Therapy of brain tumors in dogs and cats

Therapie van hersentumoren bij hond en kat

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ABSTRACT

The use of improved diagnostic techniques has resulted in an increasing demand for effective treatment of brain tumors. In this article, the literature on the use and results of different types of therapies such as surgery, chemotherapy, radiation therapy, hormonal therapy, immunotherapy and gene therapy are being reviewed. The important role of the blood-brain barrier in all its aspects is considered. Especially the nitrosoureas, their side effects and survival times are reviewed in detail. The most successful strategy in brain neoplasia is multi-modality treatment, where a combination of neurosurgery, radiation therapy and chemotherapy is applied. Multi-modality therapy can be planned ideally after obtaining a histologic diagnosis.

SAMENVATTING

Het toepassen van verbeterde diagnostische technieken bij kleine huisdieren met hersentumoren doet de vraag naar betere behandelingsmethoden stijgen. In dit artikel wordt een overzicht van de verschillende behandelingsmethoden, zoals hersenchirurgie, chemotherapie, bestraling, hormonale behandeling, immunotherapie en gentherapie samen met hun resultaten weergegeven. De belangrijke rol van de bloed-hersenbarrière wordt besproken. Vooral de groep van de nitrosoureas wordt in kaart gebracht. De meeste successen worden geboekt met combinatieprotocollen van chirurgie, chemotherapie en bestraling. Deze protocollen worden het beste gepland na het bekomen van een histologische diagnose.

INTRODUCTION

There is a lack of recent data in the occurrence of primary brain tumors in dogs and cats. The reported incidence in less recent studies is 0.0145% in dogs and 0.0035% in cats (Vandevelde *et al.*, 1984). The contemporary prevalence is estimated to be higher because of aging of the pet population. Better diagnostic methods become available for an increasing number of dogs and cats, which allow more intracranial masses to be diagnosed. The incidence in dogs may even approach 3.0% (Snyder *et al.*, 2006).

In dogs a wide spectrum of primary brain tumors occurs, most frequently meningiomas and gliomas. In cats the most often reported primary brain tumor is meningioma, commonly diagnosed as multiple meningioma, while other types of tumors are less common. The prevalence of metastatic tumors in both species is unknown, because in clinical settings diagnosis of metastases on other locations frequently forces no further examination of the central nervous system (LeCouteur, 1999).

In a previous article the diagnostic procedures for brain neoplasia were discussed (Van Meervenne *et al.*, 2005a). On the basis of signalment, history, and the results of complete physical and neurological examination, it is possible to localize a problem to the brain. In some cases, the approximate intracranial localization can even be determined. Radiographic examination and cerebrospinal fluid analysis can be suggestive of brain neoplasia, but computed tomography (CT) and magnetic resonance imaging (MRI) have a higher possibility of confirming the presence of an intracranial mass. A crucial step in obtaining a definitive diagnosis is to perform a stereotactic CT-guided or MRI-guided biopsy of the lesion for histo-pathologic examination. The use of these improved diagnostic techniques has resulted in an increasing demand for effective therapies for brain tumors. The major goals of brain tumor therapy are to eliminate the tumor, or at least reduce or stabilize its size, and to control the secondary effects of the tumor (Jeffery and Brearly, 1993; LeCouteur, 1999).

Multi-modality therapy is often the hallmark of a sophisticated and successful approach in human cancer treatment, and should be applied more often in veterinary neuro-oncology. The objective of this article is to review current treatment modalities such as surgery, chemotherapy, radiation therapy, hormonal therapy, immunomodulation and gene therapy.

THERAPEUTIC METHODS IN BRAIN NEO- PLASIA

Surgery

Introduction

Neurosurgical intervention is becoming an essential consideration in the management of intracranial neoplasia in cats and dogs, whether for complete excision, partial removal or biopsy. This is mainly because of the availability of CT and MRI, and the development of advanced techniques in surgery, anesthesia and critical care, such as continuous intracranial pressure monitoring.

The complete elimination of a solitary tumor by surgical excision depends on localization, he size of the lesion, and the infiltrative growth. In particular, meningiomas located over the frontal lobes of the cerebrum in cats may be removed completely (LeCouteur, 1999). Attempts to obtain complete excision of brain tumors can be hampered by failure to define the margins of the tumor and by the need to avoid iatrogenic trauma to the surrounding normal brain tissue. For these reasons, radiotherapy and chemotherapy often will be incorporated in the treatment protocols of brain tumors (Parker, 1990; Jeffery and Brearly, 1993).

Partial removal of a brain neoplasm may relieve signs of cerebral dysfunction, provide tissue for histologic diagnosis, and render an animal a better candidate for additional therapies. Surgical biopsy of a tumor must be approached with care to avoid tumor seeding (LeCouteur, 1999).

Surgical techniques

A detailed description of anesthetic procedures and surgical techniques for intracranial surgery can be found in the literature and is beyond the scope of this article (Lawson *et al.*, 1982; Kostolich and Dulisch, 1987; Niebauer *et al.*, 1991; Shores, 1991a; Shores, 1991b; Sorjonen *et al.*, 1991; Feder *et al.*, 1993; Gordon *et al.*, 1994; Harvey *et al.*, 1996; Meij *et al.*, 1997; Glass *et al.*, 2000; Klopp *et al.*, 2000; Mouatt, 2002; Gordon *et al.*, 2005). Only major differences with human neurosurgery will be discussed in this article.

Controversy exists regarding the need for dural closure following brain surgery. To prevent infection and brain herniation, most human neurosurgeons insist on a water-tight dural closure (Sorjoren *et al.,* 1991). In veterinary medicine, it is often found to be virtually impossible to preserve the dura mater after durotomy because the dura is very friable. The dura defect usually spontaneously seals within 30 days after surgery (Niebauer *et al.*, 1991; Sorjoren *et al.,* 1991; Glass *et al.*, 2000). In contrast to human patients, postoperative leakage of CSF seems to create no adverse effects in dogs and cats (Niebauer *et al.*, 1991).

Compared to human craniotomy, fixation of the removed bone flap for closure of the skull defect is not performed in most documented veterinary cases, and the temporal muscle is closed over the craniotomy site (Lawson *et al.* 1982; Niebauer *et al.*, 1991; Jeffery and Brearly, 1993).

Complications

In general, the morbidity and mortality associated with the surgical removal of brain tumors in dogs and cats are considered to be acceptably low. However, there may be significant morbidity associated with the surgical removal of caudal fossa or brainstem neoplasms (LeCouteur, 1999). Postoperative mortality varies between 10% and 19%, according to different studies (Niebauer *et al.,* 1991; Gallagher *et al.*, 1993; Gordon *et al.,* 1994; Meij *et al.*, 1998). The most frequently encountered complications of intracranial surgery are hemorrhage, anemia, increased intracranial pressure, seizures, brain herniation, infections and pneumonia (Niebauer *et al.*, 1991).

In cats, blood loss during craniotomy and mass resection resulting in anemia, has been cited as the most common immediate postoperative complication, with some cats requiring homologous blood transfusions (Gordon *et al.*,1994). A correlation has been made between low postoperative packed cell volume and poor prognosis for survival after removal of intracranial meningioma in cats (Fusco *et al.*, 2000).

A frequently encountered complication in dogs and cats is the development of generalized seizures days to weeks after surgery. These seizures may be due to tumor recurrence, inflammation, fibrous adhesions at the surgical site or postoperative scarring. It is uncertain, however, whether patients undergoing craniotomies need either short- or long-term anticonvulsant therapy (Jeffery and Brearly, 1993; Glass *et al.*, 2000). Transfrontal craniotomy in dogs is correlated with an increased risk of infection at the surgical site (Glass *et al.*, 2000). Pneumonia, which is suspected to be secondary to aspiration, is the most common non-neurological complication after intracranial surgery in dogs. It typically occurs within the first week after surgery, though its onset is variable, with a range of 1 to 96 days. The use of corticosteroids may contribute to the development of pneumonia, due to their immunosuppressive effects (Fransson *et al.*, 2001).

Results

Prognosis after surgery differs by tumor type (Table 1). Dogs with meningiomas have in general a survival time of less than 1 year, while cats with successfully removed meningiomas may survive for several years. The age of the cat, location of the tumor and presence of multiple tumors did not significantly affect the survival time in one study, which described a 2-year survival rate of 50% (Gordon *et al.*, 1994). The results of the surgical removal of pituitary adenomas by transsphenoidal hypophysecto-

my in cats and dogs for the treatment of pituitary-dependent hyperadrenocorticism are promising (Meij *et al.*, 2002; Hanson *et al.,* 2005). Not enough patients treated surgically for other brain tumors have been reported in the veterinary literature to draw reliable conclusions on prognosis.

Chemotherapy

Introduction

Long remissions with high quality of life can be achieved with chemotherapy, although this treatment modality is rarely curative. Specific factors that must be considered when using chemotherapy in neuro-oncology include, but are not limited to, the blood-brain barrier (BBB), the histopathology, the cell kinetics and the microenvironment of the tumor.

The brain traditionally has been thought to be "protected" by the BBB. This physiologic and pharmacologic entity is located in the endothelium of the majority of cerebral capillaries. Only drugs that have high lipid solubility are not excluded by the BBB, and to pass through the BBB, drugs must either not be ionized or must have readily reversible ionization equations. Although these concepts are important in the choice of a chemotherapeutic agent, the BBB may in fact not be anatomically or physiologically intact within the boundaries of a brain tumor, and so these traditional considerations may not apply. Many drugs previously believed ineffective in the central nervous system (CNS) may actually penetrate the BBB adequately, particularly when the tumor itself or peritumoral inflammation has damaged the BBB (Cook, 1990).

In a rat glioma model, the heterogeneity of the BBB permeability according to the stage of tumor growth was noticed. This may interfere with diffuse uptake of chemotherapeutic agents that do not cross an intact BBB (Yamada *et al*., 1982).

Recent investigation suggests that the BBB is defective in malignant gliomas, a condition which results in cerebral edema. This phenomenon may be the cause of contrast enhancement during neuroradiological examination. Schneider *et al.* (2004) suggest that malignant gliomas have acquired the ability to actively degrade tight junctions by secreting soluble factors, eventually leading to BBB disruption within invaded brain tissue. However, all the exact mechanisms underlying the BBB breakdown are still unknown. The combination of chemotherapy with other treatment modalities such as radiation or transient BBB disrupting agents may also result in improved BBB penetration (Cook, 1990). Another component of the BBB is the presence of P-glycoprotein (P-gp) transporters located in the membranes of the capillary endothelial cells. These pumps extrude many structurally unrelated drugs, including various chemotherapeutics, which leads to therapy failure.

Some breeds of dogs, such as Collies and Australian Shepherds, have a deletion mutation in the MDR1 gene, which encodes P-gp. This causes premature termination of P-gp synthesis, which results in a lack of functional

Table 1. Results of surgical procedures.

Type tumor	Number of patients	Results: median survival times	Survival rates (sr)	References
meningioma dog	4	63-203 days	/	Kostolich's *et al.*(1987)
	10	198 days	1-year sr: 30%	Niebauer *et al.* (1991)
	1	210 days	/	Feder *et al.* (1993)
	3	after 120-270 days alive and seizure-free	/	Glass *et al.* (2000)
	14	210 days	1-year sr: 18.75%	Axlund *et al.* (2002)
meningioma cat	10	1 cat died of herniation, no exact survival times known	/	Lawson *et al.* (1982)
	4	485 days	1-year sr: 50%	Niebauer *et al.* (1991)
	17	2 cats died of herniation, 1 of renal failure. 14 cats: 816 days	1-year sr: 70.6%	Gallager *et al.* (1993)
	42	780 days	½-year sr: 71% 1-year sr: 66% 2-year sr: 50%	Gordon *et al.* (1994)
pituitary tumors	52 dogs	procedure-related mortalities: 10% incomplete hypophysectomies: 8%	/	Meij *et al.* (1998)
	84 dogs	procedure-related mortalities: 7%	1-year sr: 84% 2-year sr: 82% 3-year sr: 79%	Meij *et al.* (2002)
	7 cats	1 procedure-related mortality, 1 died within 2 weeks (lymphoma), 5 cats in remission from Cushing's disease	/	Meij *et al.* (2002)
	150 dogs	procedure-related mortalities: 8% incomplete hypophysectomies: 6%	1-year sr: 84% 2-year sr: 76% 3-year sr: 72% 4-year sr: 68%	Hanson *et al.* (2005)
other tumors	10 dogs and 1 cat	414 days	1-year sr: 40%	Niebauer *et al.* (1991)
	1 dog	75 days	/	Glass *et al.* (2000)

P-gp and thus in a defective BBB. This may allow increased CNS penetration of P-gp-substrate chemotherapeutic agents, so these animals may be better candidates for chemotherapy as a treatment for brain neoplasia. On the other hand, they may be more susceptible to the toxic effects of these agents (Mealey *et al.*, 2003; Mealey, 2006).

Another factor to consider is the histological type of the tumor. Different histological types of brain tumors will respond differently to various types of chemotherapy and it remains to be seen which tumor types respond best to the various cytotoxic agents available (Jeffery and Brearly, 1993). The microenvironment of a brain tumor, including the lack of lymphatic drainage and the variability between necrotic and actively proliferating tumor cells, can complicate the treatment (Cook, 1990).

Chemotherapy agents

Many pharmacologically different drugs are identified as having anti-cancer activity. Those relevant for the treatment of brain tumors are the nitrosoureas, including carmustine (BCNU®), lomustine (CCNU®) and semustine (MeCCNU®), and the antimetabolites, including cytosine arabinoside and methotrexate.

Nitrosoureas

The nitrosoureas are highly lipid-soluble alkylating agents. This allows for rapid transport across the BBB in sufficient amounts to be at least partially effective against some brain tumors. Studies with BCNU® and CCNU® in intracerebrally implanted and spontaneous animal brain tumors have demonstrated a consistent and high level of antitumor activity. In some animal brain tumors, lomustine has had an effect superior to that of carmustine (Merker *et al.,* 1975). A frequently encountered complication in dogs treated with lomustine and carmustine is acute bone marrow suppression. The leukopenia is transient but may lead to septicemia. Lomustine has a negative cumulative effect on platelet production, which may be less reversible (Dropcho, 2001). The white blood cell and platelet count reach nadirs 1 to 4 weeks post treatment (Fulton and Steinberg, 1990). If severe neutropenia (fewer than 1000 cells/µl) develops, administration of broad-spectrum antibiotics is recommended until neutrophil counts exceed 2500 cells/µl (Fan and Kitchell, 2000).

In our department, broad-spectrum antibiotics are given the first ten days after administration of lomustine. Antibiotics are continued until neutrophil counts exceed 1500 cells/µl. The following dosage of lomustine is then postponed until neutrophil counts exceed 4000 cells/µl (personal communication of the author).

It has been suggested to use granulocyte colony-stimulating factor (G-CSF) when myelosuppression is prolonged. However, recent studies have failed to demonstrate any beneficial effects in the treatment of neutropenia in man (Fan and Kitchell, 2000). The potential development of neutralizing, potentially cross-reactive antibodies complicates the use of recombinant human G-CSF in small animals. Antibody production is not a problem with recombinant canine or feline G-CSF, and the preliminary evidence suggests that there is a reduction in the development of cross-reactive antibodies in immunosuppressed dogs (Hogge and MacEwen, 2001).

Lomustine requires hepatic microsomal enzyme hydroxylation. This has two major consequences. First, hepatotoxicity may develop in some dogs, which may be irreversible and fatal. Therefore this drug should be used with care in animals with hepatic dysfunction (Kristal *et al.*, 2004).

Second, the use of concurrent medication, which requires the same induction pathway, may lead to alterations in the antineoplastic activity of lomustine. Lomustine should be used with caution in dogs being treated concurrently with phenobarbital, cimetidine and theophylline (Selker *et al.*, 1978; Zeltzer and Feig, 1979).

Lung fibrosis has been reported in humans as a complication after chronic treatment with lomustine, but no similar observations have been reported in the veterinary literature (Weiss and Issell, 1982). However, there was one patient at the Ottenhorst that received more than 1000mg/m² lomustine during a lymphoma protocol and did develop lung fibrosis (J.P. de Vos, personal communication, 2005). Like all alkylating agents, these group of antineoplastic drugs may induce carcinogenic and teratogenic effects. Since these drugs are primarily excreted by the kidneys, they have the potential to induce renal failure. Despite the fact that this complication has not yet been reported in animals, these drugs should be used cautiously in animals with pre-existing renal pathology. With intra-arterial carmustine therapy, retinal vasculitis is a common side effect that may result in severe permanent visual deficits (Dimski and Cook, 1990). Since not all studies in Table 2 mentioned a histological diagnosis, no definite conclusion can be made concerning the effect of treatment in different tumor types. In general, survival times of 4 months to 1 year have been achieved in dogs. In humans, gliomas are more responsive to chemotherapeutic agents than meningiomas and, on the basis of the studies referred to, a similar tendency is noted in dogs. Concerning the use of these drugs in cats, only one study has been reported which focuses on the toxicity and therapeutic efficacy of lomustine (Fan *et al.,* 2002).

Antimetabolites

Another group of cytotoxic agents are the antimetabolites, which are the structural analogues of the metabolites which are required for purine and/or pyrimidine synthesis. They interfere with DNA and RNA synthesis by enzyme inhibition or by causing synthesis of non-functional molecules. Antimetabolites are cell cycle specific, acting during the S phase of the cell cycle. Cytosine arabinoside is a pyrimidine antagonist, and methotrexate is an antifolate.

Cytosine arabinoside

Cytosine arabinoside is an antimetabolite that was originally designed for the treatment of myelogenous leukemia

Table 2. Results of chemotherapy.

Product (+ additional treatment)	Number of patients	Type of tumor	Survival time (st)	Reference
cyclophosphamide, vincristine, cytosine arabinoside, prednisone and chlorambucil	2 dogs	CNS lymphomas	1 dog 9 weeks 1 dog in complete remission after 3 months	Couto *et al.* (1984)
BCNU 50 mg/m² IV 4-6weeks	3 dogs 2 dogs unknown unknown	gliomas 1 benign vascular tumor and 1 unidentified tumor meningiomas pituitary tumors	9-11 months more than 12 months 4-6 months little to no response	Cook (1990)
BCNU 50 mg/m² 6weeks +phenobarbital +oxacyllin +prednisone	1 dog	astrocytoma	7 months	Dimski and Cook (1990)
CCNU 60-80 mg/m² PO 4 weeks	2 dogs	1 glioblastoma multiforme 1 meningioma	4 months 11 months	Jeffery and Brearly (1993)
CCNU 60-90 mg/m² PO every 4-6 weeks + broad-spectrum antibiotics	56 dogs	19 once lomustine 34 more than once (2-13 times) tumor type unknown	mean st 21 days mean st 8.5 months	Van Meervenne *et al.* (2005b)

and lymphomas. In human beings it is used for central nervous system (CNS) involvement of these diseases, as well as for prophylaxis after the establishment of remission.

This drug has been used intrathecally in veterinary medicine to treat CNS lymphoma (Couto *et al.,* 1984). Recent investigation has shown that cytosine arabinoside penetrates the intact BBB readily and that cytotoxic amounts might be achieved in the CNS by intravenous administration and by subcutaneous injection, thus bypassing the technical difficulties associated with intrathecal injection (Cook, 1990).

Methotrexate

Another antimetabolite, methotrexate, has been used intrathecally to treat human beings with CNS manifestations of leukemias and lymphomas, as well as prophylactically as described for cytosine arabinoside. Protocols for use in canine or feline patients have not been described. Recent evidence suggests that in the presence of CNS disease this compound may penetrate the BBB following systemic administration (Cook, 1990).

Miscellaneous

Several other agents are under investigation. As an example, L-asparaginase has the potential to be used in malignant lymphoma because of its apoptotic effects (Story *et al.,* 1993). Another compound is methylating temozolide, which is under investigation for use in gliomas in man (Macdonald, 2001; Stupp and Newlands, 2001).Chemotherapy options are a rapidly evolving area within cancer treatment. There are many promising new drugs, drug delivery systems, and multimodality protocols which will likely enhance our ability to treat cancer with chemotherapy. Future directions that might enhance the use of chemotherapeutic agents in dogs and cats with brain tumors include transient blood-brain barrier disruption using bradykinin analogues such as RMP-7 (Groothuis *et al.*, 1990; Rapaport, 1990; Neuwelt *et al.*, 1991; Inamura and Black, 1994; Culver *et al.,* 1998, Kroll and Neuwelt, 1998), intra-arterial infusion of chemotherapy and interstitial chemotherapy (Dropcho, 2001). In human medicine several drugs have a cytostatic or cytotoxic effect on glioma cells, with the theoretical appeal of less toxicity than chemotherapy. For example, tamoxifen sensitizes tumor cells to the cytotoxic effects of platinum drugs in vitro (Dropcho, 2001).

Radiation therapy

Introduction

Canine intracranial neoplasms are known to respond well to radiation therapy (Rohrer Bley *et al*., 2005). Radiation therapy can even be the primary treatment of choice, especially if the central nervous lesion is inoperable or if there is a contraindication for chemotherapy. Some tumor types seem to be more radioresponsive than others. Growth fraction, hypoxic fraction, and rate of cell loss are important factors that may contribute to the heterogeneity of response (LaRue and Gillette, 1993). External beam megavoltage irradiation obtained from a linear accelerator or a cobalt machine is currently recommended for the therapy of brain tumors in dogs and cats (LeCouteur, 1999).

Complications

Early adverse reactions after radiotherapy of brain tumors include acute edema of the brain, causing reactive tumor swelling, which has also been reported as a problem in the management of human patients with brain tumors. Unfortunately, brain tissue is extremely sensitive to late effects of irradiation. Early delayed effects can oc-

cur from two weeks to three months after treatment and may be related to transient demyelination (somnolence syndrome). The signs are often transient and respond to systemic cortisone. Late delayed effects usually occur at least six months after therapy but can occur after several years. Such effects are associated with focal necrosis and demyelination due to vascular endothelial proliferation and occlusion of the microcirculation. Response to cortisone is limited. It is often difficult to distinguish between late effects and tumor recurrence (Jeffery and Brearly, 1993; LaRue and Gillette, 1993: Brearly *et al.*, 1999). In this regard, a lot of research efforts have been put into the development of specific radiolabelled markers for functional imaging modalities that have the ability to differentiate between fibrosis, necrosis and tumor recurrence (Giannopoulou, 2003; Van de Wiele *et al.*, 2003). Delivery of an adequate radiation dose to the tumor without causing normal tissue complications remains the therapeutic challenge of radiation therapy.

Radiotherapy techniques

Radiotherapy is conventionally given during several consecutive sessions to obtain maximal cell death. Lots of adjustments have been made to improve these schemes. In human medicine, daily sessions from Monday to Friday are recommended, although two or more fractions a day have been suggested. The latter protocol is difficult to achieve in the veterinary patient due to the need to anaesthetize the animal for each session. In dogs, the optimal treatment regime has yet to be established, but irradiation sessions usually are once weekly or three times a week, if possible (Brearly *et al.*, 1999; LeCouteur, 1999; LeCouteur, 2004).

Stereotactic radiotherapy is an external radiation technique in which multiple narrow radiation beams are used to deliver a high radiation dose to a small volume. Portal size and beam direction are based on assessment of the mass seen on the scan. Either opposing or perpendicular beams can be applied to reduce normal tissue exposure while maximizing the tumor dose. This procedure allows sparing of the normal tissue surrounding the tumor. This technique has recently been described in dogs. Unfortunately, the application is limited by the availability of special two or three-dimensional computer-assisted treatment planning systems (Jeffery and Brearly, 1993; Rohrer Bley, 2004).

Brachytherapy, or interstitial radiation therapy, a method based on the implantation of radioisotope seeds into the center of a tumor to deliver higher doses of radiation, has been used in dogs with limited success (LeCouteur, 2004).

Boron neutron capture therapy (BNCT) is a radiation-associated therapy that is currently under investigation. Data from Gavin *et al.* (1995) suggest however, that this technique is equivalent to conventional radiation therapy for the treatment of intracranial tumors in dogs (LeCouteur, 2004).

Radiation enhancers (sensitizers) may also be used to potentiate the effects of radiation therapy (LeCouteur, 2004). The precise cellular mechanisms have not been defined, although the inhibition of repair of radiation-induced cell damage, the effects on the cell cycle, and the inhibition of cell proliferation, have all been postulated (Milas *et al.*, 2003).

Many classes of drugs have been found to interact with radiation. Classic radiosensitizing agents include the halogenated pyrimidines and the nitroimidazoles; however, many conventional cytotoxic agents, such as cisplatin, also enhance cell kill by radiotherapy (Carde *et al.,* 2001).

Results

Survival times for different radiation protocols, as shown in Table 3, vary from 4.9 to 18 months. A retrospective study (N=86) reported a significant longer survival time in dogs treated with cobalt-60 radiation, with or without other combinations of therapy, compared to dogs who received surgery (+/- 125I implants), or to dogs who received symptomatic treatment (Heidner *et al.*,1991).

Meningiomas and hypophysial macroadenomas seem to be most responsive to radiotherapy, but survival was also enhanced in dogs with gliomas, granulomatous meningoencephalitis, and metastatic brain tumors. The exact reason for this is yet unknown, but it may reflect an innate sensitivity of meningiomas, or it may be related to a relatively slower rate of growth (LaRue and Gillette, 1993).

Hormonal therapy

Introduction

The mainstay of hormonal therapy for brain tumors is the administration of corticosteroids, which is not intended to cure the patient, but rather to increase his quality of life. Glucocorticoids readily cross the BBB (Cook, 1990). The clinical effects of corticosteroids appear to be due mainly to their anti-inflammatory action, by which they decrease the permeability of the tumor capillaries. Steroid administration decreases the blood supply to a tumor within hours of administration (Jarden, 1989). These changes result in reduced intracranial pressure, decreased brain edema and less clinical signs. The saturation of steroid receptor sites in hormone-sensitive tumors may also enhance the clinical improvement (Speciale, 1990). Some reduction of tumor size or decreased growth rate is possible, especially in hematopoietic tumors. Dexamethasone is preferred in acute and severe cases, while prednisolone may be used for maintenance therapy (Cook, 1990).

Should anti-epileptic therapy be required, phenobarbital is the drug best suited for the control of generalized seizures in dogs and cats (Evans *et al.*, 1993; LeCouteur, 1999).

Results

There is an extreme variation in survival times in dogs with brain tumors treated with corticosteroids, with or without phenobarbital (Table 4). Survival times overlap for malignant and benign tumors, as well as for tumors with different anatomical locations. The median survival time ranges

Table 3. Results of radiation therapy.

Number of patients	Treatment protocol	Median survival time	Type of radiation	Remarks	Reference
4 dogs (2 meningiomas, 1 undifferentiated sarcoma, 1 astrocytoma)	300-3600rad in 5-6 fractions of 600 rad/fraction over 14-19 days	46 weeks	megavoltage	complete tumor regression (CT), improvement of clinical signs, reduction of medication (1 dog + hypoxic cell sensitizer)	Turrel *et al.* (1984)
25 dogs (9 meningiomas, 8 other tumor types, 8 unknown)	3,0-49,4 Gy in 12 fractions of 3.0-4.0 Gy/fraction over 4 weeks	19.6 weeks	megavoltage	some dogs +/- hyperthermia +/- surgery	Heidner *et al.* (1991)
14 dogs (4 meningiomas, 1 lymphoma, 1 pituitary adenoma, 1 metastatic anaplastic carcinoma, 1oligodendroglioma, 1granulomatous meningo-encephalitis, 5 unknown)	9 dogs: 39 Gy 5 dogs: 45 Gy in 12 fractions over 25-41 days	21.9 weeks 74.1 weeks	orthovoltage		Evans *et al.* (1993)
25 dogs (18 meningiomas, 6 gliomas, 1 pituitary tumor presumably)	9-Gy fractions weekly min. 5 weeks	clinical improvement and a decrease in tumor size	multiarc rotational radiotherapy	modified CT-scanner	Iwanoto *et al.* (1993)
65 dogs (unknown tumor type)	45-48 Gy in 3-Gy fractions	57.9 weeks	megavoltage	some dogs + surgery	LaRue and Gillette (1993)
83 dogs: 41 extra-axial 34 intra-axial 8 pituitary	38 Gy in escalating weekly doses, over 5 weeks	43.7 weeks extra-axial: 49.7 weeks intra-axial: glial: 40.4 weeks intra-axial: pituitary: 21 weeks	megavoltage		Brearly *et al.* (1999)
28 dogs (21 meningioma, 4 glioma, 3 choroid plexus tumors, all presumably)	48 Gy in 16 fractions of 3 Gy/fraction	35.7 weeks	megavoltage		Spugnini *et al.* (2000)
28 dogs: meningiomas	7-9 Gy weekly 5 weeks	29.6 weeks	megavoltage		Platt *et al.* (2003)
34 dogs: 22 extra-axial 13 intra-axial 13 pituitary	35-52,2 Gy in 10-17 fractions of 2.5-4 Gy/fraction	167.7 weeks	megavoltage		Rohrer Bley *et al.*(2005)

(1 Gray = 1 Gy = 100 rad)

from 6 to 119 days. This means a poor outcome can be predicted for patients treated symptomatically.

Immunotherapy

Advances in biotechnology have led to considerable progress in manipulating the host immune system in efforts to treat cancer. Early attempts at immunotherapy were limited by many factors, including a lack of understanding of the relationship of host effector cells and the cytokines that they produce. Today, however, we can use a variety of biologic response modifiers that have the ability to activate macrophages to produce cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor, and interferon. Clear clinical benefit has been demonstrated in many cases. Immunotherapy is most appropriately used as adjunctive therapy with the goal of controlling residual disease (Morrison, 2002).

Recently, attempts have been made in dogs with a malignant glioma to mobilize cell-mediated immunity against the tumor by culturing autologous lymphocytes to increase their numbers and cytotoxic effectiveness, and then returning these cells to the tumor bed after tumor resection. Reduction in tumor size and clinical improvement occurred in five dogs with cerebral gliomas (LeCouteur, 2004).

The treatment of dogs with meningiomas using repeated intracisternal injections of stimulated lymphocytes also resulted in clinical improvement and reduction in tumor size (LeCouteur, 2004).

Gene therapy

Gene therapy is the introduction of genetic material into a host in an effort to correct a biochemical deficiency or disease state. The most efficient methods of gene transfer are virally based and are referred to as transduction. Current strategies are based on four different techniques: chemogene therapy, which is the introduction of genes that confer susceptibility to chemotherapeutic agents; immunogene therapy, which involves the modulation of the immune response to tumor antigen; tumor suppressor genes such as p53; and manipulation of tumor cell growth and invasiveness (Hogge and MacEwen, 2001).

Several gene therapy strategies for human gliomas are still in preclinical development. The treatment for which there is the most clinical experience is retroviral transfer of the herpes simplex thymidine kinase (HSV-TK) gene into glioma cells, rendering them susceptible to the cytocidal effect of ganciclovir. Other studies include the retroviral transfer of HSV-TK and interleukine-2 and the stereotactic injection of an adenovirus vector to transfer the wild-type p53 gene into glioma cells (Dropcho, 2001).

Bystander killing in canine meningioma cells with a recombinant adeno-associated virus vector containing herpes simplex viral thymidine kinase is described by Jimenez *et al*. (1998). Meningiomas can be successfully transduced by adenovirus vectors bearing the Escherichia coli beta-galactosidase reporter gene by using endovascular techniques (Chauvet *et al*., 1998).

Anti-angiogenic therapy

Anti-angiogenic therapy targets non-malignant vessel cells rather than neoplastic tumour cells. Because angiogenesis is virtually absent in normal adults, therapies aimed at specifically interrupting angiogenesis within tumors should be well tolerated. Anti-angiogenic therapy is indicated where proliferation of vasculature is evident in histologic examination of the tumor. The BBB is not an obstacle, because blood-borne anti-angiogenic factors can reach the endothelial cells directly (Dropcho, 2001).

Angiostatin and endostatin, VEGF inhibitors, matrix metalloprotease inhibitors, and thalidomide are under investigation in anti-angiogenic therapy (Platt, 2005). The use of endostatin for canine brain tumor treatment, administered at the site of the tumor via encapsulated, transfected cell technology, is currently being evaluated (Platt, 2005).

Table 4. Results of hormonal therapy.

Number of patients	Treatment	Survival times (st)	Reference
8 dogs (2 meningiomas, 2 astrocytomas, 2 choroid plexus tumors, 1 oligodendroglioma, 1 ependymoma)	corticosteroids and anticonvulsants	median st 56 days	Turrel *et al.* (1984)
43 dogs: 13 meningioma 7 astrocytoma	not specified	median st 13 days mean st 75 days mean st 77 days	Foster *et al.* (1988)
45 dogs	7 dogs no treatment 38 dogs symptomatic treatment	median st 6 days	Heidner *et al.* (1991)
?	corticosteroids +/- anticonvulsants	median st 59-81 days	Evans *et al.* (1993)
?	not specified	median st 6-56 days	Moore *et al.* (1996)
10 dogs: meningiomas	corticosteroids	median st 119 days	Platt *et al.* (2003)

Table 5. Results of multi-modality therapy.

Protocol	Number of patients	Type of tumor	Results	Reference
systemic chemotherapy + intrathecal cytosine arabinoside + craniospinal radiation	4 dogs	CNS lymphomas	* 1 died (transtentorial hernia) * 1 survived 12 weeks * 2 survived 1 week	Couto *et al.* (1984)
surgery + radiation therapy (40 Gy)	2 dogs	astrocytoma meningioma	survival time: 6 months (unknown cause) survival time: 24 months	Nakaichi *et al.* (1996)
surgery + radiation therapy	20 dogs	meningiomas	2-year survival rate : 68%	Theon *et al.* (1997)
surgery + radiation therapy (28-49,5 Gy)	12 dogs	meningiomas	median survival time: 16.5 months	Axlund (2002)
surgery + radiation therapy	22 dogs	meningiomas	median survival time: 14.9 months	Platt *et al.* (2003)
chemotherapy (lomustine) + radiation therapy	3 dogs	unknown	* 1 died (unknown cause immediately after radiotherapy) * 1 survived 25 months (died of CRF*) * 1 survived 4 years (died of CRF*)	Van Meervenne *et al.* (2005b)

*CRF = chronic renal failure

Multi-modality therapy

Many single-modality treatments have been tested, and although encouraging, a common belief now held in neuro-oncology is that the development of combination therapies is essential to improve survival times. Dropcho (2001) describes the novel approaches to brain tumors in humans. The standard treatment for patients with newly diagnosed glioblastoma multiforme or anaplastic astrocytoma is maximal tumor resection with preservation of neurologic function, followed by limited-field radiation therapy. In most centers, patients additionally receive "adjuvant" chemotherapy as part of the upfront treatment. Current "conventional" chemotherapy regimens include single-agent intravenous carmustine, single-agent oral procarbazine, or the combination of procarbazine, lomustine and vincristine.

The reported median survival times in Table 5 suggest the effectiveness of combination therapy on brain tumors in dogs. Especially the combination of surgery followed by radiation therapy to treat residual tumor tissue has promising results. In future, multiple therapeutic modalities should be planned to treat canine brain tumors.

CONCLUSION

Different modalities are available in the treatment of brain tumors in small animals. Conservative treatment with corticosteroids is connected with poor prognosis and short survival times. Combination therapy protocols, including surgery, radiation therapy and chemotherapy, are needed to improve survival times. Irrespective of the treatment protocols, the type of tumor and its grade are important prognostic determinators.

More advanced technologies, such as immunotherapy, gene therapy, anti-angiogenic therapy, etc. are gradually finding their role as supportive measures to conventional brain tumor therapy.

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DE HEILIGE VEERLE

Patrones van kleine huisdieren (... en pluimveeartsen?)

Onder de heiligen uit een heel ver verleden, de tijd van de Merovingers vooral, zijn er enkele historische figuren en een menigte legendarische. Vooral deze laatste muntten uit door exuberante wonderdaden. Zeker niet de minste in de tweede categorie was Sint - Veerle, Pharaïlde of, in de oudste vorm van de naam, Farahilde. Sint-Veerle is de patrones van Gent en enkele kleinere Vlaamse plaatsen. Historisch staat vast dat haar relieken in 937 overgedragen werden aan de kapel bij de Gentse grafelijke burcht waaraan het Sint-Veerleplein nu nog zijn naam ontleent (Voordeckers - Declercq, 1963). Verder is er niets wat haar met zekerheid in verband brengt met Gent. Evenmin bestaan er bewijzen voor dat ze uit het Merovingische koningshuis zou stammen en een halfzus zou zijn van de heilige Amelberga.

Volgens de Internet - Encyclopedie Katholiek Nederland is Veerle ook beschermheilige van kleine (huis)dieren en wordt ze aangeroepen voor huiselijke vrede. Dat laatste heeft ze te danken aan een bij vrouwelijke heiligen uit die tijd veel voorkomend verhaal. Hoewel Farahilde een gelofte van maagdelijkheid had afgelegd, werd ze tot een huwelijk gedwongen met een edelman. Zij werd mishandeld omdat zij haar gelofte trouw bleef en 's nachts kerken bezocht in plaats van het echtelijke bed. Dat belette haar niet haar man trouw te verzorgen toen die gekwetst was. Ook als weduwe bleef ze maagd tot aan haar dood die men in 750 situeert.

Dat Veerle van Gent patrones werd van huisdieren gaat terug op iets heel wat uitzonderlijker. Ze wordt meestal afgebeeld met een gans. Wijsneuzen menen dat de uitleg daarvoor te vinden is bij een toevallige klankgelijkenis tussen Gent (Latijn Ganda, uit het Keltische 'gandao' wat monding betekent) en ganta (één van de Latijnse namen voor gans - denk aan gent of gander: ganzerik, mannelijke gans). De voorstelling van de heilige met gans zelf zou teruggaan op een moedergodin, in Keulen bekend als Gantunae (ganzengodin). De aan Veerle toegewijde stenen 'broden' die tot op heden bewaard bleven te Gent en te Steenokkerzeel (De Keyser, 1939) zouden votiefstenen zijn en eveneens met die moedergodinnencultus te maken hebben. Veerle zou in die visie dus patroonheilige van Gent geworden zijn via haar gans.

Vergeet het. De legende is veel mooier en, meer nog, ze gaat terug op de oudste levensbeschrijving (vita) van de heilige. Deze werd neergepend in de late 11de eeuw, maar is zelf gesteund op een verloren oudere versie die uit de Noormannentijd zou stammen. Dit verhaal wil dat Veerle eens in de wintertijd in het open veld een troep ganzen zag rondscharrelen. Vol zorg bood ze de dieren onderdak in haar schuur. Toen ze op een dag in de kerk was, stal een boer een van die ganzen. Met enkele vrienden at hij het dier op. Bij thuiskomst ontdekte Veerle het gemis. Ze liet de restanten van de gans verzamelen, legde de botjes en veertjes bijeen en zie: er vloog een levende gans op. Vanwege deze legende is Veerle patrones van kleine (huis)dieren. Maar zou ze - met zo'n krachttoer! - niet meer geëigend zijn als patrones van de dierenartsen die zich met pluimvee inlaten of die alle mogelijke gekwetste vogels proberen op te lappen?

Luc Devriese

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