WORKSHOP HIGHLIGHTS
Institute of Medicine
NOVEMBER 2015

The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research

With support from a broad coalition of sponsors, the Institute of Medicine's National Cancer Policy Forum hosted a workshop on comparative oncology—the study of naturally developing cancers in animals as models for human disease. The workshop, The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research, was held on June 8-9, 2015 in Washington, DC. A webcast and a summary[1] of the workshop are available online.

Traditional preclinical cancer drug research and development (R&D) has relied on mouse models of cancer, said Beverly Teicher from the National Cancer Institute (NCI). However, the complexity of human cancer biology is often not sufficiently captured by mouse models. Thus, she said many cancer drug candidates that appear successful in mouse studies fail in human clinical trials; only 11 percent of candidate cancer drugs that demonstrate efficacy in mouse models are ultimately approved for human use. Michael Kastan from the Duke Cancer Institute added that the process of developing cancer therapies is time-consuming and costly, and newly approved therapies typically offer survival benefits measured in months, sometimes with significant toxicities. Thus, Kastan and Len Lichtenfeld of the American Cancer Society noted that there still much work to be done to accelerate progress in developing cancer therapies.

THE RATIONALE FOR COMPARATIVE ONCOLOGY

Lee Helman from NCI said that researchers are seeking new approaches to complement traditional preclinical models to better select drugs for testing in humans and to reduce attrition rates within the drug development pipeline. He said there is growing interest in comparative oncology because cancers that spontaneously develop in animals due to normal aging processes share many characteristics with human cancers. Helman noted that humans and dogs have lived and evolved together for thousands of years; thus, they tend to have similar traits that can inform cancer research, because a combination of environmental exposures and genetic susceptibilities contributes to the development of cancer.

[1] http://www.nap.edu/read/21830 (accessed November 3, 2015).

Helman and Kastan emphasized that many canine tumors have tissue origins similar to human cancers, including sarcoma, melanoma, lymphoma, and glioma. Cancers that develop in dogs also share similarities with human cancers in histologic appearance, tumor genetics, biologic behavior, molecular targets, therapeutic response, heterogeneity, acquired resistance, recurrence, and metastasis.

Kastan described the advantages of including clinical trials for pets with cancer in drug R&D. He said canine patients are relatively outbred compared to mouse models, and their larger size and anatomical and physiological similarities to humans make treatment regimens more comparable. He added that clinical trials for pet patients can be completed faster than human trials because animals have shorter lifespans and cancer often progresses more quickly in pets than in humans.

In addition to informing the development of cancer therapy for humans, Kastan said that comparative oncology has the potential to benefit pets with cancer. More than 1 million dogs are treated for cancer each year in the United States, he said, and cancer kills 50 percent of all dogs over the age of 10. Although there is a range of therapeutic options available for pets with cancer, there are few established standards of care for the treatment of cancer in pets. Deborah Knapp from Purdue University said that clinical trials for pets provide potential alternatives for treatment with novel therapies in development.

Patricia Olson, independent advisor on animal health and welfare, emphasized the importance of addressing the needs of pet patients and their owners in the design and conduct of clinical trials for pets with cancer, and Rod Page from Colorado State University highlighted best practices for the ethical conduct for such trials,

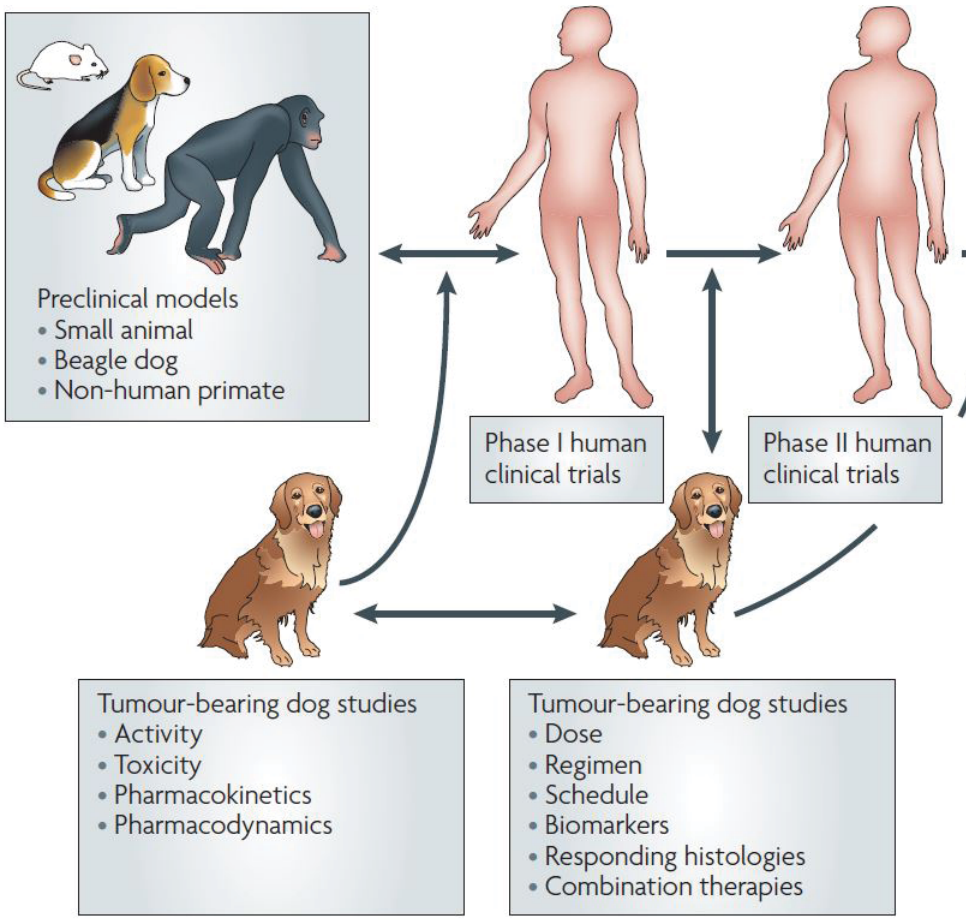

FIGURE. An approach to drug development that integrates comparative oncology trials across the cancer drug development pipeline.
Source: Helman and Khanna presentations, June 8, 2015; Paoloni and Khanna, 2008. Reprinted with permission from Macmillan Publishers, Ltd.: Nature Reviews Cancer.

including preserving well-being and providing pain relief, obtaining peer review and pet owner consent, and ensuring appropriate accountability and oversight.

INTEGRATED APPROACH TO CANCER THERAPY DEVELOPMENT

Helman said that clinical trials for pet patients with cancer are underutilized in cancer drug development, which is traditionally viewed as a linear process, with few iterative components. Helman and Chand Khanna of NCI advocated for an integrated approach in which comparative oncology trials are conducted in parallel with human clinical trials to gain additional insights into drug activity, toxicity, treatment regimen and schedule, biomarkers, and possible combination therapies (see Figure).

Khanna also described the Comparative Oncology Trials Consortium, which was established by NCI to provide infrastructure and resources for integrating clinical trials for pets with cancers into pathways for developing new cancer drugs, devices, and imaging techniques.

Several workshop speakers described examples of clinical trials for pet patients that have enhanced understanding of canine and human cancer biology, facilitated drug development, and led to the approved use of therapies for both humans and pets with cancer (see Box).

EXAMPLES OF CLINICAL TRIALS FOR PET PATIENTS WITH CANCER DESCRIBED BY INDIVIDUAL WORKSHOP SPEAKERS

- **Targeted drug delivery:** Tumor necrosis factor-alpha (TNF-α) is a cytokine with anti-tumor activity, but its use has been limited because of systemic toxicity. To circumvent this toxicity, a clinical trial for canine patients used a virus to target delivery of the TNF-α gene to the tumor. The study demonstrated that the agent only targeted tumor tissue and not normal tissue (Chand Khanna, NCI, and Doug Thamm, University of Colorado).
- **Combination therapies:** IL-2 and IL-12 immunocytokines were tested in combination in canine cancer patients (Khanna). Dogs with osteosarcoma were treated with PAC-1 (an activator of apoptosis) in combination with temozolomide or doxorubicin (Tim Fan, University of Illinois at Urbana–Champaign).
- **Modeling of precision medicine:** Genetic and molecular profiling were used to match targeted therapies to canine patients with cancer (Khanna).
- **"Pick the winner" strategy to select a lead compound for human trials:** Three novel topoisomerase inhibitors were tested in pet dogs with lymphoma to identify the optimal compound for human testing by assessing efficacy, biomarkers, and pharmacokinetics (Khanna).
- **Development of a biomarker test and drug for lymphoma:** A clinical trial for pet dogs with lymphoma demonstrated efficacy of a Bruton tyrosine kinase (BTK) inhibitor, validated a biomarker test, and informed dosing for early-phase clinical trials for human patients (Thamm).
- **Testing a drug for veterinary use:** A clinical trial for pet patients with non-Hodgkin's lymphoma evaluated GS-9291, an anti-proliferative nucleotide analog prodrug. This trial provided proof-of-concept for launching a phase I study in human patients. Although the drug did not succeed in human trials, it has progressed into animal clinical trials for FDA approval for veterinary use (Dan Tumas, Gilead Sciences, and Dan Gustafson, Colorado State University).
- **Development of ganetespib:** Data from clinical trials for canine patients supported an investigational new drug application for ganetespib, an HSP90 inhibitor. Results suggested that sustained blood levels of ganetespib were associated with measurable responses to therapy. A subsequent trial for canine patients defined a dosing regimen that was used in human clinical trials (Cheryl London, Ohio State University).
- **Development of KPT-335:** Clinical trials of KPT-335, a novel inhibitor of the XPO1 (exportin 1) protein, for canine lymphoma patients helped define the drug regimen and supportive care protocols to address toxicities in subsequent human trials (London).

CHALLENGES IN INTEGRATING CLINICAL TRIALS FOR PET PATIENTS IN CANCER THERAPY R&D

Several workshop speakers described challenges that may impede greater use of clinical trials for pet patients in cancer drug R&D. For example, Olson, Page, and Cheryl London from Ohio State University discussed a lack of familiarity with clinical trials for pet patients among drug developers, veterinarians, and pet owners. Khanna added that drug developers are uncertain about whether comparative oncology will decrease the time and expense associated with drug development.

Khanna said that the Food and Drug Administration (FDA) has not issued formal guidance on clinical trials for pet patients, and Tanja Zabka of Genentech noted that drug developers are hesitant to conduct comparative oncology trials due to concerns that safety signals observed in such trials could impede drug R&D. However, John Leighton from the FDA said that no regulatory action has been taken in response to safety signals observed in clinical trials for pet patients: "I have never seen an adverse outcome from a safety signal in a companion animal study. We have heard this over and over again, that the FDA is going to take a negative perception to any safety signal, and in 15 years I have never seen it."

Matthew Breen from North Carolina State University said there is a need for improved characterization of the canine genome and genetic mutations present in canine cancer. He added that clinical trials for pets can be used to validate targeted cancer agents, but information on what specific agents might target canine cancer is often lacking. Tim Fan from the University of Illinois at Urbana–Champaign added that specific assays and reagents that would make these trials possible are also often not available at this time.

WORKSHOP WRAP-UP

Knapp said that addressing the challenges surrounding the conduct of clinical trials for pet patients and expanding the integration of such trials in drug R&D pathways could improve translational cancer research to benefit both human and pet patients. She said that cancer is still a large burden for both human and pet patients, and complementary approaches to traditional cancer research are needed.

Lichtenfeld said he had been unfamiliar with clinical trials for pet patients, but shortly before the workshop, his own beloved family dog, Lily, was diagnosed with cancer. This personal experience, along with workshop presentations and discussions, gave him a deeper appreciation for the potential of comparative oncology to enhance and accelerate progress in translational cancer research: "The answers to our puzzles may be walking right beside us. . . . As we leave this room, let's commit to taking a look at those potentials, determining what they are, and making that happen."♦♦♦

DISCLAIMER: This Workshop Highlights has been prepared by **Erin Balogh** and **Sharyl Nass** as a factual summary of what occurred at the meeting. The statements made are those of the authors or individual meeting participants and do not necessarily represent the views of all meeting participants, the planning committee, or the National Academies.

SPONSORS: This workshop was supported by the Animal Cancer Foundation; the College of Veterinary Medicine at North Carolina State University; the Cornell University School of Veterinary Medicine; Flint Animal Cancer Center, Colorado State University; the Morris Animal Foundation; the Ohio State University School of Veterinary Medicine; Purdue University College of Veterinary Medicine and the Center for Cancer Research; the Skippy Frank Translational Medicine and Life Sciences Fund; the University of Colorado Cancer Center; the University of California, Davis, School of Veterinary Medicine; the University of Florida College of Veterinary Medicine; the University of Georgia College of Veterinary Medicine; the University of Illinois College of Veterinary Medicine; the University of Minnesota College of Veterinary Medicine; the University of Missouri College of Veterinary Medicine and the Ellis Fischel Cancer Center; the University of Pennsylvania; the University of Wisconsin–Madison Carbone Cancer Center, Institute for Clinical and Translational Research, and the School of Veterinary Medicine; and the Washington State University College of Veterinary Medicine.

For additional information regarding the meeting, visit http://iom.nationalacademies.org/Activities/Disease/NCPF/2015-JUN-08.aspx

The National Academies of
SCIENCES • ENGINEERING • MEDICINE

The nation turns to the National Academies of Sciences, Engineering, and Medicine for independent, objective advice on issues that affect people's lives worldwide.
www.national-academies.org

iom.nationalacademies.org