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CLINICAL EXPERIENCE WITH COMMON CANCER DRUGS

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Doxorubicin is a widely used drug in veterinary oncology. The standard dose for dogs is 30 mg/m² IV every 21 days for dogs weighing more than 10 kg. The standard dose for dogs weighing less than 10 kg and cats is 1 mg/kg IV every 21 days. If dogs weighing less than 10 kg and cats are dosed on a mg/m² basis, they tend to be overdosed relative to their body size and therefore will experience greater toxicity. The total cumulative dose for doxorubicin in dogs is usually somewhere between 180 and 240 mg/m² in dogs. No figure for a total cumulative dose is generally accepted for cats, although one study suggests that cats given a cumulative dose in excess of 150 mg/m² should be monitored with echocardiography. If urticaria or head-shaking is noticed, the infusion should be temporarily discontinued or the rate of infusion should be slowed.

Doxorubicin is the backbone of many combination chemotherapy protocols for lymphosarcoma in dogs and cats. Median survival for dogs with lymphosarcoma treated with doxorubicin range from 100 to 270 days (the majority of reports give median survivals close to the later figure). Median survival for more complex doxorubicin-based protocols range from 200 to approximately 357 days.

Doxorubicin as a lone agent for lymphoma in cats has been reported sparingly. Two separate reports suggest very ineffective and inconsistent responses to doxorubicin when used alone. In one study of 19 cases, 5 cats achieved a complete response to doxorubicin with a median duration of remission of 92 days (range, 54-575 days). As expected, cats testing FeLV negative had longer survival than FeLV test positive cats. Loss of appetite was a common toxicity and was observed in 9/19 cats in this series. Acute and short-term toxicoses associated with doxorubicin use include vomiting, diarrhea, colitis, anorexia, pruritus, alopecia, and sepsis secondary to myelosuppression. Rare side effects include skin hyperpigmentation, transient hypotension during administration, and pancreatitis. Prior to the era of carefully monitoring of ventricular fractional shortening with cardiac ultrasound, cardiac toxicity was reported often. The nadir of the WBC in dogs has been shown to occur between 7 and 10 days after doxorubicin administration.

Side effects in cats can include partial or complete anorexia, mild vomiting, and mild diarrhea. Mild vomiting and diarrhea that required no treatment also occurred sporadically in all cats. It has been my experience that the anorexia associated with doxorubicin therapy in some cats is a significant enough issue that it should be discussed with the owner prior to its use. If anorexia occurs and the tumor is responding to doxorubicin treatment, both the owner and the clinician should be prepared to continue doxorubicin use while at the same time provide the patient's nutritional needs by nasogastric or percutaneous gastrostomy tube feeding. We have been able to maintain many feline patients needing doxorubicin chemotherapy for cancer by using percutaneous tube feeding in response to anorexia. Generally, gastrostomy tubes were accepted by both the owner and the patient without difficulty because the patients were able to maintain a good quality of life. Renal dysfunction, characterized by increasing azotemia with progressively more dilute urine can also occur.

Idarubicin is an analog of doxorubicin and is unusual in that it is the only anthracycline that retains its antitumor activity when given orally. Oral idarubicin has been evaluated in several studies in cats. A dose for idarubicin in cats has been established at 2 mg/cat/day for 3 days every 3 weeks. Idarubicin as maintenance treatment for 18 cats with lymphosarcoma after complete remission was achieved with COP was reported to result in a median duration of remission of 162 days (range 9 - 804 days) which is comparable to results with other protocols. Toxicity associated with idarubicin in cats is primarily related to myelosuppression and GI signs.

Mitoxantrone is a completely synthetic intercalator drug. Interestingly, mitoxantrone can cause a bluish discoloration of the sclera and urine. A phase II clinical trial that treated 126 dogs with a variety of malignant neoplasms with 2.5 to 5 mg/m² IV of mitoxantrone every 21 days resulted in an overall response rate (complete remission plus partial remission) of 23%. Mitoxantrone has also been evaluated in cats with a variety of malignant tumors but the data is not easy to interpret because some cats had received prior chemotherapy, and others were also treated with radiation therapy. Nonetheless, complete or partial remission was obtained in 14/76 cats (18.4%) with malignant tumors of all kinds that were treated with mitoxantrone alone. The authors of this study recommend a dose of 6.5 mg/m² IV every 21 days for cats with malignant disease.

Bleomycin is also an antitumor antibiotic. My experience with bleomycin is that it is most useful in the context of treating squamous cell carcinoma. However remissions are usually very short, and the pulmonary side effects noted with chronic use never develop because of the short duration of use. The dose for bleomycin in dogs and cats (and ferrets) is 10 to 20 U/m² subcutaneously once a week.

Actinomycin D is an antitumor antibiotic that acts by intercalation. One study found that 9/12 dogs with lymphosarcoma that had received prior chemotherapy responded to actinomycin D treatment when given at 0.5 to 0.7 mg/m² IV every three weeks. This finding raised an expectation that this drug might be useful as a rescue agent for dogs with lymphosarcoma that had failed prior treatment. Unfortunately, this hope for actinomycin use as a rescue agent was not realized. A later study evaluated actinomycin D as a rescue agent (median dose 0.7 mg/m² IV every three weeks) for 25 dogs with lymphosarcoma failed to induce a remission in any of the patients.

Vincristine is a very useful and versatile drug in veterinary medicine. It is most commonly used in combination with cyclophosphamide and prednisone (and sometimes other drugs) to treat lymphosarcoma, leukemia and mast cell tumors, in dogs and cats. It has been reported as a successful single agent therapy for transmissible venereal tumor and mast cell tumors in dogs, fibrosarcoma in a cat, and metastatic liposarcoma in a dog. Vincristine is a broad spectrum cytotoxic drug, and it is often overlooked as a possible defense against aggressive cancers, especially in cats. Common doses used for dogs and cats range from 0.5 mg/m² to 0.75 mg/m² IV once a week. However, the high end of that dose range is associated with hematologic and gastrointestinal toxicity and should be used cautiously.
Vinblastine is used less frequently in dogs and cats than is vincristine. The primary indication for vinblastine is as a substitute for vincristine either alone or to take its place in a combination protocol. Myelosuppression (especially neutropenia) is the major dose limiting side effect of vinblastine. Gastrointestinal side effects such as vomiting, stomatitis, and constipation have also been associated with the use of vinblastine. The dose of vinblastine in dogs and cats is 2.0 mg/m² IV every 10 to 14 days. My experience is that the myelosuppression at this dose is of sufficient magnitude that the dosing interval is best tried at every 14 days rather than every 10 days.

Cyclophosphamide is another mainstay in veterinary chemotherapy. The dose of cyclophosphamide in dogs and cats is usually given at 50 mg/m² orally on 4 consecutive days a week (followed by 3 consecutive days off) in combination with other drugs, or 200 mg/m² IV once a week in combination with other drugs. The major acute side effects are myelosuppression and gastroenteritis. Both of these side effects are usually quickly reversible by drug withdrawal. A chronic toxicity that can be important is the development of hemorrhagic cystitis. Clinical signs of this side effect are the same as for bacterial cystitis and include hematuria, dysuria, and pollakiuria. The incidence of cystitis from cyclophosphamide use can be reduced by the concurrent use of furoesmide.

BiCNU (carmustine) and CCNU (lomustine) have reported efficacy against CNS malignancies in dogs. BiCNU is usually given at 50 mg/m² over 20 minutes every 6 weeks. The neutrophil count nadirs occur between days 7 and 9 and often remained low for 15 days.

CCNU has also been reported to be effective in palliative treatment of CNS tumors in dogs. The ease of oral administration makes this drug an attractive option to consider. The usual dose of CCNU is 60 to 80 mg/m² IV every 6 to 8 weeks. The hematopoietic nadirs are reported to occur 1 to 4 weeks after treatment.

Cisplatin is an incredibly useful drug. It is usually employed early in the treatment of non-resectable or widespread carcinomas. Cisplatin is contraindicated in cats because at clinically effective doses it causes severe respiratory toxicity consisting of hydrothorax, pulmonary edema, and mediastinal edema. These clinical signs have been attributed to a microangiopathy of pulmonary blood vessels. In dogs however, common side effects of transient emesis and cumulative renal toxicity are manageable and do not generally inhibit its use.

The usual dose of cisplatin in dogs is 60 to 70 mg/m² intravenously every three weeks. Cisplatin must be given with a saline diuresis protocol to avoid severe nephrotoxicity and renal failure. By giving saline at 18.3 ml/kg/ hour intravenously through an indwelling catheter over 6 hours, and piggybacking the dose of cisplatin after 4 hours, it is usually possible to use cisplatin in most dogs without significant renal compromise. Careful monitoring of renal concentrating ability, urine sediment, and serum creatinine concentrations will help detect early changes in renal function. Decreased renal concentrating ability, abnormal numbers of granular casts in urine sediment, and azotemia suggest toxicity that warrant considering suspending or discontinuing treatment.

Transient emesis will predictably begin approximately 2 hours after cisplatin administration and usually last for 2 to 3 hours. The higher the dose of cisplatin, the more likely emesis is to occur. This emesis can be mitigated or blocked with 0.4 mg/kg butorphanol IM before and after cisplatin administration.

An unusual technical aspect of cisplatin use is that it is important to avoid contact with aluminum products. Therefore, it is very important to not use needles with aluminum hubs for either preparation or administration of cisplatin.

Carboplatin is an analog of cisplatin that is not associated with the nephrotoxicity (and therefore the need for concurrent diuresis) of the parent drug. It can be very useful in patients with preexisting renal disease. In contrast to cisplatin, carboplatin is safe to use in cats. Carboplatin is reported to have a different spectrum of activity from cisplatin in human tumors. It is usually given to dogs at 300 mg/m² intravenously every three weeks.

Carboplatin is generally well tolerated by cats and data from several phase I clinical trials suggests a dose for cats of approximately 200 mg/m² intravenously once every 4 weeks. The major dose limiting toxicity in cats is myelosuppression. The nadir neutrophil count occurs at approximately 21 days after administration.

L-asparaginase is used in veterinary oncology primarily in the treatment of lymphosarcoma, lymphocytic leukemias, and mast cell tumors.

The usual dose of L-asparaginase in dogs is 10,000 units/m² SQ once a week. If hypersensitivity reactions occur, 0.2-0.5 mg/kg of diphenhydramine IV, 1-2 mg/kg dexamethasone sodium phosphate IV, and isotonic fluids IV can be given. In severe cases a pressor such as epinephrine can also be given (0.1-0.3 ml of a 1:1000 solution IV).

Glucocorticoid drugs such as prednisone are an integral part of many anticancer drug protocols. Surprisingly, comparatively little has been written on their mechanism of action relative to cancer cells. Corticosteroids act on specific cellular receptors and cause DNA fragmentation in sensitive cells. In addition, corticosteroids are useful in the management of hypercalcemia, pain, increased intracranial pressure, and hypoglycemia associated with some cancers.