Sujet de stage

Improvement of the in vivo diagnosis of canine gliomas for a translational research: Histopathological profiles and comparison with imaging data. (Apply here)

Issue:

In adults, gliomas are the most common type of primary brain tumor, with high-grade gliomas being very aggressive and local invasive tumors. Despite advances in therapy, treatment strategies are rarely curative and survival is poor.

The study of tumorigenesis and the evaluation of new therapies for gliomas require accurate and reproducible brain tumor animal models. Ideally, these should mimic key features of the human disease, be reproducible and resemble progression kinetics and anti-tumor immune response of spontaneous glioma.

Rodent glioma models have been used in gliomas’ preclinical research for over 30 years but are controversial and criticized for not reproducing the main pathological features of human gliomas. In the absence of a large animal model for the studying glioma, the outcome of novel therapies in human patients is difficult to predict when these only have been tested on small rodent glioma models. Dogs that have larger brains than rodents constitute an attractive model both to test novel therapeutics and to optimize treatment protocols. Furthermore, brachycephalic breeds such as Boston terriers and Boxers are predisposed to develop spontaneous gliomas that resemble the human disease. Moreover, clinical signs and prognosis of human and canine gliomas are similar.

Gliomas, particularly high-grade gliomas, have poor prognosis despite aggressive conventional therapies in human, combining surgery, chemotherapy and radiotherapy due especially to tumor dispersal, postsurgical recurrence and resistance to therapy. Novel cancer treatments are needed to improve this poor prognosis. Targeted lysis of cancerous cells by viruses without lysis of healthy cells is a promising treatment option that may be more effective and have fewer adverse effects than traditional cancer treatments. Poxviruses preferentially infect cells in tissues with permeable vasculature, which is a feature of many aggressive tumors. This characteristic makes them excellent candidates for use in oncolytic virotherapy.

Objectives:

The overall objective of this project is to evaluate the myxoma virus treatment in canine spontaneous gliomas in order to use this treatment in human patients.

This requires firstly to improve the in vivo diagnosis of gliomas in dogs in order to include a maximum number of animals for the myxoma virus treatment.

Position of the study in the context of current knowledge

Intracranial canine tumours have a higher incidence per year compared with human ones (14,5 cases per 100.000 dogs compared with 4-5 cases per 100.000 people (1)). Canine intracranial glioblastoma occurs most commonly in brachycephalic breeds and is most commonly located in the cerebrum and diencephalon. Computed tomography (CT) and magnetic resonance imaging (MRI) are routinely available to veterinary practitioners for diagnosis and localization of intracranial lesions. CT characteristics of some canine brain tumors have been reported to be similar to those in humans (2).
With a brain that is much closer in size and architecture to the human brain, the dog represents a relevant model for glioma studies (3-5).

Astrocytomas and oligodendrogliomas are glial tumors and account for 31% of primary brain tumors in dogs (1). The World Health Organisation (WHO) recognizes low- and high-grade variants of astrocytoma (e.g., diffuse astrocytoma [II], anaplastic astrocytoma [III], glioblastoma multiforme (GBM) [IV]) and oligodendrogliomas (e.g., oligodendroglioma [II], anaplastic oligodendroglioma [III]) (6). As humans, GBM appears to have the highest incidence in dog (7). The highest incidence of this tumor occurs in the Boxer.

The WHO classification of nervous system tumors for domestic animals goes back to 1999 and has never been updated since (8). Meanwhile, the human tumor classification has been updated twice, the later edition being issued in 2007 (9). There are now major differences between these two classifications, new entities have been added for Human and other entities have been put in different groups. Moreover, the human tumor classification now integrates immunohistochemical and molecular biologic data to define the different types of brain tumors (9-14). Until now, the domestic animal classification only uses histological criteria to define the different types of tumors, even if some immunohistochemical features are increasingly mentioned in recent papers (15-20).

Although data obtained by the histological characteristics are the gold standard for definitive diagnosis of brain tumors, Magnetic Resonance (MR) Imaging offers a non-invasive surrogate for determining tumor type, especially when a biopsy is not feasible. Differentiation between tumor types and grade is important in Human, as survival differs significantly among these groups (23).

In dogs, several reports and review articles exist concerning the MR appearance of intracranial gliomas (1, 2, 20, 24-26) using conventional MR sequences (T1-, T2-weighted spin echo, Fluid Attenuated Inversion Recovery (FLAIR), and T2* sequences). Limited attempts have been made to differentiate between glioma types. The majority of intracranial gliomas reported in dogs are intra-axial, T2-hyperintense, solitary, mass-like lesions with variable T1 signal and post contrast enhancement. A case series of 5 dogs with GBM indicated that all tumors appeared intra-axial and had heterogeneous T2 signal, low to isointense T1 signal, and significant peritumoral edema. MR imaging gives some clues in distinguishing human oligodendroglialoma from astrocytoma and provides essential information regarding tumor grade (27). The MR criteria for diagnosing human astrocytomas and oligodendrogliomas include location, tissue involvement relative to gray matter, signal intensity, and contrast enhancement (28). Oligodendrogliomas are heterogeneous in signal, typically isointense to gray matter, and are peripheral intra-axial masses (28). Cortical infiltration and marked cortical thickening is the most useful MR findings relating to the diagnosis of oligodendroglioma (28). In contrast, astrocytomas arise within white matter and are therefore located more deeply within the hemisphere, are typically T2-hyperintense to gray matter and are usually more homogeneous in signal intensity (28). Both glioma types may have internal haemorrhage, calcifications, and cystic areas, though cysts are less common in lower grade astrocytomas. Contrast enhancement is correlated with high grade tumors. High-grade varieties of each tumor type (glioblastoma, anaplastic oligodendroglioma and astrocytoma) can be indistinguishable on traditional MR techniques, being highly heterogeneous and having extensive surrounding oedema (28).

More advanced and specific MRI techniques, including diffusion and perfusion-weighted MRI, magnetic resonance spectroscopy may hold promise for more objectively differentiating astrocytoma type and grade (29, 30). These techniques have been assessed in Human but only preliminary datas have been reported in dogs (31, 32).

*The inclusion of dogs bearing a cerebral tumor for an in vivo study requires a pre-mortem diagnostic. Thus, to use this animal model for human treatment, it is imperative (i) to compare the MRI data obtained in Dog and Human, including those obtained with more sophisticated and specific MRI techniques (33, 34), and (ii) to establish clearly the histological and immunohistochemical profiles before inclusion of dogs for therapeutic trials.*
References:


8. Koestner A, Pathology Afio, Pathology Aro, Oncology WCCmRoC. Histological classification of tumors of the nervous system of domestic animals: Armed Forces Institute of Pathology in cooperation with the American Registry of Pathology and the World Health Organization Collaborating Center for Worldwide Reference on Comparative Oncology; 1999.


