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PRINCIPAL INVESTIGATOR: Peter L. Davis, M.D.

CONTRACTING ORGANIZATION: University of Pittsburgh
Pittsburgh, Pennsylvania 15260

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Peter L. Davis, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Pittsburgh
Pittsburgh, Pennsylvania 15260

E-Mail: davispl@msx.upmc.edu

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13. ABSTRACT ***(Maximum 200 Words)***

To prevent breast cancer, over 200,000 women are now taking tamoxifen and similar selective estrogen receptor modifiers (SERM). We have laboratory data that shows that approximately 30% of women have defects in their breast cell's estrogen receptor or in its intracellular signaling mechanism. As a result, these women may not experience the antineoplastic effect of tamoxifen on breast cancer risk but only its side effects. We propose that contrast enhanced magnetic resonance imaging (CE MRI) can detect this defect. CE MRI will be performed on postmenopausal women on tamoxifen therapy.

Despite very extensive procedures for recruiting subjects, we have not recruited enough to perform the planned research. Therefore, we recently met with Drs. Norman Wolmark, Thomas Julian, and Lawrence Wickerham, the leaders of the National Surgical Adjuvant Breast and Bowel Project (NSABP), and discussed this project with them. They were enthusiastic about its significance, but recognized potential limitations of subject recruitment based on the present inclusion criteria. They suggested several additional inclusion criteria and changes in the Specific Aims which would increase the potential of subject recruitment especially through their clinics and referring physicians.

These changes are under review by the Human Subjects Reserach Review Board.

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INTRODUCTION

To prevent breast cancer, over 200,000 women are now taking tamoxifen and similar selective estrogen receptor modifiers (SERM). We have laboratory data that shows that approximately 30% of women have defects in their breast cell's estrogen receptor (ER) or in its intracellular signaling mechanism. As a result, these women may not experience the antineoplastic effect of tamoxifen on breast cancer risk but only its side effects. Since ERs are just one element in a complex set of interactions necessary to induce or block cell proliferation, what is needed is a noninvasive assay that tests the intact functionality of the entire SERM pathway and whether the SERM blocks breast tissue proliferation. We propose that contrast enhanced magnetic resonance imaging (CE MRI) can be this noninvasive technique. CE MRI is very sensitive for proliferating breast tissue. We hypothesize that women with intact SERM signaling pathways who receive tamoxifen will demonstrate substantially decreased CE MRI enhancement of breast tissue. Women with defective SERM pathways who receive tamoxifen will not demonstrate decreased CE MRI enhancement of breast tissue because the tissue will not respond to tamoxifen and are at increased risk for developing breast cancers. CE MRI will be performed on postmenopausal women on tamoxifen therapy.

BODY

Progress Report

1. Methodology for recruiting subjects through direct physician or woman referral:
   - A. Repeated meetings and conversations with Dr. Victor Vogel, co-investigator, National Protocol Chairman for the NSABP Study of Tamoxifen and Raloxifene (STAR) Project, whose primary responsibility on this project is to recruit eligible women.
   - B. Presentations and attendance by the principal investigator at the Magee-Womens Hospital Breast Oncology Conferences.
   - C. Personal contact with Breast Surgeons, Oncologists and Gynecologists at Magee-Womens Hospital and elsewhere including Drs. Ronald Johnson, Marguerite Bonaventura, Albert Baffoni, Adam Brufsky, Donald Keenan, Joseph Kelly, and Jon Lloyd.
   - D. Two direct mailings to all gynecologists in Allegheny County and adjacent counties.
   - E. Two listings on the medical page in the local newspaper.
   - F. Two listings in the research column of the University of Pittsburgh Medical Center newsletter which is sent to all associated physicians, staff and employees.
   - G. Two direct mailings to all women over 50 years of age associated with the

University of Pittsburgh (professionals, staff and other employees).

H. Placed project summary in Allegheny County Medical Society Journal.

I. Two brochures or listings in the local Susan G. Komen Breast Cancer Foundation Society newsletter.

J. Brochures at the local annual Susan G. Komen Breast Cancer Foundation Race for the Cure.

K. Brochures put in charts of Dr. Ronald Johnson's patients who may be potentially eligible for the study, with his permission, just before he sees the patient in his clinic.

L. Placed project summary on Magee-Womens Hospital Research Institute web site.

M. Discussed project in the University of Pittsburgh Cancer Institute newsletter.

2. Methodology for recruiting subjects through direct identification of eligible pathology specimens:

A. In the time frame covered by the first grant period, co-investigator Dr. Kenneth McCarty, Jr., and collaborator Dr. Susan Silver have reviewed a total of 350 patients' slides. These cases were identified for review based on the original pathology report describing hyperplasia, any atypical proliferative lesion, or low grade DCIS. Among the 350 cases whose slides were reviewed, 79 cases demonstrated changes in the core biopsy material meeting the criteria of intraductal epithelial hyperplasia and the women were also postmenopausal. Twenty six (26) cases were identified as containing atypical ductal hyperplasia. Seven (7) cases contained atypical lobular hyperplasia. Sixteen (16) contained papillary proliferative lesions. However, there is now a concern regarding access of my colleagues to the required material which may decrease our ability to screen subjects using this methodology.

B. All eligible subjects' IDs were forwarded to Dr. Victor Vogel for recruitment, per confidentiality methodology approved by the Magee-Womens Hospital Investigational Review Board (IRB).

3. During the period covered, co-investigators evaluated 89 specimens (including proliferative lesions, DCIS, and infiltrating cancer) for ER, PgR, CREB binding protein, SRC1, NCoR, and GRIP1. An inverse relationship was observed between CREB binding protein and ER in non-atypical lesions. The expression of CREB binding protein did not show this relationship in several atypical lesions and in DCIS. SRC1 was variably expressed, as was GRIP1 which will be correlated with clinical data. Mechanism to establish the relationship of these findings to clinical data and imaging are being sought.

4. Performed breast MRIs on two recruited subjects.

We are not satisfied with the rate of eligible subject recruitment for MRI scans nor the difficulties in accessing tissue from MWH Therefore, we have recently met with Drs. Norman Wolmark, Thomas Julian, and Lawrence Wickerham, the leaders of the National Surgical Adjuvant Breast and Bowel Project (NSABP), and discussed this project with them. (Their offices and the headquarters for the NSABP are across town at Allegheny General Hospital.) They were enthusiastic about its potential and significance. However, they recognized potential limitations of subject recruitment based on the present inclusion criteria. Therefore, they suggested several additional inclusion criteria and changes in the Specific Aims which would increase the potential of subject recruitment especially through their clinics and referring physicians:

1. The addition of Raloxifene, in addition to the present Tamoxifen, as an anti-estrogen which the woman may be starting. It is clear from the STAR trial and published data that both compounds' mechanisms of action is through similar effects on receptor helix folding with consequence effect on receptor co-activator binding sites. Since a substantial number of women are offered Raloxifene instead of Tamoxifen and the mechanisms of actions are similar, we think that Raloxifene should be an acceptable alternative to Tamoxifen for this study. The therapeutic profile of Raloxifene is similar to Tamoxifen with the added benefit that there is not the endometrial hyperplasia seen with Tamoxifen. The benefit of the study remains unchanged: determining which women are not likely to benefit from this type of antiestrogen and would not be receiving a protective effect from them, but should be potentially placed on other newer compounds which have different mechanisms of action. The risk of the study, the contrast of the MRI examination, remains unchanged.

2. The addition of other classes of women who are quite likely to have proliferative breast dysplasias and will be taking either Tamoxifen or Raloxifene for prophylactic or chemotherapeutic effects. These include women with lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS) and small stage I infiltrating ductal carcinomas. The latter two classes, DCIS and small stage I infiltrating ductal carcinomas, are now frequently treated with local excision, radiation to the affected breast and the use of a SERM, generally Tamoxifen and occasionally Raloxifene. Since women with these latter two processes frequently have proliferative dysplasias bilaterally, we can study their other breast. The other breast will not have had acute surgery or radiation. Again the potential benefits and risks are unchanged.

3. The addition of a diagnostic MRI pulse sequences of the entire breast with diagnostic interpretation by the Dr. Peter Davis, the P.I., when requested by the subject's referring physician. This is a potential incentive for the subject and the referring physician. Presently the proposal uses a high resolution MRI pulse sequence consisting of a fast spoiled gradient echo acquired with a three dimensional volume technique over a limited volume of 12 slices which covers a breast thickness of only about 3.6 cm. The advantage of this sequence is that its total acquisition time is 23 seconds and a tissue contrast enhancement curve with multiple points can be obtained over the following 10 minutes. The diagnostic scan is an identical high resolution

scan, but it scans the entire breast with 60 slices. To perform a diagnostic scan of the entire breast with present techniques will require one precontrast and three post contrast scans each lasting 2.5 minutes. Therefore, the first 7.5 minutes (3*2.5) after the contrast injection will be utilized by the diagnostic scans, leaving only 2.5 minutes for the more rapid scanning. This is not a problem since previous work, which is already referenced in the protocol, has shown that proliferative dysplasias continue to enhance continuously for over 10 minutes and the 10 minute value will be most typically used. In addition, the data obtained during the diagnostic scans can also be quantified and utilized in the analysis.

The risk of the diagnostic scans to the patient is low for the following reasons: These women are being selected because they most likely have a proliferative dysplasia. Proliferative dysplasias and breast neoplasms frequently have similar MRI enhancement patterns. This is a frequent cause of MRI false positives. Therefore, it may not be possible to differentiate these two entities. Both the referring physician and the subject will be informed of this, and if they wish to proceed with a diagnostic scan, the risk of false positives and their potential to lead to further workup (mammography, ultrasound, biopsy, follow up MRI) as the referring physician and subject see fit. The fact that a 3 month follow up is part of this protocol may potentially decrease the incidence of false positives.

Similarly the risk of a false negative MRI scan will be explained and the need of the subject to maintain her routine breast examinations.

4. To insure appropriate input from the NSABP group, we have added Thomas Julian, M.D. as a coinvestigator. When he was the University of Pittsburgh Medical Center, Dr. Julian and Dr. Peter Davis, the Principal Investigator, worked together on several MRI breast projects including one of the earliest MRI guided wire localization of a mammographically and ultrasonically occult breast cancer which was initially detected by metastatic disease. This research was published.

These changes to the protocol and the corresponding changes to the consent forms have been submitted and approved by the Magee-Womens Hospital Institutional Review Board.

The protocol and consent forms have been submitted by Dr. Julian to the Allegheny General Hospital Institutional Review Board which is the local Institutional Review Board used by the NSABP.

The changes to the protocol and consent forms have been submitted to the Human Subjects Reserach Review board (HSRRB) and are pending review.

As of this time, no funds have been expended on personnel.

KEY RESEARCH ACCOMPLISHMENTS:

None yet. They will be reported once the research is completed.

REPORTABLE OUTCOMES:

None yet. They will be reported once the research is completed.

CONCLUSIONS:

None yet. They will be reported once the research is completed.

REFERENCES:

None.

APPENDICES:

None