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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 (event-related 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). Enrollment is ongoing.

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

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Title: "Chemotherapy-Induced Cognitive Impairment in Patients with Ovarian Cancer: A Phase II study of the cognitive effects of platinum/taxane-based chemotherapy in patients with ovarian cancer IRB#: 15-0207-F2L"

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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 past year a total of 7 subjects have been enrolled. Six patients have completed pretreatment/baseline testing including neurocognitive testing, neuroimaging testing (event-related 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 neurotesting, but had to be excluded due to being left-handed (this study is only including right-handed participants at this time).

2) Specific objectives: The accrual goal for this trial is 48 subjects, with a quarterly enrollment target of 12 patients.

3) Significant results/key outcomes: The 2nd patient completed all study related testing, resulting in collection of all planned data for pre-treatment testing, including valuable MRI data. The first enrolled patient is currently undergoing chemotherapy and is on schedule. She will complete her post-treatment study related testing during the 4th quarter as scheduled.

4) Other achievements: Accrual was significantly below target for the first quarter. After review of eligible patients in the first quarter, it was determined that there were fewer patients eligible than anticipated, secondary to recent opening of two phase 3 therapeutic trials for the

same patient. Thus, changes were made to eligibility criteria to enhance eligibility. The changes were submitted to the University of Kentucky IRB and the approval letter for the submitted changes was received on June 7, 2016. These modifications did not require a change in the consent form. Since this change an additional 4 subjects were enrolled. We feel that we will enable us to reach our initially anticipated 12 patients per month.

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?

The protocol was revised to include an update to the eligibility criteria in protocol Protocol Amendment 2.0 dtd 4-28-16. The following updates were made to the protocol:

Version #2.0 dated 4/25/16

1. Modification of eligibility criteria to allow patients with other gynecologic malignancy who are chemotherapy-naïve and scheduled to receive at least 6 cycles of intravenous platinum/taxane-based chemotherapy, as data from these patients will be generalizable to those patients with ovarian cancer. The change in eligibility criteria will provide a much large eligible patient population and will significantly enhance accrual. Detailed information on tumor histology and stage will be collected in baseline material and considered in final analysis of study material.
2. Modified exclusion criterion 3.2.1 such that patients receiving hormonal therapy for breast cancer will be permitted on study, provided that it is completed prior to study registration (rather than 5 years prior to study registration). This modification will broaden eligibility criteria in an effort to enhance patient accrual.
3. Deleted exclusion criterion (previously 3.2.2): "Patients undergoing neoadjuvant chemotherapy with planned interval cytoreductive surgery and adjuvant therapy are not included in this group." Patients undergoing neoadjuvant chemotherapy will now be included in this group, as this includes nearly all patients with stage IV disease and a significant portion of those with stage III disease possessing a large tumor burden. Including patients who are undergoing neoadjuvant chemotherapy, in addition to those undergoing primary debulking surgery, will provide a more representative group of patients to undergoing treatment for ovarian cancer and enhance accrual for this study.
4. Deleted exclusion criterion (previously 3.2.3): "Patients who are receiving any other investigational agents are excluded;" and added inclusion criterion 3.1.2: "Patients who are receiving other investigational agents will be permitted on study, at the discretion of the principal investigator." The current age of cancer treatment is moving toward individualized therapy with targeted agents. This may include immunotherapy or other targeted biologic agents. In an effort to enhance patient accrual, and in keeping with the goal to select a representative patient population, patients undergoing experimental therapy or on other

clinical trials, may be permitted on study at the discretion of the principal investigator. Records of study drugs will be captured in the medication log and entered into the data collection system for consideration during final study analysis.

5. Deleted exclusion criterion (previously 3.2.5): "With the exception of non-melanoma skin cancer and other specific malignancies noted above, patients with other invasive malignancies who had (or have) any evidence of the other cancer present within the last five years or whose previous cancer treatment contraindicates this therapy are excluded." This exclusion criterion is irrelevant as long as the patient does not have metastatic disease to the brain and has not received prior chemotherapy for this malignancy (captured in other exclusion criteria).

Enrollment has increased since revising the eligibility criteria and we intend to continue to screen patients diligently in an effort to meet our projected enrollment goal of 12 per month. We intend to monitor screening to determine if additional revisions to the eligibility criteria is needed to maximize our enrollment opportunities.

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: 2.1

Contribution to Project: Dr. Miller has served as Pl.

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

Project Role: Co-Investigator

Nearest person month worked: 0.9

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: 0.75

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: 2.3

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: 0.7

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: 0.9

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: **Emily Dressler, PhD**

Project Role: Statistician

Nearest person month worked: 0.6

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

Name: **David Powell, PhD**

Project Role: MRI Physicist

Nearest person month worked: 0.9

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: 1.0

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.