The NCI Comparative Oncology Trials Consortium (COTC): Structure, Mission and Goals

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Discussion points:

• How does the COTC operate?

• Does the current COTC structure meet the needs of the drug development community?

• What are the challenges faced by the COTC?

• What new/innovative strategies could the COTC employ to improve relevance and accessibility, while fulfilling the NIH/NCI mission?
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The COTC as a component of the NCI Comparative Oncology Program

Comparative Oncology Program

Man's Best Friend in More Ways Than One

Cancer drug development typically begins with in vitro research before proceeding through varying degrees of investigation in cell lines and laboratory animals, eventually culminating in human clinical trials. However, this often arduous development path may now find its ally in a relatively new branch of oncology research, referred to as comparative oncology. Initiated and directed by Chad Khanna, D.V.M., Ph.D., the CCR Comparative Oncology Program complements translational research through the characterization of relevant and naturally occurring cancer models that develop in pet animals as a window to evaluate novel therapies.

What's New
CCR is part of the Intramural Research Program (IRP) of NIH

The NCI supports its mission through a combination of extramural funding (grants) and intramural (on-site) research.

Office of the Director

Comparative Oncology Program
Why is the COTC an attractive option for comparative oncology trial execution?

- Investigators and sites within veterinary academic centers
  - Expertise in clinical trial design
  - Criteria for membership
  - Access to patients
- Dedicated clinical trial support
  - Not a for-profit CRO mechanism
  - Politically neutral
- Ability to leverage existing NCI resources
  - C3D data management
  - Visibility in the community
Comparative Oncology Trials Consortium (COTC)

- NCI-COTC mechanism unites clinical trial sites within academic veterinary centers with stakeholders in cancer drug development.
  - Patient = companion pet dog with cancer
  - Investigational agent = pre or post-IND intended for human use
- Program manager: Christina Mazcko
- COTC-led efforts vs. Investigator-led efforts

Members of the Comparative Oncology Trials Consortium:

- Auburn University
  - Auburn, AL
- Colorado State University
  - Ft. Collins, CO
- Kansas State University
  - Manhattan, KS
- Michigan State University
  - East Lansing, MI
- North Carolina State University
  - Raleigh, NC
- Purdue University
  - West Lafayette, IN
- Texas A&M University
  - College Station, TX
- The Ohio State University
  - Columbus, OH
- Tufts University
  - North Grafton, MA
- University of California
  - Davis, CA
- University of Florida
  - Gainesville, FL
- University of Georgia
  - Athens, GA
- University of Guelph
  - Guelph, ON Canada
- University of Illinois
  - Urbana, IL
- University of Minnesota
  - St. Paul, MN
- University of Missouri
  - Columbia, MO
- University of Pennsylvania
  - Philadelphia, PA
- University of Tennessee
  - Knoxville, TN
- University of Wisconsin
  - Madison, WI
- Washington State University
  - Pullman, WA
MOU/CDA
C3D data mgmt.
Drug/trial package
Protocol

MTA (drug)

CDA
Protocol
Budget

NIH/NCI COP

MOU/CDA
C3D data mgmt.
Drug/trial package
Protocol

Sponsor
Contract for clinical case management
Contract to perform correlative assays (PD Core)

COTC sites

IACUC
Study budgeting

- Standardized structure/fee schedule
  - Study procedures and clinical management
  - Investigator/technical support

- Separate budgeting for correlative assays
  - PD core, Antech GLP, etc

- Study sponsor responsible for provision of the agent and any assays performed within their walls
  - PK, metabolite analysis
  - Biomarker discovery
Protocol and consent

- Generated by study sponsor and NCI/COP/COTC leadership
  - Input from PD core and COTC membership

- Informed consent tailored to study agent and procedures
  - Must include AE language
  - Must include summary of risks/benefits to patient

- Study sites do not go “off-protocol”
  - Violation of Memorandum of Understanding (MOU)

- Sites maintain IACUC approval documentation
Data management

- NCI’s C3D system captures response data from each COTC site in real time
- Electronic Case Reporting Forms (eCRFs) are study and patient-specific
- Entire patient record is included for analysis
  - Eligibility/enrollment
  - On-study events and procedures
  - Drug administration
  - Owner questionnaires
  - Concurrent medications
  - Labwork
  - Response data
  - Follow-up/survival data
Data/Safety Monitoring Board

- DSMB convened for each COTC trial
- Chair + 4 members
  - All from non-participating institutions, if possible
- Quarterly discussion of all trial adverse events with site investigators and study sponsor
- Ad hoc discussion of unexpected and/or severe events
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PARP and TOP1 inhibitors

Rapamycin Pharmacokinetic and Pharmacodynamic Relationships in Osteosarcoma: A Comparative Oncology Study in Dogs

Melissa C. Paoloni¹, Christina Mazcko¹, Elizabeth Fox¹, Timothy Fan¹, Susan Lana³, William Kisseberth⁵, David M. Vail⁶, Kaylee Nuckolls⁷, Tanasa Osborne⁸, Samuel Yalkowsky⁹, Daniel Gustafson⁹, Yunkai Yu⁹, Liang Cao⁹, Chand Khanna¹,²
COTC trials: Intent and Scope

- Data generated in response to specific need in (human) drug development

- Trial design reflects specific questions being asked of the disease model in dogs
  - Tumor biology or drug target > histology
  - Dose/schedule, selection of lead compound, PK/PD relationships, biomarker validation
  - Evaluation of combination therapies
  - Efficacy often not primary endpoint
NSC725776 Enrollment
Closed

NSC743400 Enrollment
Closed

NSC706744 Enrollment

- Grade 5 event
- Grade 4 event
- Grade 3 event

Dose escalation complete:
68 dogs treated

Cohort expansion open:
7 dogs treated

Open-100mg/m2
**Best Overall Response**

- **NSC725776**
  - 3mg/m²
  - 6mg/m²
  - 9mg/m²
  - 15mg/m²
  - 17.5mg/m²
  - 20mg/m²

- **NSC743400**
  - 8mg/m²
  - 16mg/m²
  - 24mg/m²
  - 40mg/m²
  - 50mg/m²
  - 75mg/m²
  - 100mg/m²

- **NSC706744**
  - 25mg/m²
  - 50mg/m²
  - 75mg/m²
  - 100mg/m²
  - 125mg/m²

*Response Assessment (%)*
Overall response rate (PR or better)

- 7/23 (30%)
- 9/23 (39%)
- 18/23 (78%)

Response at the MTD

- 2/6 (33%)
- N/A
- 8/11 (73%)
Evidence for a dose-response relationship

- Early-cohort responders with 744 suggest dose-response may be plateaued
- Non-responders (SD + PD) across dose range with LMP 776 & 400

NSC725776

NSC743400

NSC706744

=Previously treated, =naïve disease
10x increase in tumor drug accumulation at Day 6 for 744 compared to 776 and 400

- Absolute tumor levels 776 < 400 << 744
- Day 6 exposure shows modest correlation with response for LMP 776
- Most non-responders clustered at low tumor levels
gH2AX at pre-dose, 2 hr, 6 hr, Day 6

LMP776

LMP400

LMP744

12/5/2014

Ji/NCTVL

23
How do we serve the community?

• Centralized trial management at no cost to sponsor
  – “PD-rich” studies in naturally-occurring cancer
  – Patients with both naïve and resistant disease
  – Direct access to expertise, reagents and assays to support veterinary trials

• Link to comparative cancer imaging with ability to recruit dogs for imaging studies on the NIH Bethesda campus

• Basic science laboratory component: unique resources, cell lines, animal model techniques geared toward metastasis biology
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Challenges for the COTC

• # of agreements and time to execute them
• Agreement terms relating to IP
  – Minimized by the MOU terms: sites do not go “off protocol”, so no IP is generated by COTC members
  – Drug provider ultimately owns the data

• Competition for cases
  – COTC trials typically more labor-intensive than other trials
Veterinary Oncology

Cancer is a leading cause of death in man and man's best friend. In addition to our ongoing clinical development, Omnis is developing cancer therapies to meet the needs of pets and pet owners.

Omnis utilizing a unique comparative oncology approach to improve and optimize the process of clinical drug development.

Figure 1. An integrated approach is necessary to improve pre-clinical and clinical trial design utilizing dogs as pre-clinical models, similar to mice and non-human primate work, and as 'bridges' between the different phases of clinical trials. Modified with permission from ref. 7.
Flow of agreements for COTC studies

NCI-CCR-COP

2 way CDA MTA for drug transfer

Study sponsor

PD Core Contract

Financial Contracts +/- MTAs for transfer of drug or samples

MOU (in place)

MTA (transfer of samples)

PD Core

Histo
Flow
Cytokines

COTC

COTC Site

COTC Site

COTC Site

COTC Site

Red designates responsibility of the sponsor
COTC Trial Development Process

**Protocol Development**
- Concept Discussions (Sponsor and COTC)
- 1st draft of Letter of intent & study budget (COTC)
- Review of LOI and budget (Sponsor)
- PD Core development (COTC)
- Protocol drafted (COTC)

**Estimated time: 6-8 weeks.**

**Study Implementation**
- Development of clinical database (COTC)
- Ordering of trial supplies (COTC)
- Selection of COTC sites (COTC)
- Protocol training (COTC)

**Estimated time: 4-6 weeks. Can occur simultaneously with Protocol Development.**

**Contract Process**
- Study agreement between sponsor & NCI
- Contract between sponsor and PD Core
- MTA between NCI and COTC sites (NCI)
- Contracts between sponsor and COTC sites

**Estimated time: 6-8 weeks. Can occur simultaneously with Study Implementation.**

*Blue = responsibility of sponsor*
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Comparative oncology studies should employ drug development questions that cannot be effectively asked or answered in other animal models or humans.

**Old Questions**

- Will dogs with measurable cancer respond to Drug X?
- Will Drug X make dogs with cancer sick?
- Do dogs get the same kinds of cancer as humans?
- Does tumor histology and/or grade predict the response to Drug X?

**New Questions**

- Can the dog tell us why Drug X succeeded or failed in humans?
- Will Drug X retard or prevent the onset of metastatic disease in the adjuvant setting?
- Can Drug X be safely combined with the standard of care?
- Are actionable targets shared between human and canine cancer, agnostic of histologic diagnosis?
Strengths of a multi-site consortium to solve complex issues in drug development

• When large numbers of patients are needed with a specific disease that is directly translatable to humans
  – e.g. canine osteosarcoma

• To minimize geographical and/or investigator bias

• To support early-stage investigators whom can leverage the COP’s administrative support to conduct a large trial

• To vertically integrate NCI and community preclinical drug discovery tools and methods (\textit{in vitro} & \textit{in vivo} mouse models) into the development path of a novel agent
New initiatives for consideration for the NCI-COP

- Emphasis on novel study designs
  - Combination therapies, biomarker validation
- Exploration of safety data generated in pet dogs
  - How to manage perception and risk?
- Contract core to facilitate agreements
- Directed programs in addition to clinical trials of drugs
  e.g. Exceptional responder program
  e.g. Comparative brain tumor consortium
  e.g. NCI Comparative Cancer Imaging fellowship
Summary and Conclusions

• The COTC is an integrated, high-quality, multicenter clinical trial network, conducting studies in response to a specific need in human cancer drug development

• Comparative oncology efforts have flourished worldwide after the NCI COP inception in 2004

• New initiatives that extend beyond clinical trials are needed:
  – Ongoing molecular validation of canine cancer as a model for human cancer
  – Deeper contribution to cancer drug and imaging agent development
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COTC member institutions, investigators, and support staff: past, present and future

Canine Comparative Oncology Genomics Consortium

Dogs and their owners