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Comparative oncology: Integrating human and veterinary medicine

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Abstract
Cancer constitutes the major health problem both in human and veterinary medicine. Comparative oncology as an integrative approach offers to learn more about naturally occurring cancers across different species. Canine models have many advantages as they experience spontaneous disease, have many genes similar to human genes, five to seven-fold accelerated ageing compared to humans, respond to treatments similarly as humans do and health care levels second only to humans. Also, the clinical trials in canines could generate more robust data, as their spontaneous nature mimics real-life situations and could be translated to humans.
Keywords: Canine, Human, Oncology.

Introduction

It has been an aspiration of scientific research to comprehend cancer so to reach a better diagnosis, prevention, and treatment. The exchange of knowledge and practices between human and animal researchers is becoming more common and fruitful. This comparative approach has a promising role in clinicopathological and therapeutic studies. Comparative oncology helps us to study disease pattern, inheritance, genetic history and correlation of a disease between two or more than two distinct species. It integrates the naturally occurring cancers in veterinary patients with more general studies of cancer biology and therapy in humans. Malignant disorders constitute major health problem both in human and veterinary medicine (Singer *et al*., 2014). Various historical studies suggest that the canine tumours could be informative in studying human cancers (Davis and Ostrander, 2014). However, the comparative approach of treating human and animal patients is a novice concept which has been initiated recently (Paoloni and Khanna, 2008; Gordon *et al*., 2009). Although, the world is witnessing awareness in comparative oncology but the knowledge is not translated among cancer researchers. India is still far behind in such studies. In order to uptake such a study, collaborations across fields of veterinary and human medicine must be encouraged.

Animal models and cancer research

Animals as biological models have played a very basic role in explicating the physiological and biochemical processes involved in onset, promotion and progression of cancer. Obviously, because of the practical and ethical issues with human experimentation, animals are essential in cancer research. In vitro (test tube and cell culture) and in vivo (animals) studies are required to determine the justification for drug development. Prior animal testing is required by the Food and Drug Administration (FDA) before a new molecular entity is tested in humans. The final aim of the cancer researchers is to translate their findings into practical applications. Experimentally, tumours are raised in laboratory animals like rodents which facilitate newer insights into diagnostic and therapeutic arena (Mak *et al*., 2014). Presently animals are used worldwide to test the safety, toxicity and therapeutic potential of drugs (Cook *et al*., 2012). Despite the importance of animal models, there are molecular and physiological limitations which question their utility. A large proportion of clinical trials for new drugs fail and the majority of such trials are for cancer drugs (Arrowsmith, 2011; Ledford, 2011). These failures generally occur because of the molecular mechanisms of the drugs involved, unaccepted toxicity or poor efficacy (Simon, 2008). The limitations in animal research are becoming more evident as the laboratory animal models fail to make reliable predictions about human clinical trials (Perel *et al*., 2007). Such studies generally overestimate the effectiveness of the treatment as the negative results are usually not published (Sena *et al*., 2010). Also, much of the data obtained from mouse or other laboratory animal models is not reproducible in human clinical conditions (Marchetti and Schellens, 2007). Although the in vitro models have helped us to understand molecular pathways of cancer, they don't model adequately the spontaneous human tumours because of limitations like selective transformation with a selection of certain gene sets, morphologic characters, and functions (MacLeod *et al*., 1999; Masters, 2002). The mouse has been the most frequent model for genetic studies in mammals

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with advantages like small size, average lifespan of about 2 years, short gestation period and inexpensiveness in contrast to other mammals but it has got significant limitations when used to study complex human diseases (Paigen, 1995; Strauch *et al*., 2003; Gondo *et al*., 2009; Seok *et al*., 2013). There are genetic, immunological and cellular differences between human and mice which make it a poor model for cancer study (Schuh, 2004). Many spontaneous diseases in humans must be induced in laboratory mice but it is very difficult to study polygenetic conditions and interactions between multiple genes (Karlsson and Lindblad, 2008). Certain features of human cancer like long latency periods, heterogeneous macro- and micro-environment and genetic instability cannot be modelled in mouse. Also, metastasis and recurrence cannot be easily explained in this conventional model of cancer. Furthermore, the induced cancers in mice mostly have active telomerase (Kim *et al*., 1994; Prowse and Greider, 1995), have altered pathways and the mice can tolerate higher levels of drug concentrations with less sensitive bone marrow than human patients (Teicher, 2009). Other limitations like laboratory settings, use of inbred strains and using artificial disease in an otherwise normal animal can have profound effects on the experimental results (Chesler *et al*., 2002; Karlsson and Lindblad, 2008). In addition, genetic modifications in transgenic mice and different environments produced by the xenografts can increase the differences apart from the evolutionary remoteness between human and mice (Hovey *et al*., 1999; Balkwill *et al*., 2005; Goswami *et al*., 2005; Schwertfeger *et al*., 2006).

Advantages of spontaneous canine tumours

When a model is similar to human beings and has the ability to mimic the human pathological conditions, it becomes a good option to utilise this model. Cancer is a complex disease which develops naturally in canines (Starkey *et al*., 2005). It is the leading cause of death in canines of greater than 10 years of age (Adams *et al*., 2010; Gardner *et al*., 2016). Human cancers such as lymphoma, mammary carcinoma, osteosarcoma, soft tissue sarcomas are also diagnosed and reported in dogs (Khanna *et al*., 2006; Merlo *et al*., 2008). Similar clinical parameters like organ function tests, cardiac changes, blood pressure can be taken in dogs as in humans. Dog and human have comparable drug metabolic processes and the hepatic enzyme homology of dogs is more similar to humans than to rodents, thus the canine model is considerably suitable for toxicological studies (Smith *et al*., 2002). There are striking similarities between dog and human diseases like cancer, cardiac disorders, eye diseases, epilepsy, deafness and disorders like obsessive-compulsive disorder (Loscher *et al*., 1985; Overall, 2000; Vail and MacEwen, 2000; Khanna *et al*., 2006; Gershwin, 2007). Canines suffer spontaneously from tumors which mirror the characteristics like histopathology, clinical manifestation, metastasis, recurrence, genetic predisposition and patterns of response or resistance to treatment similar to those found in human beings (McEwen, 1990; Hahn *et al*., 1994; Vail and McEwen, 2000; Paoloni and Khanna, 2008; Schiffman and Breen, 2015). Since the nature of the disease is spontaneous, the complex tissue interactions can be studied which is otherwise difficult to study in other animal model systems. Ethical concerns, as seen with induced cancer models, are not involved while treating canines with naturally occurring cancers.

In veterinary practice, short-term sedation or anaesthesia is commonly used for physical checkups and diagnostic purposes. It makes canines suitable for serial biopsies in comparative oncology trials and thus can help to understand cancer biology and validate the tumour biomarkers which can be correlated with response in ways that are usually not feasible in classical preclinical rodent studies or in human cancer trials. Dogs have a short lifespan and depending upon the breed, the ageing process is five to sevenfold in comparison to human beings (Priester, 1977). This helps to study the clinical condition over a shorter period of time resulting in the earlier assessment of drug activity and toxicity which are critical for future clinical trials in veterinary and human medicine. Also, the companion dogs remain with their owners until their old age (Cummings *et al*., 1996; Bonnett and Egenvall, 2010). Thus the use of canine population gives doctors and researchers a better resource for understanding the therapeutic outcomes in patients who live in our houses, experience same environment and sometimes eat what we eat. They could even serve as sentinels to detect carcinogenic substances in our homes and surroundings.The completion of the canine genome project and the evolution of newer technologies have expanded the scope of comparative oncology. Looking into the canine genome it seems that approximately 19,000 genes match to similar or orthologous genes in the human genome (Lindblad-Toh *et al*., 2005; Parker *et al*., 2006). The canine genome shows higher homology and close similarity with human genome in comparison to rodent genome which highlights the relevance of canine models in comparative oncology.

Challenges in the path of comparative oncology

Under Indian conditions, the human cancer research organisations are usually not interested in comparative canine oncology studies and the funding opportunities are almost trivial/ negligible. The pet owners have a feeble understanding of the crucial role of preclinical animal models and the opportunity of their companion animals to take part in inter-species clinical discoveries. The understanding of genetic changes/mechanisms which result in human cancers is far higher than those

which cause canine cancers. This lack of genetic knowledge of canine cancer is a major gap in comparative oncology and translational drug development (LeBlanc *et al*., 2016). The veterinary academic centres generally lack imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) which would otherwise be helpful in comparative oncology. In human medicine, there are various registries which collect information on incidence, prevalence, risk factors, and survival over space and time. While in human medicine the cancer registries evolved since 1940s, veterinary cancer registries were established from 1961 (Stratus *et al*., 1976) and existed in small numbers, sporadic in nature and some became nonfunctional. European and American countries have cancer registries for humans and companion animals in order to document all reported cases of cancer. In India, there is no veterinary cancer registry at present compared to many in human oncology. For example, Indian Council of Medical Research has cancer registries which assemble statistics relating to cancer mortality and trends for the whole country. However, nothing like this exists in veterinary science.

Recommendations for a successful outcome

Veterinary colleges constitute the best option to select and manage canine patients for translational studies and can help in better understanding of cancer biology, assessment of novel treatments, devices, and imaging techniques by involving companion animals with naturally developed cancers. Academic institutions, veterinarians and doctors in the clinical practice and industrial research must be included in the translational research and development. Veterinary cancer registry can be a strong advocate for companion animals as natural models for oncological studies. These registries could help to connect oncologists and researchers with common interests and to educate pet owners about the ongoing clinical trials. A centralised clinical trial registry would help owners and veterinarians to start trials for pets suffering from cancer. However, the affirmation of animal welfare is critical for the success of such a process.

There should be something similar to The Cancer Genome Atlas project (TCGA) in canines in order to address the genetic gap in comparative oncology and to provide high quality readily available data (LeBlanc *et al*., 2016). Attempts should be made to provide facilities for tumour banks which preserve tumour tissues and other biospecimens. Such banks have a high potential for supporting translational research. Diagnostic modalities like MRI, PET, and CT should be introduced in veterinary practice in order to fill up the technology gap. With the utilisation of new tools and techniques, the possibilities of comparative and translational applications will become a reality. Canines can benefit from the new discoveries made in human oncology and human research can, in turn, get inputs through canine cancer models from pre-clinical studies (Fowles, 2017).

Integrating veterinary and human clinical trials

Clinical trials in companion animals are not hindered by traditional Phase-I, Phase-II and Phase-III trial designs (Gordon *et al*., 2009) which allows pet owners to seek novel therapeutics for their pet if the conventional treatments do not meet their goals. Veterinary clinical trials have the potential to be integrated with human clinical trials in a comparative approach which can improve the drug development cycle (Fig. 1). Adding comparative oncology studies in pre-clinical settings can help to identify and cull the unfavourable and inferior drugs or drug targets at an early stage. This will help to identify those drugs or drug targets that are most likely to be working. It can also provide information about the pharmacokinetics and pharmacodynamics of the candidate drug before it enters the actual human trials. Table 1 contains some examples of spontaneous canine cancers which can be used as models for corresponding human cancers and have been used or have the potential to be utilised in anticancer drug developmental process. Using pet dogs can drastically reduce the number of human participants entering in Phase-I, II and III trials. This can increase the success rate in Phase III trials and drastically reduce the costs and potential risks in drug development.

Shared cancers between humans and dogs

Osteogenic sarcoma or osteosarcoma is an aggressive malignant neoplasm of bone. It shows the highest prevalence in teenagers and young adults (Mirabello *et al*., 2009). Similar to humans, osteosarcoma (OSA) is the most common bone tumour diagnosed in dogs and typically affects the middle-aged group. Dog breeds that are at higher risk of developing OSA include Rottweiler, Great Pyrenees, Mastiff, Dobermann Pinscher, Irish wolfhound, and Scottish deerhound (Schiffman and Breen, 2015). However, the incidence in dogs is 10-fold greater in comparison to humans (Ru *et al*., 1998). As OSA is rare in human population it poses a major challenge to the progress of human clinical trials. However, the higher number of osteosarcomas diagnosed in canine population and the interest of pet owners to take part in clinical trials gives an immense opportunity to the advancement of studies for this condition in both species. Humans develop OSA at similar sites as in dogs and have similar histology and response to therapeutics (Withrow and Wilkins, 2010). Thus, a dog can act as a good model for human OSA. Dogs have been used in clinical trials for developing limb salvage techniques that are presently used in human (LaRue *et al*., 1989).

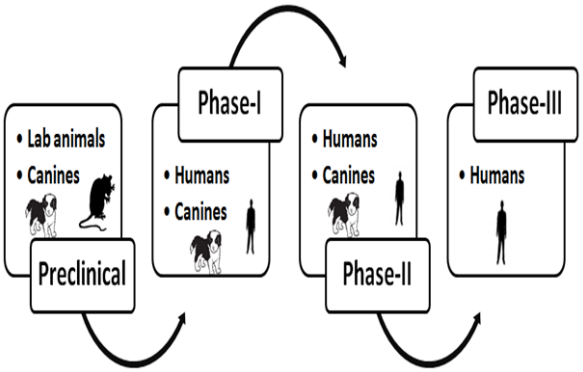

Fig. 1. Integration of veterinary and human clinical trials in drug development process.

Table 1. Spontaneous canine tumours that can model for human cancers and play a role in drug development.

Tumor	Role in drug development
Osteosarcoma	Limb salvage techniques (LaRue *et al*., 1989) Rapamycin (Paoloni *et al*., 2010) Liposome-encapsulated cisplatin (SPI-77) (Vail *et al*., 2002) Tyrosine kinase inhibitor (London *et al*., 2003)
Bladder cancer	Carboplatin (Chun *et al*., 1997) Piroxicam (Knapp *et al*., 1992)
Breast cancer	BCG combined with surgery (Parodi *et al*., 1983) Immunotherapy (Teske *et al*., 1998)
Non-Hodgkin's lymphoma	Liposomal L-asparaginase (MacEwen *et al*., 1992) Antiangiogenic thrombospondin-I peptide (ABT526) (Rusk *et al*., 2006)
Soft tissue sarcoma	Antiangiogenic thrombospondin-I mimetic peptides (Sahora *et al*., 2012) Hyperthermia combined with irradiation (Gillette *et al*., 1992)

Apart from these, canine osteosarcomas show overexpression of IL-8 and SLC1A3 which are related to poor outcome of human osteosarcoma (Paoloni *et al*., 2009). In a comparative study new genes (CDC5L, MYC, RUNX2 and CDKN2A/CDKN2B), that had not been described previously, were revealed in addition to genes (ADAM15, CTC1, MEN1, CDK7) with the known association in osteosarcoma (Angstadt *et al*., 2012).

Altered signalling pathways involving Wnt, cytokine, apoptosis signalling, interleukin, and Ras were reported in both canine and human OSA (Selvarajah *et al*., 2009). Thus, studying canine osteosarcoma and the application of new techniques will help reveal the mis-expression of other genes involved in human osteosarcoma.

Bladder cancer, also known as transitional cell carcinoma (TCC) or urothelial carcinoma (UC) and affects both canines and humans (Higuchi *et al*., 2013; Park and Hahn, 2014). TCC comprises about 2% of all malignant tumours in dogs (Meuten and Mueten, 2014). Canine TCC closely mimics the human invasive bladder cancer in various features like the microscopic features, biological behaviour and response to treatment (Knapp *et al*., 2000).

Canine and human bladder cancers have been found very similar at the level of transcriptome alterations (Ramsey *et al*., 2017). Cyclooxygenase-2 (Cox-2) has been found to be overexpressed in both human and canine bladder cancer (Mohammed 1999, Shirahama 2000; Cekanova *et al*., 2013). Cox inhibitors used in canine bladder cancer treatment have resulted in studies involving human bladder cancer (Knapp *et al*., 2014). 90% of human bladder cancers show telomerase activity (Chen and Chen 2011; Eissa *et al*., 2013). Similarly, such activity has been reported in canine TCC cell lines and clinical cases (McCleary, 2010). Hematuria and changes in urinary habits are common clinical signs in both the species. Bladder cancer is generally diagnosed in older people and dogs. The median age at diagnosis in dogs is about 11 years while as in humans it ranges from the early 60s to 70s (Knapp *et al*., 2014). These values are almost equivalent on conversion scale of ages between dogs and humans (Patronek *et al*., 1997)

The mammary tumour is the leading cause of cancer deaths in women followed by lung cancer (Jemal *et al*., 2011). In canines, mammary gland tumours are second most frequent neoplasms after skin tumours which account for greater than 50% of the diagnosed tumours (Chang and Elledge, 2001; Sorenmo *et al*., 2003). The annual incidence rate of mammary cancers in both species is comparable.

The average onset age of mammary tumours in humans is after 40 years (Lilienfeld, 1963) and in dogs, it is after 6-7 years (Cohen *et al*., 1974). These ages are almost same on the comparative scale (Patronek *et al*., 1997). Literature reveals many similarities between mammary tumours of both the species. The role of hormonal influence in breast cancer carcinogenesis has been recognised both in canines (Donnay *et al*., 1995) and humans (Bernstein, 2002).

At the molecular level, there is overexpression of steroid hormone receptors like oestrogen (ER) and progesterone (PR) (MacEwen *et al*., 1982; Rutteman *et al*., 1988). The degree of tumoral differentiation is related to the presence of ER (Block *et al*., 1975; MacEwen *et al*., 1982). Transformation-related protein-53 (TRP53) gene plays a crucial role in preventing cancer occurrence and is the most frequently altered gene in human cancer (Surget *et al*., 2013). In mammary tumours in both species, the frequency of P53 mutation is same (20%) (Lee *et al*., 2004; Kim *et al*., 2010).

Canine simple carcinomas histologically mimic typical human breast carcinomas and could serve as a cancer model for basal-like tumours (Liu *et al*., 2014). These features support the use of canine mammary tumours as a spontaneous tumour model with diverse translational value to human mammary carcinogenesis.

Lymphomas are cancers of the lymphatic system and affect lymphocytes. Lymphomas are of two types Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). The incidence of lymphoma is almost similar in humans and dogs (15.5-29 vs 15-30 per lakh, respectively) (Vail and MacEwen, 2000; Hansen and Khanna, 2004). Lymphoma of B-cells is the most common type of NHL in humans and dogs (Hansen and Khanna, 2004). There is a similarity in tumour behaviour and genetic alterations between dogs and humans, suggesting common pathways or pathological basis of lymphoma (Breen and Modiano, 2008) and allows the use of WHO criteria for the better classification of canine tumours (Vezzali *et al*., 2010). Thus, there is a great scope for using dogs with lymphoma in the evaluation of therapeutics for both human and veterinary purposes.

Soft tissue sarcomas (STS) like angiosarcoma, liposarcoma, fibrosarcoma, epithelioid sarcoma, histiosarcoma are genetically complex cancers which show high variability in their clinical picture and cellular morphology. These cancers are usually uncommon and account for less than 1% of newly diagnosed cancers in humans (Krikelis and Judson, 2010). In order to study STS in rodent models experimental induction is generally needed but in contrast, the dog represents an excellent model for such cancer because of spontaneous occurrence and similar genetic complexity (Aguirre-Hernandez *et al*., 2009). Numerous similarities, like the histological classification and pathogenesis, between canine and human rhabdomyosarcoma, have been reviewed (Caserto, 2013). Thus, the canine model has a clear edge over other models for studying human STS.

Conclusion

Considering the failures in cancer drug development and the complexity of cancer biology, the laboratory models of cancer suffer from some serious limitations. Pet dogs can be utilised as a unique model of cancer owing to their genetic relatedness to humans besides spontaneous occurrence of cancer. Utilisation of canine models, however, requires collaboration across different fields of human and veterinary medicine like genetics, molecular biology, pharmacology, epidemiology, and a series of other disciplines. This integrative and comparative study could promote research leading to novel treatments and improved health care for humans and their companion animals.

Conflict of interest

The authors declare that there is no conflict of interests.

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