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Canine sarcomas as a surrogate for the human disease

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ABSTRACT

Pet dogs are becoming increasingly recognized as a population with the potential to inform medical research through their treatment for a variety of maladies by veterinary health professionals. This is the basis of the One Health initiative, supporting the idea of collaboration between human and animal health researchers and clinicians to study spontaneous disease processes and treatment in animals to inform human health. Cancer is a major health burden in pet dogs, accounting for approximately 30% of deaths across breeds. As such, pet dogs with cancer are becoming increasingly recognized as a resource for studying the pharmacology and therapeutic potential of anticancer drugs and therapies under development. This was recently highlighted by a National Academy of Medicine Workshop on Comparative Oncology that took place in mid-2015 (http://www.nap.edu/21830). One component of cancer burden in dogs is their significantly higher incidence of sarcomas as compared to humans. This increased incidence led to canine osteosarcoma being an important component in the development of surgical approaches for osteosarcoma in children. Included in this review of sarcomas in dogs is a description of the incidence, pathology, molecular characteristics and previous translational therapeutic studies associated with these tumors. An understanding of the patho-physiological and molecular characteristics of these naturally occurring canine sarcomas holds great promise for effective incorporation into drug development schemas, for evaluation of target modulation or other pharmacodynamic measures associated with therapeutic response. These data could serve to supplement other preclinical data and bolster clinical investigations in tumor types for which there is a paucity of human patients for clinical trials.

Contents

Abbreviations: CSA, chondrasarcoma; FSA, fibrosarcoma; GI, gastrointestinal tract; GIST, gastrointestinal stromal tumors; GWAS, genome wide association studies; HS, histiocytic sarcoma; HSA, hemangiosarcoma; IHC, immunohistochemistry; LIP, liposarcoma; LMY, leiomyosarcoma; LYA, lymphangiosarcoma; MYX, myxosarcoma; OSA, osteosarcoma; PNST, peripheral nerve sheath tumors; PWT, peri-vascular wall tumors; RMS, rhabdomyosarcoma; SCS, synovial cell sarcoma; STS, soft tissue sarcoma.

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1. Introduction

Neoplasia is the leading pathophysiologic process responsible for death in 70 of 81 dog breeds and in mixed-breed dogs in North America. The breeds in which cancer is responsible for >40% of deaths include the Bernese Mountain Dog (55%), Golden Retriever (50%), Scottish Terrier (48%), Bouvier des Flandres (47%), Boxer (44%), Bullmastiff (44%), Irish Setter (41%), and Airedale Terrier (40%). Breeds with a low prevalence of cancer caused death include the Maltese (9%), Dachsund (9%), Pekingese (8%), Pomeranian (8%), Chihuahua (8%), Miniature Dachsund (6%) and Miniature Pinscher (4%). Standard breed height or weight correlates with the frequency of deaths from cancer (Fig. 1); the average weight of the breeds with a >40% cancer-caused deaths is approximately 31 kg whereas the average weight of the breeds with a <10% cancer-caused deaths is 5 kg. Overall, it is estimated that ~30% of dogs die from cancer, with the data from pure-breed dogs showing 27.2% and an analysis of nearly 18,000 mixed-breed dogs showing 27.6% (Fleming, Creevy, & Promislow, 2011). These numbers reflect not only the large cancer burden in dogs but also reveal a population of spontaneously arising tumors whose treatment may be incorporated into cancer research and drug development strategies as an advanced surrogate prior to or in coordination with human trials.

The treatment of dogs with cancer is largely quite similar to humans, with the "triumvirate" of surgery, radiation therapy and chemotherapy forming the mainstay of treatment options. Surgical approaches are generally more conservative than those used in humans, and radiation and chemotherapy dose intensity is generally reduced compared to regimens in humans. This may be responsible in part for the inferior clinical outcomes generally observed in dogs versus humans. Recently, a limited arsenal of "targeted" agents and immunotherapies has become available in veterinary oncology, but the available agents are much more limited compared to human treatment options. The majority of medical therapies used for canine cancer treatment are older therapies for which generics are available. Newer agents are rarely used clinically, largely owing to cost constraints and a lack of dosing, safety, and efficacy information in dogs.

2. Sarcomas in dogs

Sarcomas make up approximately 10–15% of malignant tumors in dogs, with 20% of these tumors originating in the bone and the other 80% representing soft tissue sarcomas (STS). The total number of canine sarcomas occurring in the United States annually is estimated to be 7700 to 31,800 based on an estimated overall cancer incidence of 99.3–272.1 per 100,000 dogs (Merlo et al., 2008) and a canine population in the US of 78 million. The relative incidence and estimated incidence in the US of specific sarcomas in the dog are shown in Table 1. The major non-STS are represented by osteosarcoma (OSA) and chondrosarcoma (CSA). The primary STS in dogs are hemangiosarcoma (HSA), fibrosarcoma (FSA), peripheral nerve sheath tumors (PNST) and histiocytic sarcoma (HS), with myxosarcoma (MYX), liposarcoma (LIP), rhabdomyosarcoma (RMS), leiomyosarcoma (LMY), synovial cell sarcoma (SCS) and lymphangiosarcoma (LYA) occurring with much lower incidence (Bastianello, 1983; Dorn, Taylor, Schneider, Hibbard, & Klauber, 1968; Gruntzig et al., 2016; MacVean, Monlux, Anderson, Silberg, & Roszel, 1978). For comparison, it is estimated that there will be 12,390 STS diagnosed in adults and children in the United States in 2017 and approximately 200 cases of OSA in children (Society, 2017).

2.1. Overview of canine soft tissue sarcomas

Hemangiosarcoma represents one of the primary STS in dogs and occurs primarily in the spleen, heart, liver, and the skin and subcutis (Brown, Patnaik, & MacEwen, 1985; Hargis, Ihrke, Spangler, & Stannard, 1992; Oksanen, 1978; Priester, 1976; Schultheiss, 2004; Srebernik & Appleby, 1991; Ward, Fox, Calderwood-Mays, Hammer, & Couto, 1994; Ware & Hopper, 1999). Hemangiosarcoma occurs more frequently in the Shepherd and Boxer dog and has also been reported to be overrepresented in Labrador and Golden Retrievers (Brown et al., 1985; Gruntzig et al., 2016; Schultheiss, 2004; Srebernik & Appleby, 1991). Hemangiosarcoma is an aggressive and highly metastatic tumor in the dog and can present with clinical signs ranging from vague, nonspecific illness to acute death from tumor rupture and massive blood loss.

Fibrosarcoma is roughly as prevalent as HSA in dog and arises from transformed fibroblasts primarily in the skin, subcutaneous space and oral cavity. Fibrosarcoma seems to be more prevalent in Dobermans, Rottweilers and Setters (Gruntzig et al., 2016). While locally infiltrative and prone to recurrence, metastasis is observed in approximately 20% of cases (Ciekot et al., 1994).

Peripheral nerve sheath tumors (PNST) have been previously termed neurofibrosarcoma, malignant Schwannoma and hemangiopericytoma, but generally all of these are currently regarded as having nerve sheath origin and are classified as PNST (Chijiwa, Uchida, & Tateyama, 2004). These tumors can occur anywhere in the body and are classified as *peripheral* (away from the brain and spinal cord), *root* (directly adjacent to the brain or spinal cord), or *plexus* (adjacent to the brachial or lumbosacral plexus) with the *peripheral* form having the most favorable treatment outcomes (Brehm, Vite, Steinberg, Haviland, & van Winkle, 1995). A recent retrospective analysis suggests that PNST does not have strong breed prevalence, but German Shepherds may be more susceptible as

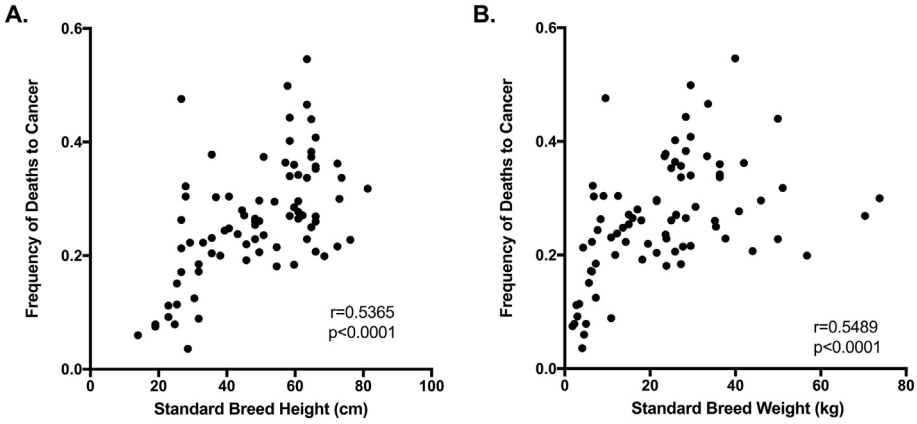

Fig. 1. Correlation of Cancer Mortality to Standard Breed Height (A) and Weight (B) in North American Dogs. Frequency of death from cancer is from Fleming et al., 2011, and standard breed height and weight were compiled from breed information from the American Kennel Club (http://www.akc.org/dog-breeds). Correlation value (r) and significance (P) were calculated using a Spearman correlation test using GraphPad Prism v7.0a (GraphPad Software, Inc., La Jolla, CA).

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