NCI Funded Clinical Research in Treatment-Related Cardiotoxicity: Moving Forward

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## Research Recommendations: 2013 - 2018

<table>
<thead>
<tr>
<th>Recommendation Category</th>
<th>2013</th>
<th>2018</th>
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<tbody>
<tr>
<td><strong>Developing Standards</strong></td>
<td>LVEF reduction of 10% to less than 50%; or &gt;15% from baseline</td>
<td>Utilize natural language processing to enhance data capture</td>
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<td><strong>Mechanisms of Damage</strong></td>
<td>Characterize signaling pathways</td>
<td>Broaden use of human induced pluripotent stem cells (cardiomyocyte, endothelial)</td>
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<td><strong>Preclinical and Animal Studies</strong></td>
<td>Utilize models with cardiac stressors</td>
<td>Move mechanistic evidence into preclinical models and validation criteria</td>
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<tr>
<td><strong>Markers of Risk &amp; Injury</strong></td>
<td>Incorporate imaging and biomarkers into risk stratification tools</td>
<td>Implement core lab processing</td>
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<tr>
<td><strong>Prevention &amp; Management</strong></td>
<td>Cardiac meds, activity, diet…When, what, how much and to whom?</td>
<td>Focus on modifiable risk factors</td>
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<tr>
<td><strong>Cancer Survivorship</strong></td>
<td>Longitudinal follow-up; care coordination</td>
<td>Risk stratification tools that inform health system resource utilization</td>
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Improving Outcomes in Cancer Treatment-Related Cardiotoxicity

- Grant Funding Opportunity Announcements (FOA)
  - PA-19-111 (R21)
    - Improving Outcomes in Cancer Treatment-Related Cardiotoxicity (R21 Clinical Trial Optional)
  - PA-19-112 (R01)
    - Improving Outcomes in Cancer Treatment-Related Cardiotoxicity (R01 Clinical Trial Optional)

- Primary intent it to mitigate cardiovascular dysfunction while optimizing cancer outcomes

- Collaborative approach to identify and translate findings

- Receipt dates: February 2019 – November 2021
Questions of Interest

▪ What is the incidence, severity and progression of cardiotoxicity among understudied populations and emerging treatments?

▪ What patient risk factors can be translated in to risk stratification for cardiotoxicity prevention, screening and management?

▪ What translation models best test cancer treatment and cardio-protective drugs?

▪ What are the best approaches to screening for asymptomatic cardiotoxicity?

▪ What cardiotoxicity prevention and management methods improve outcomes and what subgroups benefit the greatest?

▪ What is the impact of cardiotoxicity prevention, screening and management on cancer outcomes?

▪ What forms of care coordination have the greatest impact on cancer and cardiac outcomes?
Current NIH Cardio-Oncology Efforts

NHLBI/NCI Cancer Treatment-Related Cardiotoxicity FOA’s

NHLBI /NCI Cancer and Thrombosis (CLOT U01)
• Thrombosis related to cancer as well as treatment

NHLBI
• Cardiovascular Safety Testing
• In vitro methods and tools to minimize toxicity

NCI NCORP Cardiotoxicity Task Force
• Multidisciplinary group focused on standardizing clinical trial risk assessment and endpoints

NCI Symptom Management and Quality of Life Steering Committee
• Cardiotoxicity is a strategic priority
How Does the NCI Support Conduct of Large, Later Phase Clinical Trials?

Via Two Large Networks:
The NCI Clinical Trials Network – “The NCTN”

- Coordinates/supports cancer CTs at **3000 sites** across the US and Canada through **5 US Network Groups and the Canadian Network Group**
  - The Alliance
  - SWOG (Southwest Oncology Group)
  - ECOG-ACRIN (Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN))
  - NRG National Surgical Adjuvant Breast and Bowel Project (NSABP), the Radiation Therapy Oncology Group (RTOG), and the Gynecologic Oncology Group (GOG)
  - COG The Children’s Oncology Group

The NCI Community Oncology Research Network – “NCORP”

- Network of **46 community sites** in **900 locations** performing CTs and CCDR in the community. **12 sites** are minority/underserved community focused.
- Utilizes the NCTN Groups and Wake Forest and University of Rochester for their infrastructure support
Relationship of NCTN and NCORP

NCTN Focus:
- Late-Phase Treatment Trials
- Advanced Imaging Trials

NCORP Focus:
- Cancer Prevention & Control Trials
- Cancer Care Delivery
- Comparative Effectiveness Research

NCTN/NCORP Centralized Functions
CV Risk Factors & Disease Ascertainment to Understand Adverse Outcomes

Understanding and Predicting Breast Cancer Events After Treatment, *PI- Greg Hundley*

“UPBEAT” Wake Forest Research Base

- Stage I-III breast cancer w/wo anthracyclines and age matched controls (n=1000)
- Prior to cancer treatment, evaluate for pre-existing cardiovascular disease
- Baseline and post-treatment $V_{O_2,max}$
- Regular imaging evaluation
- MRI: before, during and post treatment
- Capture PROs of fatigue, symptoms CV events
Cardioprotective Interventions

Preventing Anthracycline Cardiovascular Toxicity with Statins, *PI* Greg Hundley

“PREVENT” Wake Forest Research Base

- Early stage breast and lymphoma patients (*n* = 279)
- RCT atorvastatin vs placebo
- Treatment begins prior to anthracycline therapy, then continues for 2 years
- CV Risk Factors, Imaging (pre, during, post therapy)
- Will atorvastatin preserve LV function?
Cardioprotective Interventions continued..

Carvedilol in Preventing Heart Failure in Childhood Cancer Survivors, PI-Saro Armenian

Children’s Oncology Group (COG)

- Young adult/adolescent survivors (n=177)
- At least 2 years post (high dose) anthracycline regimen in RCT low-dose carvedilol vs. placebo for 2yrs
- CV phenotyping (pre, during, post carvedilol)
- Central ECHO reviews
- Will carvedilol reduce anthracycline-related CV injury?
Balancing Sub-clinical Injury Risk with the Need for Continued Therapy

Prospective Evaluation of Carvedilol in Prevention of Cardiac Toxicity in *Metastatic* HER2+ Breast Cancer, *PI*-Justin Floyd

**Southwest Oncology Group (SWOG) (n=817)**

- Metastatic patients need chronic HER2+ blockade
- RCT carvedilol vs. no intervention
- Observation arm already on BB, ACE or ARBs
- ECHO (w/ strain) at baseline, every 3 months
- Primary endpoint: Time to cardiac dysfunction
  - Blinded ECHO core lab readings
- Second primary endpoint: Time to Traz interruption
Understanding the Timing of Adverse Events & Late Toxicity

Dexrazoxane and Prevention of Anthracycline-Related Cardiomyopathy, Pl- Eric Chow

Children’s Oncology Group (COG)

- Adult survivors of pediatric cancers (n=420)
- Retrospective eval of 4 pediatric RCTs using dexrazoxane conducted in the 1990s with a total of 1213 patients
  - Long-term Follow Up Center to reach out and consent survivors to in person CV assessment and/or release of data
- Compare pathologic cardiac function of patients who received anthracyclines w dexrazoxane vs. placebo
- Does dexrazoxane impact late CV effects?
Considerations for Cardiotoxicity Trial Designs

- Utilize core labs for **centralized review** of study endpoints.
- Consider **deep** CV phenotyping.
- Seek to fill the knowledge and evidence base **gap** to inform and refine existing clinical guidelines for treating cancer patients and managing cancer survivors.
- Explore the impact of **non-pharmacologic** and **behavioral** interventions.
- Harmonize CV and cancer data collection of both exposures and outcomes. Include patient-reported outcomes (**PROs**), common **CRFs** (ECOG/ACRIN effort).
- Harness **teamwork** between oncology/cardiology.
Role of Program Directors/Officials (PD/PO)

- Identify next funding opportunities
- Explain different grant mechanisms
- Interpret NIH submission policies and procedures
- Discuss how to frame your research so it fits with NIH strategic priorities
- Identify appropriate study sections and reviewer expertise
- Discuss summary statements and approaches to resubmission
- Serve as a scientific sounding board
Successful Proposals

✓ Significant and innovative idea
✓ Focused hypotheses
✓ Logical specific aims related to the hypotheses
✓ Convincing preliminary studies in the right amount
✓ Innovative, appropriate methods
✓ Clear path to strong conclusions
✓ Reasonable budget
Early Stage Investigators (ESI)

A principle investigator who:

▪ Completed terminal research degree or post-graduate clinical training, which ever date is later, within the past 10 years
  - AND -

▪ Not previously funded as a PI for a R01 or U01

Benefits (NCI specific):

▪ Higher funding pay line
  ▪ FY19 up to 14th percentile for R01 (established PI 8th percentile)
  ▪ Smaller standard budget cuts
  ▪ FY19 – tentatively 7% (established PI 19%)
Grant Scenario

- **Purpose:** Fully characterize the time course of adjuvant chemotherapy and identify factors that promote subclinical cardiovascular dysfunction, exercise intolerance, fatigue and subsequent cardiovascular events among women with breast cancer of different ages and races/ethnicities, to inform future therapies and risk factor prediction models.

- Serial longitudinal measures of 840 stage I-III breast cancer and 160 health controls including:
  - Cardiovascular function
  - Exercise capacity and fatigue
  - Future development of cardiovascular events

- Utilize the Wake Forest NCORP
NCI is Here to Help!

- Reach out to us with your thoughts/ideas/questions

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