



HHS Public Access

Author manuscript

ILAR J. Author manuscript; available in PMC 2020 June 19.

Published in final edited form as:

ILAR J. 2010 ; 51(3): 214–220. doi:10.1093/ilar.51.3.214.

Modeling Opportunities in Comparative Oncology for Drug Development

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Abstract

Successful development of novel cancer drugs depends on well-reasoned scientific drug discovery, rigorous preclinical development, and carefully conceived clinical trials. Failure in any of these steps contributes to poor rates of approval for new drugs to treat cancer. As technological and scientific advances have opened the door to a variety of novel approaches to cancer drug discovery and development, preclinical models that can answer questions about the activity and safety of novel therapies are increasingly necessary. The advance of a drug to clinical trials based on information from preclinical models presupposes that the models convey informative data for future use in human patients with cancer. The study of novel cancer drugs using in vitro models is highly controllable, reproducible, relatively inexpensive, and linked to high throughput. However, these models fail to reproduce many of the complex features of human cancer. Mouse models address some of these limitations but have important biological differences from human cancer. The integration of studies using pet dogs with spontaneously occurring tumors as models in the development path can answer questions not adequately addressed in conventional models and is therefore gaining attention and interest in drug development communities. The study of novel cancer drugs in dogs with naturally occurring tumors allows drug assessment in a cancer that shares many fundamental features with the human cancer condition, and thus provides an opportunity to answer questions that inform the cancer drug development path in ways not possible in more conventional models.

Keywords

Cancer; comparative oncology; dog; drug development; preclinical model

Challenges Associated with Cancer Drug Development

The Need for More Predictive Preclinical Models

Most novel cancer drugs that enter human clinical trials fail to reach approval, largely because preclinical models used in development do not provide adequate information about the efficacy or toxicity of these new agents. More predictive models of efficacy in oncology are needed (Peterson and Houghton 2004).

Based on knowledge of the complexity of cancer, it should not be surprising that many models fall short of predictive. Indeed, given evidence from human clinical trials with novel anticancer drugs, it might be reasonable to conclude that in certain settings even human beings are not predictive models of cancer in humans. Cancer agents that successfully advance from phase II to phase III clinical trials are those that have demonstrated anticancer activity (i.e., measurable response in tumors) in human patients. The fact that very few of these successful phase II agents are approved as new oncology drugs (following phase III studies) suggests that the phase II human cancer population is not a strong predictive model of phase III human cancer studies. Closer inspection indicates that the problem is not so much whether human cancers are predictive but rather that the questions asked in phase II trials are quite distinct from those asked in phase III trials. Accordingly, when considering the evaluation of a novel therapy in a species distinct from humans, it is essential to (1) ensure that the questions asked in a preclinical model can be answered and (2) interpret the answers within the totality of available information.

Preclinical studies of the antitumor activity of novel cancer drugs require the selection of model systems that can answer specific questions to advance the drugs in the development path. Failure to consider whether a model can answer these questions often impedes or impairs development. Furthermore, it is increasingly necessary to use model systems that can assess a novel agent's anticancer activity both before and after use in human clinical trials. Such assessments typically rely on conventional transplantable murine models that are best suited to the study of traditional cytotoxic agents, whereas, particularly for targeted agents, these models may be less useful. For example, it may be inappropriate to assess the therapeutic index in a xenograft model when a drug interacts with the target differently in mouse versus human tissue. Inappropriate use of models may contribute to the high rate of late attrition of oncology drugs (relative to other categories of drugs) due to toxicity and lack of efficacy.

An ideal set of cancer models would replicate many of the complex features of human cancer (Cespedes et al. 2006) and answer critical questions early in the development path. Spontaneously occurring tumors in pet dogs provide an effective opportunity to address questions for which in vitro and murine models are inadequate (Table 1), as we explain below.

In Vitro Models—In vitro culture of human tumor cell lines has enabled countless discoveries related to carcinogenesis, tumor and radiation biology, cancer immunology, and cancer therapy. Indeed, the initial development of most anticancer agents critically depends on in vitro testing. There are several advantages of working with tumor cell lines in vitro.

Conditions can be highly controllable and results reproducible. It is possible to validate, repeat, and optimize assays based exclusively on scientific interest, unconstrained by the practical and ethical considerations necessary with in vivo models. Early in drug development, the low cost and high speed of in vitro assessments permit rapid screening of potentially active agents; and later in development, in vitro studies can be used to model the optimal features of lead agents and to link mechanisms of action with potentially valuable biomarkers for codevelopment with a novel agent.

There is thus no question that in vitro testing in oncology is essential, but it does not adequately model many features of cancer and is insufficient to predict efficacy in human cancer patients (Johnson et al. 2001). Growth of tumor cells in tissue culture selects for tumor cells that thrive in this artificial environment of high serum, growth factors, nutrients, and oxygen, most often in the context of 2-dimensional growth. These conditions are likely quite different from those of tumors in patients with cancer. Furthermore, it is difficult to faithfully model host-tumor interactions in tissue culture, and there is growing evidence that such interactions play a major role in tumor progression and response to therapy. The need to model the complex cellular interactions and biology of a heterogeneous tumor have led to the development of 3-dimensional conditions for in vitro cell growth, often using tumor-associated scaffolds and matrices in the context of nontumor cellular populations. Nonetheless, the use of tissue culture is inadequate to resolve questions about drug distribution in tumors, pharmacokinetics, pharmacodynamics, and toxicity.

Mouse Models—The growth of tumors in mice has been a fundamental part of cancer drug development for over 60 years (Woodhouse 1947). Human tumors have been grown in immunodeficient mice since 1969 and have played a major role in the preclinical development of cancer agents (Rygaard and Povlsen 1969). Advances in genetic engineering during the past 10 to 20 years have enabled the use of genetically engineered mouse models of cancer to study cancer biology (Abdulkadir and Kim 2005) and, to some extent, more recently to evaluate novel cancer therapeutics (Talmadge et al. 2007).

Mouse models of cancer allow for growth of tumors in 3-dimensional architecture with interaction of stromal elements and blood supply in a manner that is not seen in simple tissue culture. The relatively small size of mice and the speed with which they develop tumors after implantation make them suitable to rapidly study the effects of treatments. In the era of cytotoxic drug development, the activity of an agent in multiple xenograft models, independent of histology, was predictive of clinical activity in human patients (Kelland 2004; Voskoglou-Nomikos et al. 2003). However, responses in a specific histology in mice were not predictive of response in human patients with tumors of the same histology. In general, mouse models are biased toward false positive results and there are many examples where tumor responses seen in mouse models have not been predictive of human response to a cancer treatment (Schuh 2004).

The shortcomings of mouse models to adequately inform the development of new drugs are the result of several factors: biological differences between transplanted cancers in mice and cancers in humans (described below), the failure of investigators to ask appropriate questions of murine models, and inadequate consideration of comparative pharmacokinetics

between the mouse model and what is likely achievable in the human patient (we address the latter two factors in our discussion of phase I and II studies in the next section).

Important biological differences.: At the biological level, there are many respects in which mouse models are not faithful to the human condition and in fact are characterized by important differences that affect oncogenesis. For example, telomerase is functionally active in most murine cells but not in most human somatic cells (Kim et al. 1994; Prowse and Greider 1995). The effects of alterations to certain genes and pathways (including p53, Rb, and Ras) vary between murine and human cells (Rangarajan and Weinberg 2003). Differences in the oxidative metabolism of mice may produce different responses to DNA-damaging agents (Cespedes et al. 2006). Finally, in many instances, mice can tolerate higher concentrations of drugs and proteins than human patients and their bone marrow may be less sensitive to many cytotoxic agents (Teicher 2009).

Xenografts.: Xenografts derived from immortalized cell lines often have genetic drift and may not retain characteristics of the original human tumor (Cespedes et al. 2006). Thus in xenograft studies, the stromal, vascular, and immune system components are not syngeneic and so treatments that involve these elements may not replicate the condition seen in cancer patients. In addition, immunocompromised mice are not suitable for testing agents that may work through immune mechanisms or may be modulated through interactions with nontumor cell populations (Sharpless and Depinho 2006). And importantly, the major causes of death in human cancer patients, recurrence and metastasis, are difficult to replicate in mouse models used in drug development (Hansen and Khanna 2004).

Genetically engineered mouse models.: Advances in the field of genetically engineered mouse (GEM¹) models have created the opportunity to develop models that are more genetically and histologically similar to human cancers (Becher and Holland 2006; Sausville and Burger 2006). The tumor stroma, nontumor cell populations, and immune systems are syngeneic and more closely approximate the human condition than many transplantable murine models. Clearly, the use of GEM models in cancer research has greatly contributed to knowledge of cancer biology.

But drug development in these models has been more difficult. At the biological level, it remains difficult to replicate the multistep progression and clonal derivation of human tumors (Schuh 2004). Furthermore, GEM models may bias preclinical development toward drugs that target the known engineered genetic defects without translating to more genetically complex cancers in humans where a single genetic driver may not be evident. The development of tumors in GEM over time requires the use of such mice in either a “clinical trial” design or transplantation of GEM tumors in naïve mice. Intellectual property issues related to the OncoMouse patents have also constrained the use of GEM models in drug development. With these shortcomings in mind, the development of new cancer drugs in GEM models should be explored and integrated into the development path (for recent reviews on this opportunity, Olive and Tuveson 2006; Sharpless and Depinho 2006).

¹Abbreviation used in this article: GEM, genetically engineered mouse

The Unidirectional Preclinical-to-Clinical Development Path

The information gained from studying the effects of a novel agent in preclinical models may result in the selection of a lead agent for further exploration in clinical trials. The longstanding paradigm for clinical testing of a new drug is to begin with a phase I study, which is largely a safety and dose finding study, followed by single-arm, small (generally 30–70 patients) phase II studies to determine whether there is an antitumor effect (i.e., tumor shrinkage). Phase III studies then compare the new treatment (frequently as a single agent) to the existing treatment for the disease with overall survival as the “gold standard” endpoint (Gutierrez et al. 2009). This paradigm has served oncology and other fields well, but as cancer drug development shifts from cytotoxic to targeted therapies it may suffer from limitations that prevent promising agents from reaching the clinic. Among other things, phase I, II, and III studies frequently leave unanswered many questions about the optimal use of new drugs (Kummar et al. 2008).

The goals of phase I studies are to identify a maximum tolerated dose, define toxicities, and evaluate pharmacokinetics. The maximum tolerated dose is the recommended dose for phase II studies based on the assumption that therapeutic and toxic effects are related to each other and are caused by the same mechanism of action. But this may not be the case for targeted agents, which may have different mechanisms of the therapeutic and toxic effects and might be more effective at a lower dose for a longer period of time. Defining an optimal biologic dose for these agents may be more relevant but requires additional assays to assess effects on the intended target, a step that can be challenging to complete within the typical constraints of a phase I study (Gutierrez et al. 2009). Although safety is the primary consideration of a phase I study, some evidence of clinical activity is included in the decision to move a phase I agent to phase II. However, measurable or bulky tumors may not respond to noncytotoxic therapies within the exposure periods of most phase I studies, and thus promising novel agents may be overlooked.

Phase II studies have historically used response rate (i.e., decrease in tumor size) as a primary endpoint. But because many novel agents may be cytostatic rather than cytotoxic, the standard response evaluation criterion in solid tumors (Eisenhauer et al. 2009), which requires at least a 30% decrease in the longest dimension of a tumor to be considered a response, may be less appropriate than using an endpoint such as time to tumor progression (Gutierrez et al. 2009). However, a relevant comparison of time to progression or progression-free survival requires a randomized trial design.

Randomized controlled trials are necessary in the evaluation of a novel agent. For targeted agents, patient selection may be critical if the agent is likely to benefit only a particular subset of patients. A drug that is effective against only a subset of tumors with known mutations or other specific characteristics may fail in trials that do not specifically assess that group. Importantly, targeted agents with modest or even no observed activity in phase III trials may show synergy and be much more effective when used in conjunction with radiation, chemotherapy, or other agents. Single agent activity may no longer be a prerequisite proof of principle to warrant consideration in a multiagent regimen. Additionally, many of these agents may work best in the adjuvant or minimal residual

disease setting, which is less commonly assessed in initial phase III trials for a novel agent (Gutierrez et al. 2009).

Novel cancer treatments likely require a more integrated approach for optimal evaluation in preclinical and clinical settings. Such an approach requires recognition of the strengths and limitations of conventional and innovative in vitro and in vivo models in order to test questions in the most appropriate systems. The information gained from preclinical models should be used to inform the design of clinical trials. Furthermore, early clinical trials should not be viewed as merely a checkpoint that must be passed; instead, their results should yield new questions that can again be evaluated in the most appropriate setting, integrating the clinical and nonclinical aspects of drug development. With some of these questions, the systems discussed earlier in this review will not be sufficient to effectively or efficiently provide answers. In these cases, one option may be to design studies of tumors that occur naturally in large animals.

Spontaneously Occurring Tumors in Pet Dogs as a Model for Human Cancer

Advantages

Among the approximately 73 million pet dogs in the United States (APPMA 2006), cancer is the leading cause of death in older dogs—up to 45% in dogs 10 years or older (Bronson 1982). This prevalence provides an opportunity both to improve the health of such dogs and to inform the development of new cancer drugs through what is generally referred to as the comparative oncology approach, which relies on several key similarities between the species. Dogs and humans are relatively similar genetically and physiologically (Felsburg 2002; Goodstadt and Ponting 2006; Neyt et al. 1998)—for many cancer-associated genes, the sequences of dogs and humans are closer than those of mice and humans (Paoloni and Khanna 2008). In addition, pet dogs develop spontaneous tumors under similar environmental conditions to humans and in the framework of a syngeneic surrounding stroma and immune system. Furthermore, these tumors are frequently driven by the same or similar genetic aberrations. And dogs treated with the same chemotherapy drugs used in humans show similar cancer progression, resistance to therapy, and metastasis as in human cancers.

It is also worth noting that pet dogs with cancer can uniquely contribute to drug development because clinical trials in these animals are not subject to the constraints of human clinical trials. With few “gold standard” treatments for dog cancers, it is possible to evaluate investigational agents as first line therapies, in combination with other treatments, or as adjuvant therapy much earlier in the drug development process. For agents intended to work synergistically with radiation therapy, the use of pet dogs enables evaluation of a radiation modifying agent (sensitizer or protector) in a model that is radiobiologically similar to humans and can reveal answers to complex questions about the optimal schedule of administration of an agent during a fractionated radiation course. Correlative studies involving multiple sample collections, biopsies, and imaging may not be feasible in humans

but are possible in trials with dogs and can establish or confirm a mechanism or provide proof of concept to support further development of an agent.

Limitations

Limitations of this model include the fact that studies in pet dogs take longer to complete than rodent studies, in part because of the need to recruit and enroll dogs with spontaneously occurring tumors. Furthermore, the cost of studies in pet dogs and the quantities of drug needed are greater than those of rodent studies. In addition, a common histology or molecular target of interest may be less commonly seen or less well studied in dogs. Last, dogs may not tolerate the same dose intensity as humans without toxicity or they may be unusually sensitive to a drug or vehicle.

Evaluation of Toxicity

The evaluation of drug toxicology in dogs has been an important component of drug testing for many years. In such studies healthy dogs (typically beagles) receive an investigational agent in a controlled setting for assessment of pharmacokinetic and pharmacodynamic parameters as well as toxicity (Tomaszewski 2004). The assessment of drug safety should continue to include such controlled studies. Comorbid disease, age, and the effects of concomitant medications complicate attempts to perform controlled toxicity studies in pet dogs with cancer. Because such variables are similar to those seen in the human cancer population, differences in pharmacokinetics, pharmacodynamics, or the development of unexpected toxicities in these pet dogs may be informative. A recent review provides recommendations on the reporting of adverse events that may develop in comparative oncology studies (Khanna et al. 2009).

Comparative Oncology

Advances and Opportunities

For over 30 years comparative oncologists have demonstrated that studies of pet dogs with cancer can yield valuable information (for reviews, Paoloni and Khanna 2008; Porrello et al. 2006; Vail and MacEwen 2000). Recent studies have also established correlations between pharmacokinetics and pharmacodynamics, imaging, and efficacy endpoints in this naturally occurring cancer model (Paoloni et al. 2009; Vail et al. 2009).

Applications—Before testing in human patients, investigators who used a tyrosine kinase inhibitor in tumor-bearing dogs found a relationship between drug exposure and target modulation in tumor and antitumor activity (Liao et al. 2005). As a result, assessment of therapeutic index during long-term exposure to a new drug was possible in a way that could not be modeled by conventional strategies before first-in-human studies. The dog models also predicted the toxicities seen in human patients that receive these tyrosine kinase inhibitors (London et al. 2003).

Comparative oncology studies have also assisted in the development and validation of new medical devices. Dog models showed that helical tomotherapy devices can successfully image, position, and treat spontaneously occurring tumors (Forrest et al. 2004).

In addition, advances in genomics have revealed conserved genomic alterations in tumors of dogs and humans (Breen 2009; Breen and Modiano 2008). There is now an opportunity to use genomic and proteomic profiles to evaluate personalized medicine through a comparative approach.

Infrastructure Support—The development of infrastructure to facilitate comparative oncology studies has advanced in recent years. The Comparative Oncology Trials Consortium (COTC) was launched in 2004 through the National Institutes of Health National Cancer Institute as a collaborative effort with academic comparative/veterinary oncology centers to oversee and execute multicenter clinical comparative oncology trials. To further support this collaboration, a pharmacodynamic core was established to develop, validate, and assess pharmacokinetic, pharmacodynamic, and biological endpoints of COTC trials. Additionally, a data safety management board monitors trials and ensures the timely reporting of data and adverse events in these trials.

In 2007 the Canine Comparative Oncology and Genomics Consortium (www.ccogc.net) was established to encourage collaborations and to develop a repository for tissue biospecimens from dogs with cancer.

Challenges and Limitations

A comparative oncology approach may not be suitable for all agents or questions about agents in development. For investigators considering a comparative oncology trial, several issues require attention.

In contrast to xenograft and in vitro studies, comparative studies require the recruitment of eligible patients that are appropriate for answering the biological questions of interest; for example, although dogs develop a wide range of tumors, the incidence of some may be too low to adequately populate a trial. In addition, specific genetic and cellular aberrations in tumors in dogs are often similar to those in humans, but some known genetic aberrations in human tumors are distinct or less well studied in dogs. Continued investigation of the basic and comparative mechanisms of oncogenesis and malignancy of tumors in dogs and humans will help to identify the targets and approaches best suited to the use of this model.

The study budget must cover initial screening tests and potential expenses related to adverse effects in addition to standard study-related expenses. It can also be helpful to provide a stipend for additional cancer treatment for animals that complete the study. The number of dogs required for a trial, the inclusion criteria, the study schedule, and the potential acquisition incentives influence (and may extend) the timeline to complete a comparative trial.

All studies involving animals require approval by the institutional animal care and use committee to ensure the humane care and welfare of the animal subjects. Because comparative oncology trials use pets and require the informed consent of the pet owner, they must take special care to prioritize the medical care and well-being of the animals involved.² Guidance for appropriate conduct of comparative oncology trials and for federal regulation and oversight is available (Khanna et al. 2009).

Conclusion

Conventional drug development pathways are relatively unidirectional—agents are first considered in preclinical (in vitro and in vivo) models and then move sequentially through human clinical trials. With novel and targeted therapies, this method leaves unanswered many questions about the optimal use of these drugs. Translational studies in pet dogs are not subject to the same constraints as human trials and may therefore provide an opportunity to answer these questions in a more appropriate and predictive model system. The resolution of such questions could allow for improved lead agent selection and clinical trial design, the failure of fewer agents late in the development pipeline, and a better success rate for new oncology drugs.

Acknowledgments

We acknowledge the support of the National Cancer Institute intramural Center for Cancer Research and the active collaboration of the Comparative Oncology Trials Consortium.

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²Pet owners are frequently interested in pursuing investigational treatments for their dogs when conventional therapies do not meet their goals or when reduced costs associated with a study allow them to pursue care they may not otherwise be able to afford.

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Characteristics of an ideal cancer model and comparison of in vitro, murine, and canine models of cancerous tumors

Table 1

Ideal model	Cell culture	Mouse models	Spontaneous tumors in dogs
Shows histopathologic similarities to the human tumor	No	Variable	Yes
Progresses through the same stages as human cancer	No	Rarely	Yes
Exerts the same physiologic and systemic effects as human cancer	No	No	Yes
Involves the same genes and pathways as human cancer in initiation, progression, and metastasis	No	Variable	Frequently
Reflects the response of corresponding human tumors to particular therapies	Variable	Variable	Frequently
Allows assessment of the influence of germline genetic variation on tumor response to drug	No	No	Yes