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Veterinary oncology clinical trials: Design and implementation

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ABSTRACT

There has been a recent increase in interest among veterinarians and the larger biomedical community in the evaluation of novel cancer therapies in client-owned (pet) animals with spontaneous cancer. This includes novel drugs designed to be veterinary therapeutics, as well as agents for which data generated in animals with tumors may inform human clinical trial design and implementation. An understanding of the process involved in moving a therapeutic agent through the stages of clinical evaluation is critical to the successful implementation of clinical investigations, as well as interpretation of the veterinary oncology literature. This review outlines considerations in the design and conduct of the various phases of oncology clinical trials, along with recent adaptations/modifications of these basic designs that can enhance the generation of timely and meaningful clinical data.

Introduction

Clinical trials represent special kinds of cohort studies in which specific interventions are performed by investigators, using designs to improve the likelihood of observing effects that are free of bias. Specific types of clinical trials are defined by modifications of the basic component parts, namely patient selection, treatment allocation, intervention and outcome measurement.

In veterinary oncology, the goal of most clinical trials is to improve the standard of care for the treatment of a specific animal tumor type; however, an additional goal of veterinary cancer clinical trials can be to inform future human clinical trial designs; that is, a 'comparative oncology' approach, whereby companion animals with naturally occurring cancers are studied in trials that advance novel human therapeutics. Several recent editorials and review articles have discussed the potential of companion animals to serve as models for human disease (Mack, 2005; Khanna et al., 2006; Waters and Wildasin, 2006; Paoloni and Khanna, 2008).

The Comparative Oncology Trials Consortium at the US National Institutes of Health (NIH) National Cancer Institute (NCI) has completed multiple clinical trials with the intent of informing future human studies (Paoloni et al., 2009, 2010, 2014). To this end, several examples from the literature utilizing companion animals are referred to as 'preclinical' studies since physician-based oncology views veterinary data as such; however, as first-in-species veterinary trials, they are 'clinical' studies in the eyes of veterinarians. Ultimately, it is hoped that some of the advances made through inclusion of companion animals in these trials will advance the practice of veterinary oncology.

A major shift in cancer drug development, both in human and veterinary medicine, concerns the change from traditional cytotoxic agents to novel, targeted agents (Booth et al., 2003). While there is generally a clear relationship between dose and efficacy for most cytotoxic agents, this may not be the case for some targeted agents. This represents a switch from a primary focus on toxicity to one of identifying a dose that optimally inhibits a specific target (Kummar et al., 2006). In other words, the biologically effective dose (BED) may not equate with the maximally tolerated dose (MTD), which is the more traditional 'working dose' for efficacy trials. This also means that the early incorporation of pharmacokinetics (PKs) and validated pharmacodynamic (PD) assays for target modulation is becoming more important in trials for targeted agents.

This review focuses on clinical trial design and implementation, rather than statistical analysis of data generated in trials or in-depth statistical considerations in trial design. It cannot be stressed enough that competent biostatisticians should be consulted prior to implementing a study to ensure that statistical design and power are appropriate.

Traditional drug development phases

Traditionally, first-in-species trials start with a phase I dose-finding trial, followed by a phase II efficacy/activity trial, concluding with a phase III comparative trial that pits the novel agent against or with the current standard of care. The goals and salient points of each phase are summarized in Table 1.

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Table 1
Goals of phase I–III clinical trials.

Clinical trial phase	Primary goals	Secondary goals
Phase I (dose finding)	Determine maximally tolerated dose (or biologically effective dose)	Pharmacokinetic/ pharmacodynamic issues
	Define dose limiting toxicity	Scheduling issues
	Describe other toxicities	Preliminary efficacy data
Phase II (activity/ efficacy)	Determine activity/efficacy in defined populations	Estimate therapeutic index
	Inform the decision to move to a phase III trial	Expand toxicity data
		Evaluate additional dosing groups
		Expand PK/PD data
		Quality of life measures
Phase III (comparative)	Compare efficacy of a new drug or combination to current standard of care	Explore predictors of outcome
		Quality of life comparisons
		Comparative cost assessments

Phase I trials (dose-finding)

Phase I trial design and statistical considerations have been reviewed elsewhere (Acevedo et al., 2004; Kummar et al., 2006; Potter, 2006). The primary goal of phase I trials is to determine the MTD to be used in future studies, by evaluating safety, tolerability and dose-limiting toxicities (DLT) in treatment cohorts of increasing dose. Activity/efficacy is not a primary goal of phase I trials; response rates in phase I trials rarely exceed 10% (Potter, 2006). This is particularly important with respect to informed consent, since, even though human phase I participants are informed that they may be receiving a drug with minimal activity or at a suboptimal dose, 50% of humans entering phase I trials believe they will experience clinical benefit (Potter, 2006). Secondary goals of phase I trials may include scheduling issues, response/clinical benefit rate, biomarker development, PK information and PD effects.

Who enters phase I trials?

In human oncology, individuals entering phase I trials are generally refractory to standard-of-care therapy. Thus, these subjects are often heavily pretreated, and have advanced disease and poor performance status; they are seriously ill due to significant tumor burden or prior treatment. In veterinary oncology, the phase I subject may have failed standard-of-care, no meaningful standard-of-care exists or the standard-of-care is beyond the financial means of the client. For example, many veterinary phase I trials offer treatment at reduced cost and/or also have financial incentives in place that can be put towards standard-of-care therapy should the novel agent prove ineffective. This is truly a win–win situation in many respects for veterinary oncology clients and their animals.

Setting the starting dose

Generally, some preclinical data exist (in other than the target species) and these data are used to inform a starting dose for phase I trials (Kummar et al., 2006; Potter, 2006; Kamb et al., 2007). If other species (e.g. rodent) toxicity data exist, one third of the 'no observable adverse event level' (NOAEL) or one tenth of the highest nonseverely toxic dose (HNSTD) in the most sensitive species is used as a starting dose. If normal laboratory dog (usually Beagle) data are available, it is prudent to start at 50% MTD in Beagles, as they may be less sensitive to toxicity than tumor-bearing dogs, owing to differences in age, comorbidity or monitoring/observation practices. If the starting dose is too low, the length of the trial is longer, there is poor utilization of resources and the number of animals exposed to less than optimal doses is increased. If the starting dose is too high, there is a risk of severe adverse effects even in early cohorts.

Dose escalation strategies

As with the starting dose, escalation strategies greatly affect the number of subjects treated at a potential ineffective dose, the length of the trial and the risk of toxicity. The traditional method of escalation (Table 2) uses a 3 + 3 cohort design, where dose escalations are made with three subjects per dose level and the MTD is based on the number of subjects experiencing a DLT (Acevedo et al., 2004; Kummar et al., 2006; Potter, 2006). A DLT is defined as ≥ grade 3 toxicity in any category (except hematologic) according to predefined adverse event categories, such as the Veterinary Cooperative Oncology Group Common Terminology Criteria for Adverse Events (Veterinary Cooperative Oncology Group, 2011), and the Veterinary Radiation Therapy Oncology Group acute radiation morbidity scoring scheme (Carsten et al., 2008). Grade 4 is the cut-off preferred for the DLT for neutropenia (±thrombocytopenia) in human trials, since grade 3 hematologic events are usually considered to be manageable and transient (Von Hoff, 1998; Booth et al., 2003; Kummar et al., 2007). The MTD is defined as the highest dose level at which no more than 1/6 of the subjects develops a DLT. Traditionally, a fixed dose modified Fibonacci method of dose escalation is used, where the dose is escalated 100, 67, 50, 40 and then 33% of the previous dose as the cohorts increase. Similar to starting at a dose that is too low, if the escalations are too conservative, more subjects receive a sub-optimal dose; however, if the escalations are too rapid, more subjects are at risk for significant toxicity and the accuracy of the MTD is poor.

Alternative, 'accelerated titration' dose-escalation strategies have been suggested (Acevedo et al., 2004; Kummar et al., 2006; Potter, 2006). These include: (1) two-stage designs where initially single patient cohorts are used and dose is increased by a factor of 2 until a grade 2 toxicity occurs, then the second stage involves more traditional three patient cohorts and acceleration strategies; (2) within-patient escalation, where the same patient receives a higher dose on subsequent treatments until a DLT is observed; however, this may mask cumulative toxicity; (3) escalations based on PK parameters,

Table 2
Standard '3 + 3' phase I dose escalation scheme from the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Phase I protocol template.[a]

Number of patients with dose limiting toxicity at a given dose level	Escalation decision rule
0 out of 3	Enter three patients at the next dose level
≥2	Dose escalation will be stopped This dose level will be declared the maximally administered dose (highest dose administered) Three additional patients will be entered at the next lowest dose level if only three patients were treated previously at that dose
1 out of 3	Enter at least three more patients at this dose level. If 0/3 patients experience dose limiting toxicity, proceed to the next dose level If 1 or more of this group suffer dose limiting toxicity, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three additional patients will be entered at the next lowest dose level if only three patients were treated previously at that dose
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase II dose (maximum tolerated dose). At least six patients must be entered at the recommended phase II dose

[a] http://ctep.cancer.gov/guidelines/templates.html (accessed 23 November 2014).