line MCF-7 (6) and the prevention of N-methyl-N-nitrosourea-induced mammary carcinoma in the rat (7). Because retinoids do not require ERs for their action, they may affect neoplastic transformation in ER-negative cells (8), in contrast to tamoxifen, whose primary mechanism of action is through the ER.

Chemoprevention trials typically use the occurrence of cancer as an end point and thus require large sample sizes and long durations of study. Given the relatively large number of potentially effective chemopreventive agents identified for testing in clinical trials by the National Cancer Institute (9), it is important to develop new strategies to test chemopreventive agents.
interventions. A serial study of biomarkers of malignant transformation during the course of a prevention trial may identify SEBs that could be used in lieu of the occurrence of cancer as an indicator of efficacy.

In an ongoing clinical trial, researchers at The University of Texas M. D. Anderson Cancer Center are attempting to: (a) assess the feasibility of identifying SEBs in noninvasive and invasive breast carcinoma; and (b) determine whether treatment with a placebo or with 20 mg of tamoxifen + 200 mg of 4-HPR given every day in a randomized study will cause significant modulation of proposed SEBs in noninvasive and invasive breast carcinoma. This report details our progress in accruing patients into this SEB trial and addresses the difficulties involved in recruiting patients into a nontherapeutic protocol.

Materials and Methods

Patient Selection. From February 1997 to February 2000, 4514 women with a mammogram highly suspicious for DCIS or T1 or T2 invasive carcinoma were screened for this study. The minimum criteria for inclusion in the study were: (a) no definitive local therapy; (b) age > 35 years (women of childbearing age not practicing effective contraception were excluded); (c) Zubrod performance status ≤ 2; (d) absolute granulocyte count > 1,500/mm³; (e) platelets > 100,000/mm³; (f) total serum bilirubin < 1.5 mg%; (g) serum creatinine < 1.5 mg%; and (h) fasting serum triglycerides < 400 mg%. Subjects meeting any of the following criteria were excluded: (a) any chemotherapy in the preceding 5 years; (b) prior radiation therapy to the chest/breast; (c) vitamin A supplementation; (d) retinoid or tamoxifen therapy in the preceding 12 months; (e) unable to obtain adequate core biopsy; (f) acute intercurrent illness and/or infection that would interfere with administration of proposed chemopreventive agents; or (g) history of thromboembolic disease or degenerative retinal disease. In addition, at the start of the study, subjects were excluded for receiving outside needle biopsy, tumor > 2 cm, or estrogen replacement therapy. The protocol was amended 6 months into the study to allow inclusion of patients meeting these last criteria.

Treatment Protocol. Women with an abnormal mammogram or diagnosed breast cancer underwent a preliminary chart screening to determine whether they met the minimum criteria for recruitment to the study. All participants who met the minimum criteria and agreed to participate were asked to sign an informed consent form, after which they underwent pretreatment evaluation consisting of: (a) complete history and physical examination, including history of hormone use and menstrual and obstetric history; (b) laboratory testing; (c) endometrial biopsy for definitive ascertainment of menstrual dating/menopausal status; and (d) core biopsy of the index lesion to confirm histology and establish baseline measurement of biomarkers. Women who were found to have benign proliferation only were excluded from the study at this point. All other qualifying women were randomized to receive either placebo or tamoxifen (20 mg/day) + 4-HPR (200 mg/day) daily for 3 weeks (± 7 days to allow continuation of treatment to the time of definitive surgery). Tissue obtained at the time of the definitive surgical procedure was used to assess modulation of biomarkers. The treatment schema is shown in Fig. 1.

The main statistical end point was pretreatment versus posttreatment change in Ki-67 in the experimental group compared with the control group. Ki-67 is a proliferation-associated nuclear antigen that has been shown to be correlated with the mitotic activity of breast cancer. A number of other exploratory markers related to the neoplastic phenotype, inducible growth regulation, and genetic instability were also examined.

The sample size of 50 patients per arm was selected, assuming that changes from baseline greater than 20% would be considered of interest. Assuming a null hypothesis that the proportion of cases with changes of interest is 5% in both arms and an alternate hypothesis that the proportion of cases with changes is >20% in the treatment arm, the sample size is sufficient to provide a power of 80% and a significance level of 0.05.

Results

During the 36-month period from February 1997 to February 2000, 4514 women who had either an abnormal mammogram or a diagnosed breast cancer underwent preliminary screening for the study. Of these 4514 patients, 52 (1%) were registered on study. Thus, at the end of 3 years, a little over half of the required sample size (n = 100) has been accrued.

The major reasons why the remaining 4,462 patients did not participate in the study are shown in Table 1. Almost half (46%) had no evidence of malignancy at initial biopsy, and an additional 8% had no residual disease after excisional biopsy. Thirteen percent were ineligible under protocol inclusion criteria, and 11% received chemotherapy or tamoxifen preoperatively. Patients receiving outside needle biopsy, patients with tumor size > 2 cm, and patients receiving estrogen replacement therapy constituted 6% of the total of nonparticipating subjects. In addition, 360 patients (8%) did not participate because of a surgery scheduling conflict, 219 patients (5%) were seen for second opinion only or FNA only, and 72 patients (2%) refused to participate. The most common reasons given by women for refusing to participate in the study were as follows: (a) patient did not want to wait 2 weeks for surgery; (b) patient was concerned about potential side effects of the medication (hot flashes, blood clots, stomach upset, and so forth); and (c) patient would receive no therapeutic benefit from participating in the study.

Subtracting out the patients who were ineligible by pro-
A modification of the therapy accounted for 38% of the exclusions of patients with clinical tumor size greater than 2 cm and estrogen replacement therapy. An examination of study records revealed that eligible patients were accrued to the trial. 345 patients were eligible for the study. Thus, 3.4% of patients were included in the study.

As of April 1997, only one patient had been recruited to the study. An examination of study records revealed that clinical tumor size greater than 2 cm and estrogen replacement therapy accounted for 38% of the exclusions of patients with known breast cancer up to that point. A modification of the protocol to include patients with tumors > 2 cm and patients receiving estrogen replacement therapy was requested, and approval from the granting agency was received in July 1997. As illustrated in Fig. 2, the number of patients accrued after this modification increased substantially. The rate of accrual increased from <1% before the modification to a median of 2.3% (range, 1–6.3%) during the period from August 1997 to December 1998 before dropping again to rates at or below 1% during the final year.

Discussion

Patient Accrual for Clinical Trials. Difficulties in the accrual of patients for clinical trials are serious impediments to clinical research in cancer. As of 1991, only 1–3% of the available patient population was being recruited into cooperative group adjuvant trials, with only 10–30% of the eligible patients finally enrolled in the studies (10). For breast cancer, less than 2% of patients are included in clinical trials (11).

Accrual into nontherapeutic SEB protocols has been especially challenging for a variety of reasons. Only a fraction of women with a suspicious mammogram will prove to have a malignancy, and only a fraction of those will consent to and/or qualify to participate in a clinical trial (12). In the current study, almost one-half of the women initially screened had no evidence of malignancy by core biopsy, and an additional 8% had no evidence of disease after biopsy. There are no potential direct benefits to the participants to counterbalance the possible side effects from the drugs and the delay in definitive surgery. Given these difficulties and the observation that previous studies have been unsuccessful in recruiting sufficient patients (12), we believe that our ability to recruit over half of our total required number of patients in a 3-year period is respectable. This accrual rate has been due, in part, to our flexibility in reassessing the validity of exclusionary criteria for the study.

Although low patient recruitment levels have been attributed in part to patient attitudes (11, 13, 14), that does not seem to have been a factor in this study to date. Less than 2% of the patients who were initially screened refused to participate. Of those who did refuse, most listed such factors such as concern about treatment side effects, lack of therapeutic benefit, and not wanting to wait for surgery as reasons for their refusal.

Another factor that is likely to have influenced the decision to participate is the number of competing clinical trials currently recruiting patients in a tertiary referral cancer center. The availability of a clinical trial with probable therapeutic benefit to the patient, for which pretreatment with tamoxifen and 4-HPR might be an exclusion factor, would obviously weigh heavily in the decision to participate.

Many researchers now believe that the largest impediment to patient accrual is overly restrictive eligibility criteria (12, 14–16). In two independent studies examining reasons for nonenrollment in clinical trials in single oncology clinics, nearly half of patients for whom an appropriate trial was available based on diagnosis were not eligible under study criteria (17, 18). Fuks et al. (16) found that NSABP trials had a mean of 37 eligibility requirements, compared with only 9 eligibility requirements in Pediatric Oncology Group trials, with the most striking difference being the complete lack of safety criteria in Pediatric Oncology Group studies, where such concerns are left to the judgment of individual clinicians. Although there are disease-related differences in these two general classes of study (breast cancer versus leukemia), this nonetheless suggests that complex questions can be successfully addressed without extensive inclusion and exclusion criteria.

Besides making patient accrual more difficult and generally making a study more complex and costly, overly exclusionary eligibility criteria generate problems in generalizing data from a study. Patients who meet a long list of criteria will represent only a small and relatively homogeneous fraction of the total number of patients with the disease in question. This select subgroup is unlikely to be representative of the more heterogeneous mix of patients who would be encountered in clinical practice. Thus the clinician is left with the problem of determining whether the published results of clinical trials will be relevant to a specific patient who clearly does not meet study criteria.

On the other hand, reducing the number of eligibility criteria may make the interpretation of the clinical trial more difficult, with the requirement for additional stratification and/or covariate analysis. These difficulties in analysis may weigh heavily in the decision to participate.

The protocol was amended in mid-study to allow patients with outside needle biopsy, tumor size >2 cm, and estrogen replacement therapy. The protocol criteria (n = 575) or who had no evidence of malignancy (n = 2,081) or no residual disease after excisional biopsy (n = 345), 1513 patients were eligible for the study. Thus, 3.4% of patients were included in the study. The number of patients per 6-month period accrued into a chemoprevention protocol over the 3-year period from February 1997 to February 2000.

![Fig. 2](https://example.com) Number of patients per 6-month period accrued into a chemoprevention protocol over the 3-year period from February 1997 to February 2000.
Recruitment Considerations in Selecting a Model to Test Drug Effects on SEBs. Several models are currently being used for testing drug effects on SEBs (12). The short-term DCIS model uses women with DCIS with or without small invasive tumors who are randomized to receive drug or placebo in the interval between biopsy and definitive surgery. The directed core biopsy hyperplasia model randomizes women with core biopsy-detected hyperplasia to receive drug or placebo for a more extended period of time, usually months or years, before being reassessed with core needle biopsy. Variations of the hyperplasia model use FNA, with either random four-quadrant sampling or random periareolar sampling, for patient assessment before randomization. Again, the treatment period is usually months or years before being reassessed with FNA. Core needle biopsy has the advantage of providing larger tissue specimens, but it samples only one area of the breast, and the possibility of morbidity with repeated samplings is greater. FNA has the advantage of being minimally invasive, and random site models obtain tissue from multiple areas rather than a single focal lesion. The principle disadvantage with models based on FNA is the small volume of tissue acquired. Although all of the current hyperplasia models require drug treatment for longer time periods, so that compliance might become an issue, they offer the advantage of possible therapeutic benefit.

This trial is using a short-term model in which women with DCIS and/or early invasive cancers detected through core biopsy are randomized to receive either tamoxifen + 4-HPR or placebo during the 2–4-week period between biopsy and definitive surgery. This model was selected because the treatment time is very brief, so that potential side effects of the drugs being tested are minimized, and patient compliance is maximized. It also has the advantage of not requiring invasive procedures that are not medically indicated. The disadvantages of this model are that it requires a waiting period before definitive surgery that some patients find worrisome. In addition, although the drug treatment period is short, there are potentially uncomfortable side effects, and many potential candidates have found this unacceptable, given that no therapeutic benefit will be realized.

In summary, accrual to nontherapeutic protocols with delay in definitive cancer surgery is difficult but feasible. In the challenging presurgical model presented here, refinement of the protocol infrastructure and referral network has allowed patient accrual of 52% of our target sample size.

References
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