Perspectives

Clinical Cancer Research

Defining the Value of a Comparative Approach to Cancer Drug Development 🖎

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Abstract

Comparative oncology as a tool in drug development requires a deeper examination of the value of the approach and examples of where this approach can satisfy unmet needs. This review seeks to demonstrate types of drug development questions that are best answered by the comparative oncology approach. We believe common perceived risks of the comparative approach relate to uncertainty of how regulatory bodies will prioritize or react to data generated from these unique studies conducted in diseased animals, and how these new data will affect ongoing human clinical trials. We contend that it is reasonable to consider these data as potentially informative and valuable to cancer drug development, but as supplementary to conventional preclinical studies and human clinical trials particularly as they relate to the identification of drug-associated adverse events. *Clin Cancer Res; 22(9); 2133–8. ©2015 AACR.*

Introduction

The study of naturally occurring cancer in companion animals, known as comparative oncology, forms the basis of a translational drug development strategy that primarily includes tumor-bearing pet dogs in clinical trials of novel cancer therapies destined for use in human cancer patients (1–5). The recognition of spontaneous cancer development in companion animals, and potential for inclusion of such animals in drug development studies, is based upon observations of canine malignancies that share morphologic, histologic, and biologic characteristics with human cancers. Dogs' physical size, amenability to serial biologic sample collections, compressed survival compared with humans, comparable tumor biology, intact immunity, and relevant responses to cytotoxic therapies provide clear support to their inclusion as a complementary animal model (4, 5).

Currently, the field of comparative oncology is focused on tumor-bearing dogs as they comprise the majority of those presented to veterinarians for cancer diagnosis and management, which is in turn facilitated by scientific knowledge of malignancies they develop, the collective veterinary clinical experience with anticancer therapies such as chemotherapy and radiation, and availability of basic annotation of the canine genome and immune system. A major milestone was establishment of the NCI's Comparative Oncology Program (NCI-COP) at the NIH in 2004. A component of this program is the Comparative Oncology Trials Consortium (NCI-COTC; https://ccrod.cancer.gov/confluence/display/CCRCOPWeb/Home), an infrastructure uniting study sponsors, such as pharmaceutical and biotechnology companies, with 21 academic veterinary centers within North America to support multicenter clinical trials of investigational therapeutics, wherein centralized trial support and data management is provided by the NCI (6, 7). This mechanism provides access to a clinical trial infrastructure that delivers trial results in a facile manner, considerate of timelines generally required in drug development strategies. Furthermore, a body of published work now exists to demonstrate the feasibility and applicability of the dog cancer model in drug development to ensure data that are both scientifically sound and robust, thus supporting inclusion into FDA applications. Although not formal FDA guidance, direction for clinical trial conduct and data reporting exists for drugs evaluated in comparative oncology studies in the pre- and post-Investigational New Drug (IND) settings, and has been used effectively by groups actively involved in these efforts (8).

Methods

Today's challenge is how to best capture and convey the value of these studies, given the timeline for drug development and the diversity of data that collectively informs decisions in the development path. Various attempts at defining value have been made, including a financial model that proposes savings of billions of research and development dollars, achieved primarily through the effective design of better phase II human studies (9). We propose that the value of the comparative approach lies in the answers to critical drug development questions that are not answered in human trials or conventional preclinical models. Herein, we present a summary of the types of questions that are best asked and answered by comparative oncology studies (Table 1), along with a discussion of selected studies that generated answers to such questions, thus are demonstrative of the value of the comparative oncology approach.

Results

Small molecules and the relationship of pharmacokinetics, pharmacodynamics, and clinical assessment of tolerability and efficacy

A highly soluble prodrug of ganetespib, STA-1474, was studied in dogs with cancer to establish clinical toxicity, to identify

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Table 1. Examples of drug development questions that can be answered within the comparative oncology approach

Question	Outcome	Selected supporting references
Safety and efficacy		
What is the clinical response to an investigational agent, and can this response be characterized using standardized, quantitative metrics, including imaging techniques, that are translatable to human clinical studies?	Common criteria employed to communicate tumor responses between veterinary and human patients	35–40
What is the success of an investigational agent in the context of treatment-naïve disease?	Ability to observe responses in patients without preexisting drug resistance as seen in human phase I	41–45
What is the acute and chronic toxicity profile of an investigational agent, both as a single agent and in combination with conventional chemotherapy? Can this be described with standardized metrics?	Common criteria employed to communicate tumor responses between veterinary and human patients; provide insight into what to expect/monitor for within human patients.	10, 11, 14, 15, 41, 45
Which histologies appear to be most likely to respond to a specific investigational drug or drug class?	Insight into comparable tumor types for study within human patients	10, 11
Pharmacokinetics/pharmacodynamics		
What are the relationships between therapeutic index, demonstration of pharmacodynamics endpoints, and tolerable drug exposure?	Provides supporting data to select a biologically effective dose in conjunction with or instead of an MTD	10, 11, 23, 24, 45, 46
Can pharmacokinetic/pharmacodynamic data obtained in dogs be used to define the optimal dose and schedule of a new drug?	Optimization of dose/schedule prior to prescription of RP2 dose in humans; identification of MTD in dogs	10, 11, 42, 45
Can differential pharmacokinetic/pharmacodynamic relationships within blood versus tumor be characterized to identify which biologic sample is most indicative of pharmacodynamic effect?	Ability to tailor biologic sample collection and correlative assay development for human trials	12
Given a comparable therapeutic index of a given drug between humans and dogs, do therapeutically relevant levels of drug accumulate in tumors at a given (tolerable) dose, schedule, and pharmacokinetic profile?	Provides further proof-of-principle or lack thereof for systemically administered drugs across a range of doses	NCI Comparative Oncology Trials Consortium (COTC): A clinical trial of iniparib in tumor-bearing dogs (in press)
Drug target investigations		
Can comparative cancer studies in tumor-bearing dogs identify potential new targets that are druggable in both dogs and humans, and/or identify new molecular signatures that correlate with prognosis?	New candidate genes identified from dog data to support investigations in human patients; shared molecular derangements identified to add comparative relevance to the canine model	15
Can biospecimen repositories be populated with sufficient canine samples to allow matched tissues from primary and metastatic sites within the same patient to allow elucidation of drug targets within the metastatic pathway?	Provides an unparalleled high-quality resource for canine comparative cancer biology investigations	26, 27
Imaging agent validation		
Can imaging agent performance and validation (target: background ratios, off-target binding, normal biodistribution, lesions distribution kinetics) be assessed in canine cancer patients?	Validated imaging signal against clinical findings and tissue histology; allowed exploration of imaging agent dose and subsequent performance to be validated both *in vivo* and with *ex vivo* tissue imaging taken during surgical procedures	17, 39, 47, 48, 49
Can validation of novel imaging agents or feasibility of new imaging protocols be assessed in canine cancer patients?	Allowed exploration of novel combinations of different imaging agents, particularly those with variable radiopharmaceutical composition	17, 50–54
Nontraditional study design		
How can a drug's performance in the minimal residual disease (MRD) setting be assessed? Can clinical endpoints that do not involve regression of clinically measurable lesions, rather delay of onset of metastasis, be evaluated?	Provided an opportunity to assess impact on disease-free interval after removal of a primary tumor with a known high risk of metastatic progression	55
Can the dog serve as a model for personalized medicine studies to validate processes?	Validated a workflow for prospective genomic profiling of individual canine tumors, enabling future basket trial designs	56
Biomarkers		
How can biomarkers of drug exposure in both normal (plasma, PBMCs) and tumor tissues be identified and validated?	Demonstrates the strengths of the canine cancer model for collection of biologic samples within various compartments (blood, tumor tissue, normal tissue)	7, 23, 24, 26
Can new biomarkers for prognosis be identified from dogs receiving a novel drug?	Showed baseline expression of key tumoral factors, such as necrosis, inflammation was prognostic for clinical outcome	47, 57
Can immune response data be collected from dogs receiving tumor-specific immunotherapy that is correlative and/or predictive of tumor response?	Demonstrates the availability and utility of immune cell assays as valid pharmacodynamic readout for immune-based therapies	15, 30

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Table 1. Examples of drug development questions that can be answered within the comparative oncology approach (Cont'd)

Question	Outcome	Selected supporting references
Prioritization of candidate drugs		
Can comparative oncology studies play a role in lead candidate drug selection for advancement in the human clinic?	Provided robust correlative data to enhance the preclinical data package to discern and prioritize candidates for human use	NCI Comparative Oncology Trials Consortium (COTC): Indeno-isoquinoline candidates in canine lymphoma (in progress)

surrogate biomarkers of response and pharmacokinetics between two proposed dosing schedules, and to provide evidence of biologic activity. This study met all defined objectives, and assisted in devising a dosing strategy to provide prolonged drug exposure to support efficient inhibition of drug target via modulation of a surrogate biomarker in blood [HSP70 upregulation in peripheral blood mononuclear cells (PBMC)] and tumor levels of c-kit (an HSP90 client protein). Collectively, this data informed the design of human clinical trials of ganetespib and demonstrates the strengths of a naturally occurring canine model by highlighting the ease of serial biopsy procurement, rapid assessment of differential dose and schedule, and correlative assessment of multiple clinical parameters (10). In another similar example, an orally bioavailable XPO1 inhibitor verdinexor, a companion agent to a lead human compound KPT-330 (Selinexor, Karyopharm Therapeutics), was studied in tumor-bearing dogs. Based upon profound clinical benefit observed in dogs with non-Hodgkin lymphoma (NHL) and the marked similarities between canine and human NHL, the data generated within this study provided critical new information in support of related compounds in humans with hematologic malignancies (11). Selinexor is currently being evaluated in phase I and II clinical trials for a variety of human cancers.

Biomarker validation and optimization of pharmacodynamics assays within the context of drug exposure in tumor-bearing dogs

The irreversible inhibitor of Bruton tyrosine kinase (Btk), ibrutinib, was studied in dogs with B-cell lymphoma to establish tolerability, preliminary efficacy data, and to validate a pharmacodynamic assay within PBMCs and tumor tissue. Validation of the fluorescently labeled derivative of ibrutinib to monitor occupancy of Btk by the drug has led to adoption of this approach as pharmacodynamic readout in subsequent human trials, while also supporting the use of ibrutinib in humans with B-cell malignancies (12, 13).

Another valuable example is study of hydroxychloroquine, an autophagy inhibitor, given to dogs with NHL. The pharmacodynamic response evaluated in both PBMCs and tumor tissue, obtained via serial peripheral lymph node biopsies, demonstrated that reliance on surrogate PBMC for demonstration of sufficient drug levels for effective autophagy inhibition within the tumor tissue cannot always be inferred, thus underscoring the strength of the canine cancer model (14).

Immune-modulating agents for cancer therapy

A comparative oncology study of an immunocytokine, NHS-IL12, administered subcutaneously to dogs with malignant melanoma was conducted to identify tolerability and immunologic activity of this agent across a range of doses (15). Pharmacokinetic and pharmacodynamic endpoints, in the form of serum IFNγ, IL10 levels, and intratumoral CD8$^+$ lymphocytes, were assessed alongside clinical measures of response and toxicity. This study provided data that directly informed the design of the ongoing phase I human trial of this agent (NCT01417546). The study demonstrated both initial safety and efficacy signals in a relevant species bearing a naturally arising tumor. This data was crucial to the rigorous scientific review of the clinical trial at the NCI Center for Cancer Research (NCI/CCR) and facilitated the CCR holding the IND for this agent at a time when the study sponsor had deprioritized this compound. This currently is now a high priority agent for planned combination studies in man.(James Gulley, MD; personal communication).

Comparative cancer genomics

The use of dogs in cross-species genomics studies provides a unique opportunity to identify regions of potentially shared and clinically relevant genomic changes. In one such example, candidate genes IL8 and SLC1A3 were identified in canine osteosarcoma as overexpressed; these same genes had variable expression in human osteosarcoma but nevertheless were associated with a poor clinical outcome (16). Additional studies adopting this line of investigation could help identify yet-characterized candidate genes and/or pathways for future application to human cancer genomic studies.

Preclinical assessment of cancer imaging agents in tumor-bearing dogs

Dogs with measurable malignancies that are considered surgical candidates represent a unique opportunity to assess intraoperative imaging agents to provide, in real time, an assessment of surgical margins to inform on the extent of resection and thus optimize outcome. BLZ-100, a near-infrared imaging agent currently in phase I human studies, is a peptide–fluorophore conjugate that was evaluated in a comparative oncology study of dogs with a variety of cancer histologies. (17; Blaze Bioscience, Inc.) Canine tissues were imaged both *in vivo* and *ex vivo* to identify an efficacious dose of BLZ-100. These data provided a foundation and rationale to assess performance of this agent in human patients with soft-tissue sarcomas.

Challenges and perceived risks to comparative oncology studies

Perspectives from those within the pharmaceutical industry against using a comparative oncology approach generally include the relatively higher cost of comparative oncology trials compared with other conventional animal models, the greater amount of drug needed for dosing of dogs, and the time needed to complete such trials from inception to analysis of data. Responses to these points must include consideration of the uniqueness of the data generated within heterogeneous, spontaneous cancer that develops within an immunocompetent host, which is not generated with the intent of describing toxicity as a primary endpoint. The amount of drug and time to execute the studies should be considered in context of when the data is desired within an individual drug's development. Good

Manufacturing Practices (GMP)-level material is not generally needed for comparative oncology clinical studies, although basic purity and release criteria have been previously described (7, 18). Capitalization on a multicenter clinical trial consortium such as the NCI-COTC can assist in hastening the conduct of a trial, but interim analyses will introduce natural and important pauses within the study timeline. Nevertheless, the timeline for comparative oncology studies are much shorter than typical phase I/II human trials and are conducted at a much lower cost, while providing data that can directly inform the design of human trials, representing a valuable return on investment.

Similarly important to consider are questions that cannot be effectively asked within a dog model. It is important to note that prior to initiation of comparative oncology drug trials in dogs, consideration of existing normal dog toxicology data, generated in most cases by the study sponsor during toxicologic assessment, is important to proper and ethical design of the trial. In cases where the dog is a known sensitive species for severe toxicity, and no reasonable margin of safety can be applied to demonstrate therapeutic efficacy, the tumor-bearing dog would not be appropriate for exploration of potential pharmacokinetic/pharmacodynamic relationships and how they correlate to clinical efficacy and tolerability.

The field of cancer genetics and genomics is rapidly evolving, with particular emphasis on specific knowledge of druggable pathways that are critically linked to malignant behavior, supporting the ongoing development of targeted therapies. Indeed, a deeper knowledge of the naturally occurring canine cancer genomic landscape is crucial to defining the pertinent questions that can be asked within canine cancer patients, and how relatable canine cancers are to human cancers on the genomic level. The comparative chromosome alignment technique and the differential organization of the dog genome may narrow key regions of the genome associated with cancers. Recent work in this area demonstrates that recurrent aberrations correlate with cancer subtype, and that corresponding cytogenetic lesions may exist in human patients (16, 19–22). Several examples of where the value of a cross-species approach to cancer genomics has been demonstrated exist in the literature. For example, recent work in canine melanoma demonstrates that although canine tumors possess rare mutations in BRAF and NRAS, they exhibit similar differential gene expression changes to human melanoma within downstream MAPK and PI3K/AKT pathways (25). Thus, although the driving mutations between human and canine melanoma may differ, similar activation and sensitivity to inhibition of such shared signaling pathways underscores the translational value of studying comparative melanoma biology. This aspect of comparative oncology will continue to develop and could support initiation of so-called "basket" trials wherein response of tumors with shared, credentialed biology to a specific targeted therapy are assessed, agnostic of histologic diagnosis. To facilitate future studies in this area, high-quality biologic samples from dogs with various malignancies are available via the Pfizer-Canine Comparative Oncology and Genomics Consortium (CCOGC) biospecimen repository (www.ccogc.net refs. 26, 27). This resource is uniquely suited to provide the necessary molecular background that is currently missing from the comparative oncology armamentarium. CCOGC samples are treatment-naïve, clinically annotated, and include both tumor and matched normal tissues, including peripheral blood, urine, plasma, and serum. Seven histologies were selected based upon their translational relevance

at the time the resource was populated (2007–2011), totaling 1,800 individual patients and approximately 60,000 samples.

A rapidly growing field in cancer drug development is the conception and creation of biologic agents that affect an antitumor response via immune response manipulation and/or reprogramming within individual patients. For such an approach, the type of the agent may critically influence the applicability of the dog model for ongoing development. Incomplete knowledge of shared tumor antigens between humans and dogs may limit the questions that can be asked of such agents that are destined for human use. Furthermore, even with successful targeting of a specific tumor-associated antigen shared between humans and dogs, immunocompetent canine cancer patients will effectively clear any foreign (human or murine) antibodies, thus potentially limiting use of a dog model for evaluation of mAbs intended for repeated therapeutic dosing schemes unless an equivalent canin-ized or canine chimeric product is manufactured alongside the parent compound. Tumor vaccines, particularly those which rely on a shared tumor antigen(s) may be viable candidates for validation studies in a dog model (28, 29). Success in autologous tumor cell lysate vaccination strategies in canine meningioma, melanoma, and lymphoma and others have provided insight for comparative human trials (30–32). Similarly, oncolytic viruses, which capitalize on malignant cells' defects in viral response gene pathways, may be effectively translated between dogs and humans (33, 34).

A path forward: a reasonable regulatory response has been provided

During discussion at an Institute of Medicine (IOM) meeting on June 9, 2015, which included individuals from FDA, NIH, and various academic and industry stakeholders in cancer drug development, Dr. John Leighton of the FDA's Center for Drug Evaluation and Research (CDER) provided public insight into regulatory review of comparative oncology data, of which a summary is available within the IOM proceedings (http://www.nap.edu/catalog/21830/the-role-of-clinical-studies-for-pets-with-naturally-occurring-tumors-in-translational-cancer-research). Although these comments are not considered formal regulatory guidance, their importance is underscored here:

1. The FDA is aware of the role of pet dogs may play as research subjects in human drug development settings. Such data collected in dogs is expected to be filed under the IND as it becomes available. A New Animal Drug (NAD) application is not needed for clinical studies evaluating drugs in this specific research setting.
2. Data collected in the context of a comparative oncology clinical trial setting would be viewed in context. The FDA is aware that companion dogs are housed and treated in the home environment and may have comorbidities reflective of their age and naturally occurring malignancies.
3. Data collected from tumor-bearing pet dogs would never "trump" human data, particularly with respect to drug tolerability and clinical response.
4. Over the past 15 years, safety signals have never been identified in tumor-bearing pet dogs that have resulted in a clinical hold for an existing human IND study.

Conclusions

The questions asked and answered within comparative oncology studies are informative, unique, and not easily provided by

conventional preclinical models or by most human trials. These data do not replace controlled toxicokinetic studies in purpose-bred dogs and other laboratory animal species. Regulatory review of these data would include consideration of context and the recognized complexities of working within a naturally occurring disease model system. It is imperative that investigators actively engaged in comparative oncology studies both report and characterize unexpected adverse events they observe so as to understand and attribute these events fully.

Disclosure of Potential Conflicts of Interest

C. Khanna is an employee of Animal Clinical Investigation and Ethos Veterinary Health, and has ownership interests (including patents) at The Oncology Service. No potential conflicts of interest were disclosed by the other authors.

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