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TITLE: Cytokine Response to Subclinical Cytomegalovirus Reactivation as a Cause of Severe Fatigue in Women Undergoing Chemotherapy for Breast Cancer

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14. ABSTRACT

Cancer treatment related fatigue (CTRF) has a major impact on quality of life both during and after treatment, and the causes are not completely understood. The major aim of this study is to determine whether the activation of cytomegalovirus (CMV) by chemotherapy contributes to the severity of CTRF for women going through chemotherapy treatment for stage I-III breast cancer. The long-term goals of this work are to determine whether CMV reactivation can cause CTRF, to understand the mechanism, to identify patients at risk for CMV-induced CTRF prior to chemotherapy, in order to conduct a clinical trial of anti-CMV drug treatment to prevent CTRF in susceptible individuals. This study will evaluate fatigue and immune parameters (cytokines and T cells) in equal numbers of CMV+ and CMV- women, 26 in all, undergoing cytotoxic chemotherapy for stage I-III breast cancer. We will study women prior to the start of chemotherapy and at home visits in the weeks between treatments, because this is when fatigue is greatest. Sixteen eligible and interested breast cancer patients have enrolled in the study during the first 12 months of active recruitment, 15 of who have had successful baseline and subsequent testing appointments. Of the 12 participants tested so far, 64% are CMV seropositive. Preliminary analysis for all blood and urine outcomes measured will be measured in October, 2012.

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Fatigue, cancer cytomegalovirus

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Table of Contents

Page

INTRODUCTION

Cancer treatment related fatigue (CTRF) has a major impact on quality of life both during and after treatment, and the causes are not completely understood. The major aim of this study is to determine whether the activation of cytomegalovirus (CMV) by chemotherapy contributes to the severity of CTRF for women going through chemotherapy treatment for stage I-III breast cancer. The long-term goals of this work are to determine whether CMV reactivation can cause CTRF, to understand the mechanism, to identify patients at risk for CMV-induced CTRF prior to chemotherapy, in order to conduct a clinical trial of anti-CMV drug treatment to prevent CTRF in susceptible individuals. Given the limited scope of this mechanism, the minimal specific goal of this proposal is to determine whether there is sufficient evidence for a role for CMV in CTRF to justify a larger study, and to calculate the size of the study that would be needed to confirm the result. Secondary goals are to determine the associations between CTRF and inflammatory cytokine levels, CMV reactivation, CMV antibody levels, and CMV-specific T cell responses. This study will evaluate fatigue and immune parameters (cytokines and T cells) in equal numbers of CMV+ and CMV- women, 26 in all, undergoing cytotoxic chemotherapy for stage I-III breast cancer. We will study women prior to the start of chemotherapy and at home visits in the weeks between treatments, because this is when fatigue is greatest.

BODY

Over the previous year, significant progress has been made toward addressing the aims of this project and the tasks in our approved Statement of Work.

1. Obtain IRB approval for the study including design of study flyer (pre award, month -6-0). During the pre award time and first few months of the funding period, the study preparation phase of the project successfully took place and consisted of the following: revisions and approval of the IRB protocol and consent forms; development of standard operating procedures for all protocols; development of recruitment plan for oncologist referrals; development of study materials; and training of study staff.

2. Recruitment (Months 0-18). Participant recruitment was delayed for the initial 3 months as the study obtained IRB approval for modifications which included approval of study staff and as we developed processes for referral specific to each of our participating oncologists. After consultation with several referring oncologists, we decided to bring a registered nurse (RN) on to the study team to be able to collect blood samples from participants who had Port-a-catheters (Ports) as a way to minimize any pain and discomfort for participating in this research. It is common practice for breast cancer patients to have a port placed prior to their first chemotherapy infusion so they do not have to have repetitive peripheral blood draws during their course of treatment, and we wanted to be able to provide participants in this study the choice of location for their blood sample collection. The RN on our study staff enrolled in and completed a required research training to update her scope of practice to include port acccess sample collection in August, 2011. Thus, we began official recruitment in September, 2011 through oncologist referrals at the OHSU Marquam Hill hospital and OHSU community oncology clinics. Participating oncologists are sent weekly email reminders of potential breast cancer patients who may be eligible for the study by our study staff who search hospital medical records for

oncologist schedules. In addtion, our project coordinator attends a weekly oncology meeting to review upcoming patient lists to identify potential study participants. The participating breast cancer oncologists discuss partipation in the study during patient appointments and refer interested persons to our research staff. Upon receiving the patient referral, our study staff contacts the patient to explain study procedures, check eligibility, answer questions, and schedule study visits. Overall, the study has been well received by breast cancer patients and the most common reason for refusal given to the oncologist by the patient is '*feeling too overwhelmed to participate in research during cancer treatment'*.

In order to maximize our number of enrollees, the eligibility criteria were modified to include breast cancer patients who would be receiving trastuzumab in addition to their cytotoxic chemotherapy for their treatment plan. During the first few months of active recruitment, many of the new breast cancer patients being seen at OHSU were not eligibile for our study because their oncologist recommended trastuzumab as part of their chemotherapy plan. To our knowledge, there is no body of data to indicate that trastuzumab will directly interfere with the outcomes of this study. In light of the fact that there is a growing use of trastuzumab in breast cancer care, the inclusion of these patients will allow our results to inform a broader group of breast cancer patients who have had chemotherapy.

As of September 20th, 2012 we have 16 women enrolled in the study and three new interested persons from oncologist referrals that we are contacting this week. As indicated in the Statement of Work, we screen potential participants for eligibility after they have made a treatment plan with their oncologist, and we arrange a home visit prior to the start of their chemotherapy to obtain informed consent, collect demographic and fatigue data, clinical history, and blood and urine samples.

For the remaining study timeframe, we plan to continue recruitment as needed until early winter 2013 in order to maximize our ability to reach the target sample size (N=26). Recruitment efforts include continued physician referrals from OHSU Marquam Hill hospital and OHSU Community Hematology and Oncology Clinics in the Portland Metro area. In total, as of 9/20/12, a total of 26 women have been referred by their oncologist for this study and of these 4 were ineligible, 6 were not interested in participating because they felt too overwhelmed or felt too busy, and 16 enrolled in the study. Of the 15 enrollees, 1 was discontinued from the study due to complications in obtaining a baseline blood sample. A total of 15 women were eligible to participate and successfully completed baseline appointments prior to their chemotherapy. As of Septemeber 15th , 2 women have completed their chemotherapy and follow-up testing. By October 31st, 2012, eight participants will have completed their baseline, chemotherapy and follow-up testing. The response to the study among oncologists and their patients has been extremely positive.

3. Obtain fatigue data, blood and urine at each clinic visit. Additional fatigue data, and blood and urine will be collected twice per treatment cycle (one week after infusion, and one week later) during home visits. Additional fatigue data, blood and urine will be collected from each study participant at the 3 month clinical follow-up appointment with their medical oncologist. (Months 1-24). Based on IRB regulations and in consultation with oncologists, the initial sampling time point protocol was modified in order to meet regulatory guideline procedures for study participants with cancer who are providing blood samples. According to the

OHSU IRB collection procedures, *the amount of blood drawn from an adult may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week*. In order to meet this regulation, we decreased the number of study visits to a total of four ((1) baseline prior to chemotherapy, (2) a mid-treatment during the week following the mid infusion, (3) a final treatment time point during the week follow the last chemotherapy infusion, and (4) a follow up home visit 3 months after the completion of their chemotherapy). This decision was made because each visit required 50mls of blood in order to have adequate serum and blood cells to address the primary and secondary aims of this study. Using this modified sampling protocol, we have successfully obtained fatigue data, blood and urine at each designated study for our 15 participants. We are continuing to collect these data for our active participants and as of October, 2012 we will have 8 participants complete all testing appointments and data collection procedures. Using this modified protocol, we can still address our primary and secondary study aims and test our hypotheses.

4. Process and store blood and urine samples on day of collection (months 0-22). All blood and urine samples have been successfully processed by study staff on the day of sample collection. Samples are stored frozen in the Wood and Hill laboratories until final analysis.

5. Monthly meetings of both research teams. Dr. Torgrimson holds weekly team meeting to discuss the study progress and work with the team on resolving any issues. Meetings are attended by members of both teams. In addition, Dr. Torgrimson sends out email updates to both teams to keep all members informed of research decisions.

6. Determine CMV seropositivity for each patient following first visit (months 1-18). In total, we have 15 participants with blood samples from the baseline visit. As of today, n=4 are CMV-, n=7 are CMV+ , and n=4 have not yet been analyzed, but are on schedule to be analyzed in October, 2012.

7-11. Identify candidate CMV peptide epitopes, measure serum cytokines, serum neopterin and hepcidin, measure CMV DNA in urine and blood, and measure T cell subsets and CNW-Specific T cell responses in CMV+ participants. By the end of October, 2012, eight participants will have completed all study time points including the 3 month follow-up visit. We plan to complete a preliminary analysis of results on this subset of 8 women who will have completed study testing by November 30, 2012. We will continue sample collection and run a second subset analysis of our n=7+ participant samples in January, 2013.

12. Obtain data from clinical records: CBC, relevant clinical history during study period. This data will be collected throughout the study period. Data acquistion, entry and verification of collected data are on-going and on-track.

13-15. Data collation, cleaning and analysis. Preparation of reports and manuscripts (months 20-24). These objectives are on-track for the final phase of this project. Preliminary analysis will begin in November and analysis will be ongoing through the budget period.

KEY RESEARCH ACCOMPLISHMENTS

- 16 eligible and interested breast cancer patients have enrolled in the study during the first 12 months of active recruitment.
- 15 participants have had successful baseline and subsequent testing appointments.
- CMV seropositivity is 64% in this subset sample.
- Preliminary analysis for all blood and urine outcomes will be measured in October, 2012.

REPORTABLE OUTCOMES

We currently do not have any reportable outcomes. Plans for the this budget period focus on continuation of participant recruitment, acquisition of blood and urine samples, administration of study questionnairres, data analysis, preparation to disseminate results and apply for funding based on the work supported by this award.

CONCLUSIONS

The study data collection is ongoing and there are no conclusions to report at this time.

REFERENCES

N/A

APPENDICES

There are no supplementary appendices to include at this time, but any study document will be provided as requested.

SUPPORTING DATA

None at this time