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Invited review

Companion animals in comparative oncology: One Medicine in action

O.A. Garden[a,*], S.W. Volk[a], N.J. Mason[a,b], J.A. Perry[a]

[a] Department of Clinical Sciences and Advanced Medicine, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA
[b] Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, PA 19104, USA

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ABSTRACT

Comparative oncology is poised to have a far-reaching impact on both animals and human beings with cancer. The field is gaining momentum and has repeatedly proven its utility in various aspects of oncology, including study of the genetics, development, progression, immunology and therapy of cancer. Companion animals provide many advantages over both traditional rodent models and human beings for studying cancer biology and accelerating the development of novel anti-cancer therapies. In this review, several examples of the ability of companion animals with spontaneous cancers to fill a unique niche in the field of oncology are discussed. In addition, potential caveats of the use of companion animals in research are reviewed, as well as ethical considerations and efforts to standardize veterinary clinical trials.

Introduction

Cancer is a major cause of morbidity and mortality in companion animals (Landes et al., 1984; Albert et al., 1994; Misdorp, 1996; Moore et al., 2001; Bonnett et al., 2005; Egenvall et al., 2005; Vascellari et al., 2009; Adams et al., 2010; Di Cerbo et al., 2014; Miller et al., 2016). Epidemiological studies in dogs, the companion animal species for which most data are available, suggest that canine cancer kills 40–50% of individuals over the age of 10 years (Albert et al., 1994; Bonnett et al., 2005; Egenvall et al., 2005; Vascellari et al., 2009).

Cancer in dogs resembles cancer in humans in various ways, including: (1) its latency, clinical manifestation and metastatic potential; (2) its pathobiological characteristics, including tumour cell heterogeneity and permissive microenvironment; (3) its genomic instability and pharmacogenomic signatures, including chemoresistance; and (4) its multifactorial nature, including both genetic and environmental risk factors. The inability of murine models to recapitulate many of these characteristics of human tumours, and the frequent failure of such models to inform Phase II and III clinical trials, is increasingly being recognized. This has brought to light the huge potential value of spontaneous canine and, to a lesser extent, feline cancer in the drug discovery and validation 'pipeline', for the mutual benefit of all parties (Rankin et al., 2012; Alvarez, 2014; Ito et al., 2014; Fürdös et al., 2015; Riccardo et al., 2015; Richards and Suter, 2015). The term 'Comparative Oncology', the study of naturally occurring cancers in animals as models for human disease, has been coined. This 'One Medicine' approach to disease, espoused by luminaries such as Hippocrates, Plato, Virchow and Osler, promises to play a critical role in advancing cancer care for veterinary species and human patients, alike (Bradley, 1927; Teigen, 1984).

Bridging the gap between human patients and murine models: Spontaneously occurring cancer in companion animals

A mere 11% of anti-neoplastic therapies that demonstrate efficacy in murine models have been approved for human use, representing a very disappointing and expensive attrition of candidate therapies (National Academies of Sciences, 2015). Apart from the multiple failures of murine models to recapitulate the complexities of human cancer, murine bone marrow is generally less sensitive to chemotherapy-induced toxicity than human bone marrow, precluding the use of mice in the generation of safety data for novel chemotherapeutic agents. Furthermore, the microenvironment of tumours modelled in mice is often different in a number of ways from that of human cancers, resulting in overly favourable predictive responses to chemotherapy, radiation therapy and immunotherapy (Holden et al., 1997; National Academies of Sciences, 2015). Although rodents will remain a critical first province of preclinical research for cancer biology and therapeutics, their shortcomings and the need for additional animal models are being increasingly recognized.

There are numerous advantages of spontaneous large animal models that increase their clinical fidelity. Although companion animals are relatively outbred compared to laboratory rodents,

* Corresponding author.
E-mail address: ogarden@upenn.edu (O.A. Garden).

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selective breeding has led to breed predilections to particular cancers in dogs and cats, providing additional advantages in determining genetic susceptibility towards the development of many cancers. Client-owned dogs and cats living in non-laboratory settings are exposed to external and environmental factors (e.g. chemical toxins and second-hand smoke), and are susceptible to various disease states (e.g. obesity, diabetes mellitus) that may influence carcinogenesis and the treatment efficacy of chemotherapeutic agents or other therapies. In-bred strains and standardized experimental design in rodent studies may reduce the variability of results in initial exploratory studies. However, the heterogeneity that exists in veterinary species with spontaneously occurring cancer, at the animal and tumour levels, more closely models the heterogeneity that exists in human patients. Compared to rodents, basic biochemical and physiological processes of dogs more closely resemble those in human beings (Parker et al., 2010). The size of companion animals permits imaging and repeated biological sampling, manoeuvres that are difficult or impossible in rodent models, thereby increasing the ability to detect untoward side effects of novel therapies and minimizing both veterinary and human patient risk. Finally, the increase in demand for sophisticated, state of the art, care for animal companions has led to a surge in clinical trials in veterinary species, which provide a unique opportunity for assessing both efficacy and safety of novel cancer therapies.

Given the recent interest and success in the human immuno-oncology field, it follows that one of the strongest arguments for the integration of veterinary species into the drug development pipeline is their propensity to develop tumours spontaneously in the presence of an intact immune system. The significant barriers to effective immune therapy, particularly in solid tumours, can only be recapitulated in immune competent animals with naturally occurring tumours. In many instances, the permissive tumour microenvironment develops as the tumour co-opts the immune response, driving cells of both the innate and adaptive immune system to become regulatory in nature rather than tumouricidal (Tominaga et al., 2010; Goulart et al., 2012; Pinheiro et al., 2014). Tumours developing in the presence of an intact immune response are sculpted by that response, resulting in the emergence of edited tumours that are invisible to anti-tumour T cell-mediated immunity. Furthermore, dogs with advanced cancer exhibit intrinsic T cell defects and T cell exhaustion, which pose significant barriers to effective induction and maintenance of anti-tumour immunity (Coy et al., 2017). Lastly, side effects associated with profound immune activation, including cytokine release syndrome and autoimmunity, present significant challenges in clinical case management in the human immuno-oncology field. These effects are likely to be recapitulated in veterinary species, enabling investigation of the safety of novel immune therapies and the effectiveness of strategies aimed at preventing these adverse effects (Bergman et al., 2006).

Current drug development pipeline

Costs, success rates and clinical trials

The development of new cancer therapies is protracted and expensive; 16 years and a staggering US$1.8 billion[1] may be required to bring a new therapeutic agent from target validation to the marketplace (Paul et al., 2010). Attrition rates for therapies in oncology are also significantly higher than those in other therapeutic areas; approximately 59% of anti-neoplastic drugs entering Phase III clinical trials fail, more often as a consequence of therapeutic inefficacy than toxicity (Kola and Landis, 2004; Hay et al., 2014). In the conventional drug development pathway, Phase I human clinical trials are used to assess toxicity and dose, Phase II trials explore anti-tumour activity and Phase III trials compare outcomes of patients treated with the new agent vs. standard of care. Therapies demonstrating better outcomes than the standard of care emerge successfully from this pipeline, but its reliance on preclinical murine models that poorly predict efficacy and toxicity, and its largely linear, non-iterative trajectory, markedly limit the frequency of success using this strategy.

A superior paradigm is clearly needed. An integrated model, in which comparative studies are undertaken immediately before or after Phase I human clinical trials to help predict pharmacokinetic (PK) and pharmacodynamic (PD) properties, as well as dosing regimens, is likely to reduce attrition and cost considerably (Paoloni and Khanna, 2008). To this end, the National Cancer Institute (NCI) established the Comparative Oncology Program (COP) and, under this initiative, the Comparative Oncology Trials Consortium (COTC) in 2003 to provide the infrastructure to integrate data derived from clinical trials in cancer-bearing companion animals into the development pathway of new drugs, devices and imaging modalities for human cancers (Paoloni et al., 2009b). This bold initiative has already begun to be successful, as the exemplars in the next section will showcase, supporting the promise for this approach to change the trajectory of veterinary and human cancer clinical care.

Comparative oncology and One Medicine

Cancer in dogs: Pathobiology, genomics and pharmacogenomics

Of the companion animals, the dog is the species in which the discipline of comparative oncology has shown the most growth (Gordon et al., 2009; Di Cerbo et al., 2014; Fürdös et al., 2015). Cancer in dogs often shares clinical, histopathological and molecular similarities to cancer in humans. The shorter lifespan of dogs and the generally faster progression of cancer in this species also allows more timely assessment of clinical outcomes. The growth and metastatic patterns of many canine cancers mimic those for human malignancies. Examples include osteosarcoma (OSA), with its propensity for metastasis to the lungs, and mammary carcinoma, with its risk of metastasis to local lymph nodes, lungs and other distant sites, and the influence of hormones (MacEwen, 1990; Vail and MacEwen, 2000).

Drivers of oncogenesis are also similar between many cancers in human beings and dogs. Inconsistencies in specific driving mutations have been noted within particular human and canine cancer histopathological types, thereby allowing for the study of particular mutations independently of tumour type. As an example, while a large proportion of human cases of malignant melanoma (Pollock and Meltzer, 2002) and histiocytic sarcoma (Go et al., 2014) are positive for *BRAF* mutations, such mutations are rare within these tumour types in dogs (Mochizuki and Breen, 2015). In contrast, *BRAF* mutations are very common (almost pathognomonic) in urothelial (transitional cells) carcinoma of the canine urinary bladder and prostate gland (Mochizuki and Breen, 2015; Mochizuki et al., 2015). The ability to study the effects of certain molecular phenotypes across various histopathological types between species is likely to shed light on mechanisms of carcinogenesis, metastasis and chemosensitivity or resistance.

The dog also affords a rich resource for the genetic dissection of cancer by virtue of the distinctive breed structure of the species. This is characterized by striking heterogeneity between, but minimal heterogeneity within, breeds, coupled with the known predisposition of particular breeds to certain cancers (Dobson,

[1] US$1.00 = £0.78 = €0.87 as at 21st August 2018.