Advances in Feline Oncology

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The mysterious feline species is fraught with a variety of neoplasms. Some of the tumors that arise in the cat are more likely malignant than benign when compared to the histologic counterpart diseases in dogs, as is true for masses that arise in the skin and mammary gland. It is also true that the biologic behaviour of certain of the malignancies that arise in the feline species have apparently differing clinical courses than counterpart histologies in dogs or humans. Coupled with different underlying carcinogenic responses and biologic behaviors in cat tumors is the unique pharmacologic responses of the cat's metabolism and excretion of many drugs important in cancer chemotherapy. Feline oncology thus presents additional challenges in veterinary medicine.

Feline Lymphoma

Lymphoma in the cat can have disparate forms, ranging from the aggressive high grade multicentric and thymic diseases that arise spontaneously or as a consequence of retroviral infection, to the more indolent gastrointestinal (GI) lymphoma forms.

Therapy

Cure is seldom achieved in lymphosarcoma (LSA) in cats, but life can be prolonged with good quality. Therapy chosen depends largely on the presentation seen.

Local therapy may be used in patients with Stage I disease (localized to one site) with the potential to be curative. Radiation therapy to the local site or surgical resection may be helpful.

Systemic therapy is the most important part of the therapy for LSA in cats. Several chemotherapy protocols have been published, including the popularly used feline version of the Wisconsin-Madison rotating sequential protocol, with most reporting approximately 60-80% of cats obtaining a durable remission of lasting a median of 7-10 months. Approximately 50-60% of cats can be expected to live beyond one year.

Alimentary Lymphoma

This has become the most common presentation seen in older cats in the United States. Nutritional support becomes very critical for these cats, as gut involvement often is associated with malassimilation of some degree. Also, chemotherapeutic agents that attack rapidly dividing cells (intestinal crypt epithelial cells) should be avoided initially.

We institute therapy with prednisolone and l-asparaginase (400 IU/kg SQ) for 1-3 weeks in these cats, along with metronidazole therapy for bacterial overgrowth disease and intense nutritional support including B vitamin supplementation, before adding cyclophosphamide (25 mg PO twice weekly) and vincristine (0.5 mg/m2 IV), in an effort to minimize effects on gut mucosa or motility. Anecdotally, we have had several cats that were intolerant to cyclophosphamide but tolerant of chlorambucil in their induction protocol. It appears that many cats with GI lymphoma have a disease process that is indolent and analogous to the mucosal associated lymphoid tissue lymphomas of people. These lesions are diseases of accumulation rather than excess cell replication in the beginning, and low-grade protocols may be extremely helpful. We use chlorambucil at a dose of 2 mg twice weekly PO, and prednisone at 5 mg BID PO for management of low grade GI lymphoma in cats. We have managed several cats with alimentary

lymphoma using mitoxantrone (5.5 mg/M2 IV infusion over 1 hour) or doxorubicin (1 mg/kg IV infusion over 20 minutes every 21-28 days) and prednisone therapy with success for several months. Finally, Lomustine (CCNU) is tolerated by cats at a dose of 60 mg/m2 PO every 21-28 days. These capsules must often be reformulated for cats from the standard 10 mg size to achieve dosing accuracy.

Feline Mast Cell Tumors (MCT)

MCT occurs in the skin and in visceral sites in the cat. Visceral MCT tumors occur in the spleen, mediastinum and nodes. There is no FeLV association. Cats also are prone to an aggressive intestinal form of MCT that is associated with vomition, weight loss, diarrhea and anorexia. Tumors in the intestine are composed of poorly differentiated cells. Most cutaneous MCT of cats are well differentiated and benign, but occasionally have been reported to metastasize and often appear as multiple lesions in the skin. Visceral MCT of the spleen may cause massive splenomegaly and vomiting due to GI ulceration from histamine release. When visceral organs such as spleen and liver are involved, mastocythemia and bone marrow involvement may be detected on staging evaluation. Occasionally cats with visceral MCT will develop multiple metastatic foci in the skin. Mediastinal involvement presents like thymic lymphosarcoma, with dyspnea and pleural effusion. The histologic grading system, as applied to canine MCT has been shown in repeated studies not to be predictive of tumor behavior or of clinical outcome. Mitotic rate within feline tumors may be correlated with biologic behavior.

Treatment

Treatment of dermal MCT is surgery, which occasionally must be multiple due to the tendency of cats to have multiple solitary tumors over long periods of time. Corticosteroids (1 mg/kg/day prednisone) may be helpful. Radiation therapy can be useful for nonresectable or invasive tumors.

Visceral MCT in cats is variable in behavior. Cats may present with massive splenomegaly, prompting the clinician to render a poor prognosis. However, splenectomy alone results in median survival times of 12 months, with some cats reported to live 3 years or more. Intestinal MCT carries the poorest prognosis of all of these presentations. Intestinal MCT often is associated with systemic involvement and patients are debilitated from malassimilation before diagnosis. If possible, bowel resection with 5-10 cm margins should be performed. Corticosteroids may be palliative for these cats, but most with intestinal involvement die within 4 months of diagnosis.

Systemic chemotherapy has been attempted for cats with disseminated MCT. Agents such as used for the dogs may be tried. However, no reports of prolonged survival as a result of chemotherapy have been published. Lomustine (CCNU) chemotherapy (mean dose of 56 mg per cat Q 21 days) was recently reported to provide a response rate for 50% in this setting. While the precise role of the receptor tyrosine kinase mutation in feline MCT is less well defined than in the canine disease, there is evidence that imatinib mesylate (Gleevec) can be beneficial to some cats with visceral MCT. The drug is costly and must be given for up to 6 consecutive weeks before a clinical benefit is seen in some cases. Thus it is important to select clinically stable cases if therapy with this molecularly targeted therapeutic is to be attempted. The dose that has been most commonly used is 10 mg/kg PO daily, although some trials are being conducted on an every other or every third day dosing basis in cats. The drug appears safe and well tolerated, with modest GI toxicity being the most commonly observed adverse effect.

Treatment of Solid Tumors in Cats

Several new drugs and protocols have become available to treat cats with non-resectable or metastatic solid tumors. The standard broad spectrum chemotherapeutics in feline oncology include doxorubicin, mitoxantrone, and carboplatin, and have been widely described.

We have been evaluating a combination of a synergistic doublet of gemcitabine and carboplatin in the cat. We have seen a modest response rate with this protocol, which is administered as follows:

Day 1: Gemcitabine 2 mg/kg IV over 20 minutes, followed by a 4 hour period to allow for prodrug activation, then carboplatin at 10 mg/kg IV bolus

Day 8: Gemcitabine 2 mg/kg IV over 20 minutes

Day 15: CBC only

Day 21: If CBC is recovered, administer the next cycle of the protocol

Ifosfamide is a third generation alkylating agent that is similar to cyclophosphamide. This agent has been efficacious in some cats with metastatic carcinomas and sarcomas in our hands. This drug is somewhat unique in the cat, in that while the canine dose is 375 mg/m2, the feline dose is 900 mg/m2. It is unclear why the maximally tolerated dose is so high in the feline species. The drug is both nephrotoxic and a potent inducer of sterile hemorrhagic cystitis. Thus, it must be given with extensive fluid diuresis and with the drug MESNA administered as a urothelial protectant. The protocol is as follows:

Normal (0.9%) saline IV diuresis at a fluid rate of 6 times maintenance (!) over 30 minutes

Ifosfamide diluted to 20 mg/ml or less over 20 minutes

Normal saline IV diuresis at 6 times maintenance over 5 hours

MESNA urothelial protectant at 1/5 the patient's calculated mg dose at time 0 (immediately before ifosfamide administration), and repeated 2 and 5 hours after ifosfamide

This therapy may be repeated on a 21 day basis

A version of **vinca alkaloid called vinorelbine (Navelbine)** has been used in the cat for the treatment of a variety of malignancies. Doses have ranged from 7.5 to 9.0 mg/m2 administered as a rapid intravenous bolus, on a 5 weeks on, one week off schedule of administration.

Paclitaxel (Taxol) has been used successfully in the cat particularly in the setting of metastatic mammary carcinoma. The dose that has been recommended for cats is 80 mg/m2 as a slow IV infusion, with careful attention paid to the potential for anaphylactoid reaction to occur. This agent is anaphylactogenic, although, in our hands, it appears to induce this response less frequently in the cat than in dogs. It is therefore recommended that the premedication protocol used in dogs be applied to cats, as follows:

For 5 days preceding the anticipated date of paclitaxel administration, administer prednisolone (5 mg/cat SID PO), diphenhydramine 1 mg/kg PO BID, and famotidine 0.5 mg/kg PO SID

Immediately prior to instituting the paclitaxel infusion, dexamethasone sodium phosphate is given as a 2 mg/kg IV bolus, as is famotidine (1 mg/kg IV) and diphenhydramine (4 mg/kg IM)

Anaphylactoid response should result in transient discontinuation of the infusion, followed by additional premedications as determined by the clinician, and reinstitution of the infusion at a slower rate. However, the longer the duration of the infusion, the greater the likelihood of increased GI and myelosuppressive toxicity.

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