AD_____

Award Number: DAMD17-02-1-0621

TITLE: Randomized, Double Blind, Placebo Controlled Trial of Neuroprotective Effects of Epoetin alfa in Patients Receiving Adjuvant Chemotherapy for Breast Cancer

PRINCIPAL INVESTIGATOR: Jame Abraham, M.D.
Marc Haut, Ph.D.
Gary Marano, M.D.
Edward Crowell, M.D.
Sobha Kurian, M.D.

CONTRACTING ORGANIZATION: West Virginia University Research Corporation
Morgantown, WV 26506-6845

REPORT DATE: October 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
01-10-2005	Annual	1 Oct 03 – 30 Sep 05

4. TITLE AND SUBTITLE
Randomized, Double Blind, Placebo Controlled Trial of Neuroprotective Effects of Epoetin alfa in Patients Receiving Adjuvant Chemotherapy for Breast Cancer

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-02-1-0621

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Jame Abraham, M.D., Marc Haut, Ph.D., Gary Marano, M.D., Edward Crowell, M.D., Sobha Kurian, M.D.

E-Mail: jabraham@hsc.wvu.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
West Virginia University Research Corporation
Morgantown, WV 26506-6845

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Adjuvant treatment with Adriamycin and cyclophosphamide (AC) clearly prolongs the overall survival in women with breast cancer. Cognitive deficits (e.g. problems with memory and concentration) are common during and after adjuvant breast cancer chemotherapy, but the pathophysiology of cognitive phenomena is unknown. The goal of this project is to study the pathophysiology of cognitive dysfunction in patients receiving adjuvant treatment using Positron Emission Tomography (PET) scan.

This study opened to accrual in April 2003. Three patients have been enrolled.

15. SUBJECT TERMS
No subject terms provided.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	6	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Introduction

In the United States approximately 60-80% of patients diagnosed with breast cancer will receive adjuvant chemotherapy. Of these patients more than 30% will experience short-term and long-term cognitive impairment (e.g., problems with memory and concentration) for at least 1-2 years after completion of chemotherapy. Despite the effects cognitive impairment can have on a patient's quality of life very few studies have been conducted to learn more about this side effect.

This study aims to evaluate the pathophysiology of cognitive dysfunction in patients receiving adjuvant chemotherapy with Adriamycin and cyclophosphamide for breast cancer using [^{15}O] water PET scans and neuropsychological tests.

A total of 24 eligible patients with early stage breast cancer, who are candidates for adjuvant chemotherapy, will be enrolled in this study. Each patient will undergo [^{15}O] water PET scans at baseline and after completing 4 cycles of adjuvant chemotherapy to measure the differences in regional blood flow of the brain during working memory. Neuropsychological tests will be done to determine attention, speeded processing, memory, and executive functions outside of the [^{15}O] water PET scans.

Investigators will analyze several categories of data once the accrual goal (24 patients) is met:

- Participant Characteristics (demographics)
- Neuropsychological Measures (differences in attention/processing, memory, and frontal lobe processing)
- PET Behavioral Performance (total number of responses and correct responses will be recorded
- t-Statistic Volumes (examine patterns of neural activation)
- Group and Time Comparisons (to test if there are significant differences between the two times for peaks obtained by the t-Statistic volumes)
- Exploratory Analysis (explore relationship between changes in blood flow during working memory and cognitive defects)

The data for this study is entered into an electronic database that is password protected. The data manager is responsible for maintenance of this database as new information is provided per the Principal Investigator or study coordinator. All data is kept in a secure location at West Virginia University in the Clinical Trials Research Unit. Additionally, some PET scan data and neuropsychological data will be kept in a secure location in the Center for Advanced Imaging (in Dr. Marc Haut's office) at West Virginia University.

In April 2004 this study was amended due to published data regarding the safety of Epoetin alfa (EPO). This data showed that patients with normal hemoglobin levels who receive treatment with EPO have increased morbidity and mortality. Due to this information the Investigators were prompted to change the protocol to look at pre-post chemotherapy changes in the brain with PET scan, but without treating patients with EPO. Therefore the protocol aims to understand the pathophysiology of cognitive

dysfunction without studying the role of EPO. All three patients were notified of this change to the protocol.

Body

Task 1. Study the baseline cognitive function

- Three patients with early stage breast cancer receiving adjuvant chemotherapy have been enrolled in this study prior to the amendment.
- Baseline cognitive function assessments with neuropsychological measures have been completed by each patient.
- The baseline study of regional blood flow of the brain using [^{15}O] water PET scans during working memory has been completed by each patient.

Task 2. To study the cognitive function after 4 cycles of chemotherapy with [^{15}O] *water Positron Emission Tomography (6-12 months)*

- Each patient completed PET scans and neuropsychological measures 2-4 weeks after the completion of 4 cycles of AC.

Task 3. Analysis of the data and writing of the final report (12-18 months)

- All data is maintained in a secure database. Data analysis will occur after the accrual goal is met.

Key Research Accomplishments

- Development of animal study titled: **Proinflammatory Cytokine Expression as a Possible Mechanism of Chemotherapy Induced Cognitive Dysfunction** (Approved by local IRB for the period of April 6, 2005 to April 5, 2006)
    - The objective of this study is to characterize the effects of chemotherapeutic drugs on cytokine production in an experimental animal model.
    - Hypothesis: Chemotherapy induces the expression of proinflammatory cytokines both in the blood and in the brain. These proinflammatory cytokines damage nerve cells thus leading to brain malfunction.
    - The long-range goal is to understand the mechanisms of chemotherapy-induced brain damage and to understand how these mechanisms can be controlled for therapeutic purposes.

Reportable Outcomes

Presentation

Invited Speaker, "Use of PET Scanning in Assessing the Pathophysiology of Cognitive Dysfunction: The Future of Supportive Therapy in Oncology an International Congress," Hamilton, Bermuda, March 13, 2003.

Presentation

"Cognitive Dysfunction in Adjuvant Breast Cancer Treatment," Mary Babb Randolph Cancer Center Research Retreat, Stonewall Jackson Resort, July 13-15 2005.

Poster Presentation
"The Effects of Adjuvant Chemotherapy for Breast Cancer on Cerebral White Matter and Cognitive Function: A Diffusion Tensor Imaging Pilot Study," American Society of Clinical Oncology Annual Meeting, May 15-18, 2005.

Conclusions
Accrual for this study began in April 2003 and three patients have been enrolled. An amendment temporarily stopped accrual in April 2004. The site received permission from the DOD to resume enrollment in April 2005.

Data for this study will be analyzed upon meeting the accrual goal of 24 patients.