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TITLE: Assessment of Clonal Hematopoiesis and Its Relationship to Cardiovascular Disease in Hodgkin Lymphoma Survivors

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CONTRACTING ORGANIZATION: University of Virginia, Charlottesville, VA

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

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The funded project is proceeding forward without major difficulty. The proposal was approved by the Children's Oncology Group (COG), the DCP, and CIRB approval was obtained on. The study encompassing this research project (ALTE21C1) was activated within COG on xxx and COG member centers within the US have both agreed to participate and have proceeded with steps to activate the study at their institution . A webpage within the COG website has been constructed which contains the CIRB approved protocol and other resources to provide guidance, and answer questions for the participating centers. The workflows for certification of imaging centers for the cardiac MRI's has been launched and two centers have already been certified. The workflows for blood sample acquisition for clonal hematopoiesis have been defined and is ready to be executed once enrolled patients have begun participation in the study The committee members for the protocol meet monthly to address emerging issues, to enhance workflows and recruitment strategies. To date, there have been no major obstacles or delays in advancing this project toward its desired outcome.

15. SUBJECT TERMS
Late onset cardiac toxicity, Childhood cancer survivorship, Cardiac MRI, Clonal Hematopoiesis

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1. INTRODUCTION

The goal of this project is to establish the prevalence of therapy related clonal hematopoiesis (t-CH) in a population of Hodgkin's Disease survivors treated uniformly on a clinical trial (AHOD1331) with anthracyclines, a cardiotoxic agent. Secondly, we wish to see if patients possessing such t-CH demonstrate objective signs of cardiovascular disease (CVD) as measured by cardiac MRI (cMRI). Data supporting this observation will transform our approach toward CVD in childhood cancer survivors which will lead to studies to see if blocking the effects of t-CH can influence the development of CVD in childhood cancer survivors, a major source of mortality in this population.

2. KEYWORDS:

Clonal hematopoiesis, cardiovascular disease, childhood cancer survivors, Hodgkin Lymphoma, cardiac MRI. Anthracycline chemotherapy

3. ACCOMPLISHMENTS:

What were the major goals of the project?

The major goals of the project are defined by the specific aims:

1) **Specific Aim 1:** To assess the prevalence of participants in AHOD1331 with therapy-related clonal hematopoiesis (t-CH) possessing somatic mutations associated with cardiovascular disease (CVD) which are detected after Hodgkin Lymphoma therapy
    a. **Subtask 1** – **Obtain Institutional Review Board Approval**: This study will be performed within the Children's Oncology Group,(COG), Protocol #: ALTE21C1, and thus IRB approval through the Central IRB (CIRB) utilized by COG was obtained (Washington University/Hayashi). All participating institutions routinely use this CIRB mechanism for COG studies and each institution must endorse the CIRB approval to enroll patients.
    b. **Subtask 2 CH analysis:** Archived specimens from AHOD1331 and two specimens from blood samples obtained from enrolled study subjects one year apart from each other are available for use (University of Va./Walsh).
2) **Specific Aim 2:** To assess participants of AHOD1331 with t-CH for the presence or absence of objective signs of CVD using cardiac MRI.
    a. **Subtask 1 Assess cMRI for CVD:** cMRI obtained from enrolled subjects will be submitted to the radiology core (Washington University/Woodard). All cMRI will be evaluated by the partnering site PI and the presence of MRI findings consistent with CVD will be entered in the database.
    b. **Subtask 2 Collection of treatment data and clinical data for CVD risk factors** Treatment data and clinical data including clinical assessments and laboratory assessments for CVD will be collected by the coordinating site (Washington University/Hayashi) and entered into the database in preparation for analysis.
    c. **Subtask 3 Analysis of Data:** Data from the t-CH analysis and the radiologic findings will be complied along with the clinical data obtained from data collected in participation in AHOD1331 to assess a) whether t-CH emerge from therapy b) whether t-CH expand with time. c) whether patients possessing t-CH correlate with those possessing signs of CVD as documented by cMRI

d) whether other specific patient characteristics (age, gender, race, etc.), or treatment variables (radiation) correlate with a higher incidence of CH with mutations associated with cardiovascular disease (secondary aims).

What was accomplished under these goals?

Specific aim1

a. Subtask 1: Formal CIRB approval was obtained on January 4, 2023.
b. Subtask 2: Workflows for two additional blood samples for CH analysis enrolled on the study have been refined and are available on the COG website and contained within the Protocol (ALTE21C1). Specimens will be retrieved as participants are enrolled. Enrollment will span the duration of the project but it is expected to be completed within the first 36 months. The last specimen will be collected one year after the last patient is enrolled (each enrollee will have two specimens collected one year apart. CH analysis will be performed using all specimens collected for each enrolled subject together so that the quantitative changes in CH can be displayed over time.
c. An exempt application was transitioned to a NON-UVA IRB application upon request from the UVA IRB HSR on 24 February 2023, given that samples processed by the UVa lab for clonal hematopoiesis analysis and quantification for this study involve only deidentified specimens. The paperwork has been completed and currently, we are awaiting NCI CIRB approval of the final paperwork which will then allow completion of the UVA local IRB protocol process.

Specific aim 2

a. Subtask 1: Workflows for obtaining the cMRI are contained within the protocol. A certification process documenting that the participating centers can perform the cMRI according to protocol standards has been established as a Protocol Specific Requirement (PSR) and centers receiving certification will receive a certificate documenting successful acquisition of this status and will be recorded on a central database for future reference. The protocol is officially activated; 2 centers have already been certified, and additional centers are at different stages in this process. There have been no difficulties in executing this process that would impede the timeline of completion of project.
b. Subtask 2: The database for collecting specific data derived from the protocol has been generated and is live, and participating centers can now enter data from the patients they enroll into this database.
c. Subtask 3: Demographic and therapy specific data from the research subjects when they participated in the original treatment study (AHOD1331) remains in the COG database specific for that study. Upon completion of enrollment and once all of the data from ALTE21C1 has been completed, the data will be imported into the database from AHOD1331, so that the demographic, Hodgkin Lymphoma prognostic variables, and treatment variables can be merged with this data so that correlations of the variables can be calculated to the development of t-CH and the development of CVD as demonstrated by cardiac MRI.

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

Nothing to Report.

Nothing to Report.

How were the results disseminated to communities of interest?

Nothing to Report

Nothing to Report.

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

The protocol was activated on 5/22/23. The centers with eligible patients have been contacted to raise awareness of the study and there has been universal enthusiasm for participation. A dedicated breakout session will be held at the Annual COG meeting in Atlanta Ga. in September. We anticipate updates on the number of centers who have the study open, the number of enrollees, the number of cMRI's obtained and the number of blood samples obtained. We also expect to report the prevalence of cardiovascular disease in the enrolled subjects as documented by cMRI. Data on CH analysis will be shared once sufficient numbers of samples (including two samples obtained 1 year apart) are collected so that the trajectory of expansion of t-CH can be assessed.

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

There have been no significant changes to the project or its direction.

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

Protocol study startup is proceeding at all centers. There have been no significant problems or delays encountered to date.

Changes that had a significant impact on expenditures

There have been no significant changes that have impacted expenditures.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Significant changes in use or care of human subjects

There have been no changes or unexpected outcomes that have any influence to the care of human subjects

Significant changes in use or care of vertebrate animals

There have been no changes in use or care of vertebrate animals

Significant changes in use of biohazards and/or select agents

There is no use of biohazard agents in this study.

6. PRODUCTS:

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

  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)**

  This study is listed on Clinical Trials.gov with the following URL
  https://classic.clinicaltrials.gov/ct2/show/NCT05705531

- **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: *Robert J. Hayashi, MD*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID): *0000-0002-1140-1139*
Nearest person month worked: *3*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Kenneth Walsh, Ph.D.*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID): *0000-0001-7580-2276*
Nearest person month worked: *3*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Pam Woodard, MD*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID): *0000-0001-9012-0812*
Nearest person month worked: *3*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Saro Armenian DO*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0003-2604-8603*
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Sharon Castellino, MD*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0001-8367-2002*
Nearest person month worked: *1*

Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Eric Chow MD*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0002-3665-1249*
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*
Changes: *R01CA211996 (closed)*
Andy Hill Care Fund (FY23-POP-01) new (0.6CM)
R61CA280978-01 (new subaward, 0.6 CM)
W81XWH-22-1-0184, CA210884 (new subaward, 0.24 CM)
R21CA277746-01A1 (0.6CM)

Name: *David Hodgson MD*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0003-4687-4582*
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Joshua Mitchell MD*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0001-7371-5742*
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*
Changes: *NIH R34 HL14692701(closed)*
DoD: A Novel Risk Prediction Model for Checkpoint Inhibitor-related Autoimmune Toxicities(closed)

Name: *Aecha Ybarra MD*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0002-1813-407X*
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Lisa Roth MD*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0002-6040-8644*
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Caroline Mohrmann*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID): *0000-0002-1198-0433*
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Name: *Jennifer Seelisch*
Project Role: *Principal Investigator*
Researcher Identifier (e.g. ORCID ID): *0000-0002-2187-0051*
Nearest person month worked: *2*
Contribution to Project: *no change*
Funding Support: *none*

Name: *Qinglin Pei*
Project Role: *Statistician*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *1*
Contribution to Project: *no change*
Funding Support: *COG*

Name: *Anna Gilmore*
Project Role: *Study Committee Member*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *2*
Contribution to Project: *Administrative support for protocol development and implementation*
Funding Support: *COG*

Name: *Tyler Brown*
Project Role: *Research Coordinator*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *2*
Contribution to Project: *Administrative support for protocol development and implementation*
Funding Support: *COG*

Name: *Kara Felts*
Project Role: *Lead Clinical Research Associate*
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: *3*
Contribution to Project: *no change*
Funding Support: *W81XWH2210665*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Organization Name: Children's Oncology Group (COG)
Location of Organization: Seattle Children's Research Institute, Seattle Washington, Doug Hawkins, Chairman
Partner's contribution to the project (identify one or more)

- *Financial support; (Provides organizational, and infrastructure support for clinical trial execution.)*
- *Collaboration* Provides statistical and protocol administrative support as part of the COG infrastructure*;*

Organization Name: Public Health Institute
Location of Organization: Oakland California
Partner's contribution to the project (identify one or more)

- *Collaboration :* PHI provides administrative support for grants involving COG and assists in the disbursement of funds for per case reimbursement for this study.

Organization Name: Division of Cancer Prevention, NCI
Location of Organization: Bethesda Maryland
Partner's contribution to the project (identify one or more)

- *Financial support;* Provides additional per case reimbursement from their budget to support the execution of this trial through the COG/PHI.

Collaboration **Oversees this and other clinical trials involving Cancer Control and Survivorship in the COG**

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES:

1). CIRB approval
2.) DCP approval
3.) Study activation