NIH/NCI Funding Opportunities for Cardio-Oncology Clinical Trials and Research Projects

Lori Minasian, M.D., FACP
Deputy Director
NCI Division of Cancer Prevention

September 30, 2016
Outline

- Perspective
- Research Gaps and Funding Opportunities
- NCI’s Network for Funding Trials
- Partnerships
Perspective Example: Hypertension

Cardiologists say...

- Hypertension is a major cause of long-term morbidity and mortality in the US
- Good blood pressure control is a key *preventive* strategy

Oncologists say...

- Patients with advanced cancer have a limited life-expectancy
- Why treat *asymptomatic* hypertension?
- But, hypertension can be dose-limiting and prevent the delivery of adequate anti-cancer therapy

Need for Collaborations or Partnerships Between Oncologists & Cardiologists
Data for Cardiotoxicity of Cancer Therapy

- Cancer Clinical Trials
  - Exclude pre-existing cardiovascular disease
  - Capture Cardiovascular Adverse Events
    - AE not adjudicated or uniformly evaluated
    - AE may not occur immediately

- Claims Data
  - More generalizable information
  - Hard to dissect out attribution
    - Agent(s) or Modalities (radiation, chemotherapy)
    - Underlying disease
Age Distribution by Major Disease Category of Patients Enrolled in NCI-sponsored Group Treatment Trials – 2004-2013

From NCI/DCTD Clinical Data Update System
August 2016
Phenotypic Characterization differs between Oncology and Cardiology

- **Oncology**
  - Characterize the cancer *(histology)*
    - “Tissue” Phenotype (histology, genetic and other markers)
    - Determine Cancer Treatment based upon the tissue phenotype and stage of disease

- **Cardiology**
  - Characterize the physiology of the patient’s cardiovascular system *(function)*
    - Cardiovascular Phenotype (imaging, markers, EKG, etc)
Collaborations to Address the Differences

Bring Oncology and Cardiology investigators and clinicians together to focus on the translational and clinical issues of acute and late effects of treatment-related cardiotoxicity.
Research Gaps and Funding Opportunities
Cancer Treatment–Related Cardiotoxicity: Current State of Knowledge and Future Research Priorities

Nonnieke Sheiburne, Bishow Adhikari, Joanna Brell, Myrtle Davis, Patrice Desvigne-Nickens, Andrew Freedman, Lori Minasian, Thomas Force, Scot C. Remick

Manuscript received May 6, 2014; revised June 27, 2014; accepted July 1, 2014.

Correspondence to: Nonnieke Sheiburne, CRNP, MS, AOCN, Clinical and Translational Epidemiology Branch, DCCPS, 9809 Medical Center Drive, Rm 4E110, Rockville, MD 20850 (e-mail: nshelburne@nih.gov).

Cardiotoxicity resulting from direct myocyte damage has been a known complication of cancer treatment for decades. More recently, the emergence of hypotension as a clinically significant side effect of several new agents has been recognized as adversely affecting cancer treatment outcomes. With cancer patients living longer, in part because of treatment advances, these adverse events have become increasingly important to address. However, little is known about the cardiovascular pathogenic mechanisms associated with cancer treatment and even less about how to optimally prevent and manage short- and long-term cardiovascular complications, leading to improved patient safety and clinical outcomes. To identify research priorities, allocate resources, and establish infrastructure required to address cardiotoxicity associated with cancer treatment, the National Cancer Institute (NCI) and National Heart, Lung and Blood Institute (NHLBI) sponsored a two-day workshop, “Cancer treatment–related cardiotoxicity: Understanding the current state of knowledge and future research priorities,” in March 2013 in Bethesda, MD. Participants included leading oncology and cardiology researchers and health professionals, patient advocates and industry representatives, with expertise ranging from basic to clinical science. Attendees were charged with identifying research opportunities to advance the understanding of cancer treatment–related cardiotoxicity across basic and clinical science. This commentary highlights the key discussion points and overarching recommendations from that workshop.

NCI and NHLBI Response to Cardiotoxicity Research Gaps: **Support Research Efforts**

- Partnering Internally Working Group NCI & NHLBI staff
  - Workshop to Identify Research Gaps
  - Funding Opportunities Announcements
  - Ongoing Collaboration to Address Issues

- Partnering Externally via the NCI Community Cardiotoxicity Task Force
  - Partnering with Researchers
    - Cardiologists, Oncologists, Statisticians, Clinical Trials Investigators
    - NCI and NHLBI staff, FDA
Selected Research Questions:

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

2. What patient risk factors can be translated into risk stratification for cardiotoxicity prevention, screening and management?

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

4. What are the best approaches to screening for asymptomatic cardiotoxicity?

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

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

7. What forms of care coordination have the greatest impact on cancer and cardiac outcomes?
Active Funding Opportunities #1

NCI/NHLBI Improving Outcomes in Cancer Treatment-Related Cardiotoxicity:

PA 16-035 (R01)
PA 16-036 (R21)


Reviews through Existing Study Sections
Mechanisms: Targets for Cancer

- Molecularly Characterizing Tumors
  - Targeting Pathways to Block Cancer Growth
  - Toxicities Occur because:
    - Agents Are Not So Selective
    - Targets Are Not Unique to Cancer Growth

- What Function Do These Signaling Pathways Have in Other “Normal” Tissue?
  - Identify Mechanisms for the Basis of Drug-Induced Cardiotoxicity
Active Funding Opportunities #2

NCI *Adult* Provocative Questions


- **PQ - 9**
  What are the molecular and/or cellular mechanisms that underlie the development of cancer therapy-induced severe adverse sequelae?

- **PQ - 12**
  What methods and approaches induce physicians and health systems to abandon ineffective interventions or discourage adoption of unproven interventions?

- RFAs with Study Sections Designed to Address Each PQ
Active Funding Opportunities #3

NCI Pediatric Provocative Questions

- **PPQ-6:**
  
  How can mouse or other preclinical models be used to study how standard of care and investigational therapies affect normal tissue and lead to adverse events later in life?

- **PPQ-9:**
  
  What are the underlying molecular mechanisms that cause accelerated aging seen in some pediatric cancer survivors?
Active Funding Opportunities #4

- **NHGRI (NCI participating) PAR**: Serious Adverse Drug Reaction Research (R01/R21)

- Special Study Sections for these PARs

- **NCI PA**: Mechanisms of Cancer and Treatment-related Symptoms and Toxicities (R21)
NCI Funding for Clinical Trials & Partnerships
NCI Policy For Phase III Trials

NCI Issued an official Notice (NOT-CA-13-012) in June 2013, announcing a policy to no longer support clinical trials with medical interventions or trials that could not be completed in a 5-year timeframe under the R01 or P01 mechanisms.

A large phase III trial evaluating cancer disease endpoints or cardiovascular endpoints:

- NCI Clinical Trials Network (NCTN)
- NCI Community Oncology Research Program (NCORP)
NCI Clinical Trials Network

- Fund Infrastructure for the Conduct Clinical Trials Across Multiple Credentialed Sites (academic and community)
- Phase 3 clinical trials open across the Network
- Standard processes across groups
  - Single regulatory process
  - Central IRB
- Sites have multiple trials open at any one time
- Funds for clinical trials
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
NCORP

- Design and conduct cancer prevention, control and screening/post-treatment surveillance clinical trials and Cancer Care Delivery Research (CCDR) studies

- Cancer Control Trials have non-cancer endpoints
  - Symptom Endpoints
  - Toxicity Endpoints

- Cardiotoxicity has been identified as a priority research area for NCORP cancer control studies
Challenges: Understanding the Funding for Trials

- NCORP funds the trial infrastructure
  - Concept and protocol development
  - Regulatory processes (IRB, credentialing, etc)
  - Per case reimbursement for accrual
  - Blood collection and storage
  - Data collection, statistical analysis, publication

- NCORP does not fund
  - Physician investigator salary (*volunteer effort*)
  - Patient assessment beyond usual care
  - Analysis of correlative/translational markers
Positive Partnerships:

- Joint understanding of the research gaps
  - How to manage cardiovascular side effects of cancer treatment
  - Addressing important cross disciplinary clinical issues
  - Learning to speak each others language (or at least understand one another)
- Together addressing the education and training gaps
  - Clinicians
  - Patients
- Formal collaborations between professional organizations
  - ASCO and ACC
NCORP Cardiotoxicity Studies:

- Wake Forest: PREVENT statin for prevention
- Wake Forest: UPBEAT CV events after treatment (pending)
- COG- *new* Carvedilol to prevent heart failure
- COG- Dexrazoxane effects on biomarkers of heart failure
- SWOG- low dose Carvedilol to prevent LVEF decrease

Closed Studies:

- Suncoast RCT adjuvant breast cancer patient receiving Herceptin
  - Beta Blocker vs Ace Inhibitor vs Placebo
- Cardiologists actively engaged as study investigators