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TITLE: Chemotherapy-Induced Cognitive Impairment: A Novel Prospective Study of the Cognitive Effects of Platinum Taxane-Based Chemotherapy in Ovarian Cancer Patients

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14. ABSTRACT: Background: Chemotherapy-induced cognitive impairment (CICI) is a spectrum of neurocognitive deficits experienced during and after chemotherapy for cancer. As therapeutic options for cancer improves, so too does survival. With more patients living longer after cancer treatments, the number of patients with these cognitive complaints is increasing and quite significant. Hypothesis: At least 30% of patients undergoing platinum/taxane-based chemotherapy for ovarian cancer will experience CICI. Primary Objective: To quantify cognitive changes in patients with ovarian cancer undergoing platinum/taxane chemotherapy. Secondary Objectives: 1) To assess the correlation between biologic markers of oxidative stress and neurocognitive test results; 2) To assess the correlation between brain imaging and neurocognitive test results. Exploratory Objectives: 1) To identify the cognitive domains most affected in CICI; 2) To develop a screening tool for CICI. Study Design: This is a prospective, phase II study, quantifying cognitive changes in patients with ovarian cancer undergoing platinum/taxane chemotherapy. "Cognitive changes" will be defined by significant reliable change index (|RCI| > Z0.975) calculated between pre- and post-chemotherapy neurocognitive measurements for the MoCA total score. Patients will undergo testing prior to, and after 6 cycles of chemotherapy. Testing includes neurocognitive assessments, serum markers of oxidative stress (tumor necrosis factor alpha, protein carbonyls, 4-hydroxynonenal proteins), and neuroimaging (cognitive event related potentials, functional magnetic resonance imaging). Cancer Relevance: The investigators of this innovative trial hope to generate new data on neurocognitive testing for CICI in gynecologic cancers, provide validation for counseling gynecologic oncology patients, and offer insight for prevention or future therapeutic interventions for CICI.

During the past year, a total of 7 subjects have been enrolled. Six patients have completed pretreatment/baseline testing including neurocognitive testing, neuroimaging testing (eventrelated potentials during cognitive tasks), and collection of serum markers of oxidative stress prior to and at the time of cycle 1 chemotherapy. One patient is scheduled for pretreatment testing to occur at the end of November. At this time, one patient has completed the posttreatment neurocognitive and neuroimaging testing. Of the seven patients enrolled, four patients have (or will have had) undergone the optional MRI component of the study. A fifth patient was very interested in participating in the MRI neuro-testing, but had to be excluded due to being left-handed (this study is only including right-handed participants at this time).

15. SUBJECT TERMS:
OVARIAN CANCER,COGNITIVE IMPAIRMENT,CHEMOTHERAPY, CANCER

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Chemotherapy-Induced Cognitive Impairment: A Novel Prospective Study of the Cognitive Effects of Platinum Taxane-Based Chemotherapy in Ovarian Cancer Patients

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1. INTRODUCTION:

Chemotherapy-induced cognitive impairment (CICI), also known as "chemobrain," is a spectrum of neurocognitive deficits experienced during and after the administration of chemotherapy for cancer. The incidence of CICI is significant, affecting anywhere from 25 to 75% of survivors[1], and the biologic basis is unknown. This novel study is designed to address the questions of incidence and biological cause for CICI, while gaining a better understanding of the structural and functional effects of chemotherapy on the brain. In order to address these important objectives, a diverse team of experienced investigators has been assembled to design and implement the proposed protocol. The research team for this project seeks to accomplish the proposed objectives through following mechanisms: 1) assessment of the neurocognitive domains affected in CICI using a tailored battery of cognitive tests to define CICI; 2) measurement of serum markers of oxidative stress and correlation of these markers with neurocognitive test results; and 3) exploration of structural and functional changes in the brain during cognitive tasks and correlation of results with markers of oxidative stress and neurocognitive test results. Outcomes from this study will have a major impact on current cancer research and clinical care by standardizing the approach to patient assessment for cognitive

changes related to chemotherapy. This study will also provide a more comprehensive understanding of the etiology of CICI, which will direct future preventative or therapeutic interventions. No studies to date have included correlative studies of cognitive testing with biologic markers of oxidative stress and neuroimaging.

In this prospective, phase II clinical study, we will test the hypothesis that ovarian cancer patients receiving platinum/taxane-based chemotherapy will experience quantifiable declines in cognitive function when measured pre- and post-chemotherapy. Specific mechanistic markers of cognitive impairment hypothesized to change with platinum/taxane-based chemotherapy include serum markers of oxidative stress and brain function measured through neuroimaging.

2. **KEYWORDS:**

OVARIAN CANCER, COGNITIVE IMPAIRMENT, CHEMOTHERAPY, CANCER

3. **ACCOMPLISHMENTS:**

What were the major goals of the project?

GOAL 1: Enroll patients on clinical trial (months 0-16)
GOAL 2: Collect and analyze neurocognitive testing data (months 4-24)
GOAL 3: Collect and analyze serum markers of oxidative stress (months 4-24) GOAL 4: Collect and analyze neuroimaging data (months 4-24)

What was accomplished under these goals?

1) **Major activities:** During the course of the trail a total of 14 subjects have been enrolled. At the time of this report, a total of 15 subjects consented to participate on this trial; two participants withdrew consent prior to pre chemotherapy neurocognitive testing. These two participants cited logistic and time barriers as the reason for their withdrawal. Twelve participants have completed pre chemotherapy testing, and six of these twelve participants have completed post chemotherapy testing, completing all protocol-defined tests and procedures and are now off study. Six patients are currently undergoing treatment and will complete post treatment testing within the upcoming months. The first patient enrolled onto this trial was unable to complete post treatment testing due to psychosocial circumstances.

2) **Specific objectives:** The accrual goal for this trial is 24 subjects, with a quarterly enrollment target of 6 patients.

3) **Significant results/key outcomes:** Twelve participants have completed pre chemotherapy testing, and six of these twelve participants have completed post chemotherapy testing, completing all protocol-defined tests and procedures and are now off study. Six patients are currently undergoing treatment and will complete post treatment testing within the upcoming months.

4) **Other achievements:** Study was closed to accrual on 12/19/2018.

What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

Enrollment is closed. We plan to complete treatment on patients and continue follow up.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. **CHANGES/PROBLEMS:**

- **Changes in approach and reasons for change**

Nothing to Report.

- **Actual or anticipated problems or delays and actions or plans to resolve them**

Nothing to Report.

- **Changes that had a significant impact on expenditures**

Nothing to Report.

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents** Nothing to Report.

Significant changes in use or care of human subjects:

Nothing to Report.

Significant changes in use or care of vertebrate animals.

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to Report.

6. **PRODUCTS:** Nothing to report.

- **Publications, conference papers, and presentations**

Nothing to report.

- **Journal publications.**

Nothing to Report.

- **Books or other non-periodical, one-time publications.**

Nothing to Report.

- **Other publications, conference papers, and presentations.**

Nothing to Report.

- **Website(s) or other Internet site(s)**

Nothing to Report.

- **Technologies or techniques**

Nothing to Report.

- **Inventions, patent applications, and/or licenses**

Nothing to Report.

- **Other Products**

Nothing to Report.

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS** ▪

What individuals have worked on the project?

Name: **Rachel W. Miller, MD**

Project Role: Pl

Nearest person month worked: See attached budget justification Contribution to

Project: Dr. Miller has served as Pl.

Name: **Daret St. Clair, PhD**

Project Role: Co-Investigator

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. St. Clair has provided mentorship regarding basic science aspects of this trial and will perform serum testing for markers of oxidative stress and facilitate analysis and reporting of test results.

Name: **D. Allan Butterfield, PhD**

Project Role: Co-Investigator

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. Butterfield has provided provide mentorship regarding basic science aspects of this trial and will coordinate serum testing for markers of oxidative stress.

Name: **Amelia Anderson, PhD**

Project Role: Co-Investigator

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. Anderson will administer the test battery to all patients enrolled in the trial, on two separate occasions. She will be responsible for analysis of the neurocognitive test results.

Name: **Kathryn J. Dunham, Psy.D**

Project Role: Co-Investigator

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. Dunham will work with Dr. Anderson to administer the test battery to all patients enrolled in the trial, on two separate occasions. She will be responsible for analysis of the neurocognitive test results.

Name: **Yang Jiang, MD**

Project Role: Co-Investigator

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. Jiang has provided mentorship regarding the neuroimaging component of this novel trial. She will coordinate analysis and reporting of test results.

Name: **Brent Shelton, PhD**

Project Role: Statistician

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. Shelton has provided statistical support for this trial.

Name: **Lauren Baldwin, MD**

Project Role: Co-Investigator

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. Baldwin is assisting in the identification of potential participants.

Name: **Stacey Brothers**

Project Role: Coordination support

Nearest person month worked: See attached budget justification

Contribution to Project: Stacey will perform neurocognitive testing.

Name: **Frederick A. Schmitt, PhD**

Project Role: Neuroimaging

Nearest person month worked: See attached budget justification

Contribution to Project: Dr. Schmitt will perform Neuroimaging.

Name: **David Powell, PhD**

Project Role: MRI Physicist

Nearest person month worked: See attached budget justification

Contribution to Project: Dr Powell will set up all parameters associated with each sequence on the scanner; he will oversee the sequence development, MRI tech training and data collection and storage.

Name: **Chrisanthi Masero**

Project Role: Clinical Research Associate II

Nearest person month worked: See attached budget justification

Contribution to Project: This individual consents and enrolls patients on this trial. She performs regulatory duties, assist with data management for this clinical trial.

- **What other organizations were involved as partners?**

Nothing to report.

8. **SPECIAL REPORTING REQUIREMENTS**

Nothing to report.

9. **APPENDICES:**

None.

Budget Justification

A. Key Personnel

Rachel W. Miller, MD, Principal Investigator (1.0% Effort). Dr. Rachel Miller is an associate professor and board certified physician in OB/GYN and Gynecologic Oncology. Dr. Miller has experience as the principal investigator for both cooperative group and investigator-initiated clinical trials. She will serve as the principal investigator on this project and will oversee the study design, participant enrollment, testing, and data analysis and reporting. Dr. Miller will work with the other key personnel to ensure that all aims of the project are completed satisfactorily.

Daret St. Clair, MD, Co-Investigator (0.5% Effort**).** Dr. St. Clair is the Associate Director for Basic Research in the Markey Cancer Center and Professor in the Graduate Center for Toxicology. Dr. St. Clair is an expert in the fundamental mechanisms by which reactive oxygen species and reactive nitrogen species contribute to normal tissue injury and cancer formation. Dr. St. Clair will I will provide mentorship regarding basic science aspects of this trial. She will perform serum testing for markers of oxidative stress and facilitate analysis and reporting of test results.

D. Allan Butterfield, MD, Co-Investigator (0.5% Effort)**.** Dr. Butterfield is the Director of Free Radical Biology in Cancer Shared Resources Facility and Center of Membrane Sciences at the University of Kentucky. Dr. Butterfield is an expert in redox proteomics and has done extensive work measuring reactive oxygen species in serum after exposure to chemotherapy. Dr. Butterfield will provide mentorship regarding the basic science aspects of this trial, coordinate serum testing for markers of oxidative stress, and facilitate interpretation and reporting of test results.

Frederick Schmitt, MD, Co-Investigator (0.5% Effort). Dr. Schmitt is a professor in the department of Neurology. His research focus is brain-behavior associations in neurological diseases with a focus on (1) early detection of dementia and (2) outcomes of therapeutic interventions in Alzheimer's disease. Other projects include behavioral and neuroimaging predictors of HIV dementia, Mild Cognitive Impairment, and descriptions of neuropathological changes in brain with advancing age. He has also developed methods for the evaluation of outcomes in the treatment of brain tumors (brain irradiation). Dr. Schmitt participates as an investigator in a number of clinical trials in Alzheimer's disease and Mild Cognitive Impairment. Dr. Schmitt will provide continued guidance regarding all aspects of neurocognitive testing in this trial. He will continue to work closely with the principal investigator in the development of the neurocognitive test battery. He will be responsible for ordering all neurocognitive test materials (cost of test materials is included in Other Direct Costs). Dr. Schmitt will administer the test battery to all patients enrolled in the trial, on two separate occasions. He will be responsible for analysis and interpretation of the neurocognitive test results.

Yang Jiang, MD, Co-Investigator (0.5% Effort)**.** Dr. Jiang will provide mentorship regarding the neuroimaging component of this novel trial. She will coordinate functional magnetic imaging testing and testing for cognitive event related potentials, in addition to analysis and reporting of test results.

Brent Shelton, Co-Investigator (5.0% Effort)**.** Dr. Shelton is the Division Chief of Cancer Biostatistics and CoDirector of the Biostatistics Shared Resource Facility at the Markey Cancer Center. His statistical interests are focused on analysis of datasets with missing data and selection bias topics in general as well as design and analysis of group-randomized behavioral intervention studies. Dr. Shelton will work with the research team in analyzing and interpreting the data.

David Powell, Co-Investigator (5.0% Effort)**.** Dr. Powell has extensive experience working at the MRISC, Magnetic Resonance Imaging and Spectroscopy Center, at the University of Kentucky as a systems specialist and MRI physicist helping with analysis, protocol development, equipment integration and systems administration. He will work with the research team in analyzing and performing the tests as prescribed in the research protocol.

B. Other Personnel

Research Associate II (1.2 calendar months)**.** The research associate will assist in screening patients, and work with the principal and co-investigators to consent and enroll patients on this trial. They will perform regulatory duties and assist with data management for this clinical trial. They will work with Dr. Schmitt and the neuroimaging technician to coordinate neurocognitive and neuroimaging testing for this trial.

Neuroimaging Technician (1.8 calendar months). The neuroimaging technician will be responsible for assisting with functional magnetic resonance imaging (fMRI) experiments and electroencephalogram (EEG) recordings in enrolled patients. The technician will oversee MRI and EEG data collection, data backup and coding. Additionally, he/she will analyze behavioral performance data collected during fMRI and EEG environment, and initial processing of the EEG data. Additionally, the technician will coordinate with the research assistant at the Cancer center for neuroimaging data quality control and storage, and provide assistant with statistical analysis of advanced neuroimaging data analysis.

C. Equipment None

D. Travel

None

E. Participant/Trainee Support Costs

None

F. Other Direct Costs

<u>Neurocognitive testing materials: $700</u>

Neurocognitive testing will include a fairly extensive battery of tests for 10 patients. These tests will be completed on two occasions by each patient. The study budget accounts for purchasing these proprietary tests. Neurocognitive testing materials: 10 patients x 2 visits x $35 = $700

<u>Laboratory testing: $450</u>

Laboratory testing will include measurement of tumor necrosis factor-alpha, protein carbonyls, and 4-hydroxynonenal protein adducts on three occasions, and will be performed under the direction of Drs. Butterfield and St. Clair. The budget accounts for estimated costs of processing and storage of specimens, in addition to the laboratory costs of performing 3 different tests on 30 specimens (10 patients undergo blood testing at 3 time points).

Laboratory testing: 10 patients x 3 visits x $15 = $450

Functional magnetic resonance imaging (fMRI): $14,000

fMRI will be performed at two time points during this trial. Testing will be performed according to a research protocol developed at the University of Kentucky under the guidance of Dr. Yang Jiang.

fMRI testing: 10 patients x 2 visits x $700 = $14,000

Cognitive event-related potentials (ERP): $400

ERP's will be performed at two time points during this trial. Testing will be performed according to a research protocol developed at the University of Kentucky under the guidance of Dr. Yang Jiang. ERP testing: 10 patients x 2 visits x $20 = $400

Participant Incentives: $1,500

Incentives will be provided to solicit participation and compensation for time commitment required for testing.

ERP testing: 10 patients x ($100 initial visit + $50 study completion) = $1,500