Cardiovascular Phenotyping in Cooperative Clinical Trials – What and How to Measure?

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Cardiovascular Toxicity Assessment in Oncology Clinical Trials Workshop
September 22, 2016
Outline

• Key Considerations in Cardiovascular (CV) Phenotyping in Cooperative Clinical Trials

• Ongoing Work Focused on Robust Data Collection as it Relates to Exposures and Outcomes
  • ECOG Cardiotoxicity Working Group
  • RADCOMP

• Roadmap for Clinical Studies

• Needs and Opportunities
What and How to Measure?

Key Considerations

- What is the overall objective of the study?
- What is the CV question of interest? What is the goal?
  - Deliver personalized and evidence-based medicine by determining therapeutic benefit and off-target toxicities of therapies
- How do we obtain high-quality data, as it relates to both exposures and outcomes?
  - What is the optimal strategy to characterize the disease?
  - When should we measure, and how often?
  - What is the most robust analytic platform? What are the test characteristics?
  - What is the feasibility, patient burden, and cost?

Cardiovascular Phenotyping Tools

- Clinical parameters (exposures, outcomes)
- Imaging measures (Weissman, Hundley)
- Biochemical Measures (Croce)
- Genetics
- Functional/physiologic measures
Cardiovascular Data Collection in Cooperative Clinical Trials – Exposures

- Robust data collection is critical to successful study execution

- Need for data harmonization with comprehensive and consistent collection of CV exposures in oncology studies
  - Risk factors (e.g. hypertension, diabetes, dyslipidemia, body mass index, blood pressure)
  - Medications
  - Disease (e.g. coronary artery disease, stroke, heart failure, cardiomyopathy)

- Allows for the opportunity to perform retrospective studies, meta-analyses, and build data repositories/registries
ECOG Efforts to Develop a Cardiotoxicity Case Report Form

• **Objective** – Develop a common case report form (CRF)/data repository of elements that can be used across trials

• **Methods** – Participants: ECOG Cardiotoxicity Working Group
  • Comprised of cardiologists, oncologists, biostatisticians, patient advocates
  • Held monthly conference calls over the course of 1 year to review data elements

• **Processes** – Modeled using established CRFs
  • Research into recent CRFs of cardiology and cardio-oncology studies performed
  • NCI PREDICT study (Lenihan, PI); E5103 (O’Neill, co-I); MESA, Framingham Heart Study
  • Iterative process of review and feedback incorporation
Cardiotoxicity CRF - Results

- Shared amongst multiple investigators across ECOG, RTOG, NRG, SWOG, NCI Community Oncology Task Force
- All terms mapped to MedDRA

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Cardiovascular Data Collection in Oncology Clinical Trials – Adverse Events and Outcomes

0531 and 03P1 evaluated same treatment

0531 used targeted toxicity (3 events) with enhanced infection monitoring (specific CRF)

In contrast, 03P1 only used targeted toxicity (6 events)

Underestimation of Adverse Events in COG Study AAML0531

• Potential reasons: limited time and resources, complexity of CTCAE definitions and adverse events

ECOG Efforts to Harmonize CV Adverse Event Reporting in CTCAE

- ECOG Cardiotoxicity Working Group proposed modifications to the following in order to harmonize grading/definitions:
  - Heart Failure, Ejection Fraction Decreased, Restrictive Cardiomyopathy, Pericardial Effusion, Myocardial Infarction, Conduction Disorder, Arterial Thromboembolism, and others

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CTCAE v5.0
Final Draft Open for Review/Comments
- CTCAE v5.0 Final Draft Comments due: August 1, 2016
  - Send comments to NCCITCAEcomments@mail.nih.gov

Tentative Timeline:
- August 1, 2016 — Final Draft comments due
- Mid-August 2016 — Final CTDP review
- Mid-September 2016 — Publication of v5.0
- February/March 2017 — Implementation of v5.0 in CTEP IT systems
Efforts to Collect Robust CV Exposures and Outcomes

- Pragmatic randomized trial of proton versus photon therapy in patients with non-metastatic breast cancer receiving comprehensive nodal radiation

- **Primary Objective:** To assess the effectiveness of proton vs. photon therapy in reducing major cardiovascular events (MCE)

- **Sample size:** 1,716 patients across 30 centers nationwide

- **PI:** Justin Bekelman, MD

- **Multi-disciplinary team:** Radiation oncologists, biostatisticians, cardiologists, symptom scientists, patients
RADCOMP – An Example of One Approach to CV Phenotyping

- **Broad CV phenotyping approach**: Detailed assessment of clinical exposures and outcomes

- **Clinical events center (CEC)**: Detailed collection of CV outcomes, central adjudication of all CV events (Ky, CEC Chair)

- **Detailed CV phenotyping approach**: Ancillary studies, leveraging resources and infrastructure, utilize central core lab review of all data (Ky, R01 submission)
  - **Specific questions of interest**: Biologic mechanisms, intermediary markers, functional effects of radiation therapy
Which CV Phenotyping Tools?

- Our longitudinal prospective cohort studies in cardio-oncology (breast, renal cell, radiation, lymphoma) are currently evaluating the utility of echocardiography and blood based measures in diagnosing and predicting cardiotoxicity.


Which Adverse Events and Outcomes are Important to Report?

**COMMENTARY**

The Imperative for a New Approach to Toxicity Analysis in Oncology Clinical Trials

Gita Thanarajasingam, Joleen M. Hubbard, Jeff A. Sloan, Axel Grothey

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• Important Needs:
  • Patient-based Reports of Outcomes over Time
  • Time Profile of Adverse Events
  • Comparison of Toxicity over Time
  • Focus on Longer-Lasting, Lower-Grade Toxicities
  • Implementation of Technology to Report Outcomes

One Potential Roadmap for CV Phenotyping in Cooperative Clinical Trials

• **Goal:** Comprehensive and harmonized phenotyping to inform the delivery of personalized and evidence-based medicine

• To use our “broad” phenotyping tools to understand adverse events and outcomes
  • Clinical variables, common CRF, adjudicated CV outcomes

• To then use our “deep” phenotyping tools to better understand the biologic/physiologic heterogeneity that occurs in response to cancer therapies
  • Repository of biomarkers (plasma, serum, DNA); imaging measures (echocardiography); functional measures ($V0_2$)

  Central, core lab review to reduce variability

CV Phenotyping in Cooperative Clinical Trials: Needs and Opportunities

• Critical need to leverage cooperative group clinical trials to create necessary infrastructure to ask impactful questions

• Unique opportunities to understand mechanisms of disease; gain insight into the role of markers as intermediary measures; better understand cardiovascular outcomes

• Ongoing work to improve upon the robust collection of clinical exposures and adverse outcomes

• Focus collaborative resources on:
  • Harmonization and collection of robust data (management, accessibility, application of technology to improve reporting)
  • Development of biobanks (biomarker, genetics) and imaging banks
Needs and Opportunities

A national cancer data ecosystem for sharing and analysis. Create a National Cancer Data Ecosystem to collect, share, and interconnect a broad array of large datasets so that researchers, clinicians, and patients will be able to both contribute and analyze data, facilitating discovery that will ultimately improve patient care and outcomes.

Symptom management research. Support research necessary to accelerate the development of guidelines for routine monitoring and management of patient-reported symptoms in all care settings, throughout the cancer continuum (from diagnosis throughout survivorship and at end-of-life) and tailored to differing patient and survivor needs. Systematically gathered patient-reported outcomes data and evidence-based symptom management are needed to improve patients’ quality of life and the likelihood that they will adhere to effective treatments that are effective rather than abandoning them because of intolerable side effects.
Needs and Opportunities

1. Understand normal biological function and resilience
2. Investigate newly discovered pathobiological mechanisms important to the onset and progression of HLBS diseases
3. Investigate factors that account for differences in health among populations
4. Identify factors that account for individual differences in pathobiology and in responses to treatments
5. Develop and optimize novel diagnostic and therapeutic strategies to prevent, treat, and cure HLBS diseases
6. Optimize clinical and implementation research to improve health and reduce disease
7. Leverage emerging opportunities in data science to open new frontiers in HLBS research
8. Further develop, diversify, and sustain a scientific workforce capable of accomplishing the NHLBI’s mission
THANK YOU
Use of Genetics to Understand Anthracycline Cardiotoxicity

• Genetic variants in carbonic reductase 3 (CBR3) associated with cardiomyopathy with anthracyclines, modified by dose

• Hyaluronan synthase gene (HAS3) also exerts a modifying effect on cardiomyopathy in patients exposed to high dose

5. Potential Effects on Skeletal Muscle and Cardiovascular Fitness

Exercise VO₂