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 novel 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 (Cummins et al., 1996; Bonnett and Egervall, 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, Doberman
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).
Altered signalling pathways involving Wnt, cytokine, apoptosis signalling, interleukin, and Ras were reported to be related to poor outcome of human osteosarcoma (Paoloni et al., 2003). The Wnt/β-catenin pathway is a major prerequisite for osteosarcoma development 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 mammory tumour is the leading cause of cancer deaths in women followed by lung cancer (Jemal et al., 2011). In canines, mammory 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 mammory cancers in both species is comparable. The average onset age of mammory 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 mammory 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 mammory tumours in both species, the frequency of P53 mutation is same (20%) (Lee et al., 2004; Kim et al., 2010).

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).

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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 rhabdomysarcoma, 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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