

Proceedings of the World Small Animal Veterinary Association Sydney, Australia – 2007

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Next WSAVA Congress

**33rd Annual
World Small Animal
Veterinary Association
14th FECAVA
Congress**

**DUBLIN, IRELAND
20th - 24th August 2008**



TAKING IT HOME...NEW APPROACHES TO CHEMOTHERAPY IN YOUR PRACTICE

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Chemotherapy is the principal modality used to treat systemic cancers such as haematologic malignancies, and metastatic carcinomas or sarcomas. The goal of chemotherapy in human oncology usually is to cure the patient, while in veterinary medicine, palliation is often a more appropriate goal and hence the drug dosages and schedules used are less likely to result in side effects. In palliative treatment the primary goal is to improve quality of life, which in veterinary medicine may result in prolonged survival because euthanasia is delayed. Communication between the veterinarian and the owner is essential. Open and honest dialogue will allow an owner to make an informed decision and will ultimately create a "team" approach to treatment of the pet.

Although it is tempting to think of chemotherapy protocols as a "recipe" for treating cancer, in fact they should be considered as a guide. Just as every patient is an individual, their cancer is also, an individual, and the patient's metabolism and excretion of the drugs is individual. Complete evaluation of the cancer and the patient is therefore very important before administering the first dose of what are potentially very toxic drugs.

In general chemotherapy drugs are most active against cells which are actively dividing cells and in a particular phase of the cell cycle. Although most tumour cells are in an active phase of the cell cycle, only a small percentage of normal cells are actively dividing. Normal tissues can be classified as static (nerve, striated muscle) in which the capacity for mitosis is limited; expanding (organs, glands) in which mitosis can be induced; and renewing (hematopoietic cells, mucosa, epidermis, gametes, fetal tissues) in which the proliferating proportion approaches that of tumour tissue. Toxicity from chemotherapy is most common in tissues that are renewing and is usually related to the dosage of the drug. This has implications for both the patient (toxicity and efficacy) and for the owner and veterinary staff's safety in handling the drugs during administration and follow-up care.

Calculating a dose of chemotherapy: By dosing chemotherapy on a metabolic basis, the risk of toxicity to the patient is decreased. Current dosage recommendations are often based on body surface area (BSA, m²). For veterinary use, dosage based on BSA for many drugs (e.g., doxorubicin, platinum drugs) is imperfect, and small dogs and cats should be dosed at a lower rate than larger dogs. Despite limitations, until further guidelines are available, the veterinarian should use a BSA conversion table as the best practical solution, *and become familiar with the individual drugs* that require lower dosage for small pets.

Dose intensity: Dose intensity is the amount of drug given per unit time (mg/m²/wk) and should be the highest tolerated by the animal with minimal toxicity. There is ample evidence in both human and veterinary oncology that optimal dose intensity improves the outcome for chemotherapy. Dose intensity can therefore be increased by increasing the dosage of a particular drug, or by shortening the time interval between drug administrations.

Chemotherapeutic Strategies in Veterinary Practice: Tumour cells are most rapidly dividing and have had the least opportunity to acquire drug resistance mutations, when the tumour is small. In general, therefore, chemotherapy is most active against small tumours, either following early detection, or following a cytoreductive ("debulking") procedure.

Tumour cells may be resistant to chemotherapy drugs before treatment, but acquire resistance rapidly after drug exposure. Therefore, it is important to remember that:

1. Treatment should begin as early when the tumour cell population is smallest.
2. Multi-drug regimens minimize likelihood of developing resistant clones.
3. Drugs should be administered at the maximum tolerated dose and schedule.

Combination chemotherapy can help counter drug resistance by affecting different metabolic pathways in cells that are resistant to other drugs in the combination. While combination chemotherapy could potentially be more toxic to normal cells, patterns of toxicity vary between drugs, and judicious scheduling of chemotherapeutic agents so that their toxicities do not overlap appears to improve tumour kill without compounding toxicity.

While combination chemotherapy may circumvent individual drug resistance, it does not completely avoid the problem of cross-resistance to multiple chemotherapy drugs. The transmembrane pump protein P-glycoprotein is present at increased levels in some tumour cells, and both the level and prevalence increase with exposure to chemotherapy. This phenomenon of multiple drug resistance (mdr) occurs between anthracyclines, vinca alkaloids, and certain other drugs. To reduce the risk of drug resistance occurring, it is important not to administer drugs at sub-therapeutic dosages; again, the highest dose intensity possible should be delivered. It is important not to modify the planned dosages or schedule in anticipation of a toxicity that has not occurred.

Effects of the body on chemotherapy drugs: There are four major factors that affect dosing of chemotherapeutics and need to be assessed for each individual patient:

Absorption: Cyclophosphamide or methotrexate absorption may be reduced in an animal with malabsorption syndrome (such as GI lymphoma). This could lead to decreased efficacy of the drug.

Distribution: Drugs affected by protein binding such as vinca alkaloids, mitoxantrone, or cisplatin may be affected when an animal is hypoproteinaemic; a larger proportion of the drug may remain pharmacologically active, or may be more rapidly cleared from the body.

Excretion: The blood concentration of drug over time is a function of total clearance by all eliminating organs. Decreases in glomerular filtration rate may affect drugs such as carboplatin. Bile transport disruption could reduce clearance of vincristine or doxorubicin.

Metabolism: Hepatic dysfunction may affect reductase metabolism of doxorubicin, thereby increasing toxicity. Cyclophosphamide and DTIC require hepatic metabolism for activation, so reduced metabolism may reduce efficacy (and toxicity).

Timing of chemotherapy

Adjuvant chemotherapy is used following resection of a primary tumour, where the animal is at significant risk of recurrence or metastasis. The most obvious veterinary example is the effectiveness of adjuvant cisplatin, doxorubicin, or carboplatin in the treatment of canine osteosarcoma. The effectiveness of adjuvant chemotherapy is greatest at the earliest stages of growth. When a primary tumour is resected, micrometastatic foci of tumours cells have a high growth fraction and a low number of resistant cells. The disadvantage of adjuvant chemotherapy is that those patients cured by surgery are exposed to needless risks of toxicity. Thus the decision whether to use adjuvant chemotherapy rests on the risk of recurrence or metastasis of the individual.

Neoadjuvant chemotherapy is used prior to localized treatment modalities such as surgery or radiation therapy, with the objective of reducing the size of the primary tumour and reducing the scope and side effects of other definitive treatment.

Toxicity Following Chemotherapy

Myelosuppression is the toxic effects of chemotherapy on the bone marrow. The nadir (or low-point) of peripheral neutrophil counts usually occurs around 5 to 10 days after therapy. If myelosuppressive drugs are given when the stem cell pool is dividing (i.e., soon after the previous administration), then severe prolonged myelosuppression due to stem cell destruction may occur. The usual interval between for myelosuppressive drug administrations is every 2 to 3 weeks. Some drugs (such as lomustine and carboplatin) may have delayed or prolonged nadirs, and dosing intervals are longer for these drugs.

After chemotherapy, a complete blood count (CBC), including a platelet count, should be collected at the expected neutrophil nadir, usually one week after administration. The absolute neutrophil count (not the percentage, or the total leukocyte count) should be evaluated. Although many animals have a low neutrophil count without clinical signs, a count of less than $1.0 \times 10^9/L$ is sufficient reason to reduce all subsequent dosages of that myelosuppressive drug. A dosage reduction of 25% is a good rule of thumb. In addition, a CBC should be evaluated immediately prior to each chemotherapy treatment. If the neutrophil count is less than $3.0 \times 10^9/L$ at the time myelosuppressive chemotherapy is due, it is best to delay administration until the count is more than $3.0 \times 10^9/L$.

Owners should be instructed in the use of a rectal thermometer and take the pet's temperature twice a day around the neutrophil nadir. A fever or other sign of sepsis should be treated as an emergency and the veterinarian should provide intravenous fluids as well as broad-spectrum antibiotics.

Thrombocytopenia rarely causes clinical signs, however at counts of less than $50 \times 10^9/L$ the risk of bleeding increases and the veterinarian should be alert to petechiation, ecchymoses or mucosal bleeding. Myelosuppressive chemotherapy should not be administered if the platelet count is less than $100 \times 10^9/L$.

The gastrointestinal mucosa is another site of renewing tissue, and toxicoses may occur anywhere in the GI system. Clinical signs include nausea, vomiting, inappetence, anorexia or diarrhea. The management of these toxicoses will depend on the severity of signs. Severe hemorrhagic colitis following doxorubicin administration increases the risk of subsequent sepsis, due to breakdown of the protective mucosal barrier to gram negative intestinal bacteria at a time when the animal is myelosuppressed. Antibiotics should be administered to these animals in addition to supportive and symptomatic care.

In veterinary oncology, cardiotoxicity is only clinically a problem with doxorubicin. While both cats and dogs show histologic cardiac changes, dogs are more sensitive to clinical cardiac damage than do cats. Cardiotoxicity is a chronic toxicity related to the lifetime cumulative dose of doxorubicin rather than the amount of each individual dosage. The end result resembles dilated cardiomyopathy, and may progress to congestive heart failure. Although cardiotoxicity in dogs can occur at any cumulative dosage, it is most frequent above 180 mg/m^2 , and doxorubicin should not be given above this level without echocardiographic monitoring. Breeds susceptible to dilated cardiomyopathy, particularly Dobermans, appear to be more sensitive to this toxicity, and should only be treated with caution and pretreatment cardiac evaluation, as well as close monitoring.

Nephrotoxicity is the primary dose-limiting toxicity of cisplatin and depends on both the individual and cumulative dosage. Cisplatin should not be administered to dogs with pre-existing renal disease, and should be used with caution in dogs with urinary tract tumours. Cisplatin *should not be administered* if the serum creatinine is above the normal range and *should never be administered to cats* under any circumstances. In addition, cisplatin should always be delivered to dogs with appropriate saline diuresis. Doxorubicin has been associated with a cumulative nephrotoxicity in cats.

Urothelial toxicity (sterile hemorrhagic cystitis) is associated with cyclophosphamide and ifosfamide administration. Signs of stranguria, dysuria and hematuria can be severe and prolonged over many weeks. This toxicity should be distinguished from infectious cystitis by bacterial culture, however, even if bacteria are isolated and signs resolve with antibiotic administration, the drug should not be administered again as infection can be secondary. Concurrent furosemide administration reduced the risk of urothelial toxicity.

Hypersensitivity reactions may occur during rapid administration of doxorubicin, and is not usually a problem if the drug is given as a slow infusion over 15 to 20 minutes. True anaphylaxis may occur following L-asparaginase administration, particularly by the intravenous or the intraperitoneal route. This toxicity occurs very rarely if L-asparaginase is administered intramuscularly or subcutaneously. Polyethylene glycol (PEG) conjugation of L-asparaginase helps to abrogate the immune response, and extends drug half-life while preserving efficacy. If anaphylaxis occurs, treatment with corticosteroids and antihistamines plus any other necessary supportive measures should be instituted immediately. The patient should never receive further L-asparaginase.

Basic Chemotherapy Drug Handling: Most chemotherapeutic agents are both toxic and mutagenic. Alkylating agents have been associated with the highest risks to handlers. Organ damage and increased risk of fetal loss have been reported in persons handling and administering chemotherapy with inadequate attention to personal safety. Precautions should be taken when handling chemotherapy drugs during every phase of preparation, administration and disposal of drugs or waste.

All chemotherapy vials should be stored in a separate area, in resealable plastic bags. Any prepared drugs should be transported to other areas of the clinic in resealable plastic bags. Chemotherapy preparation should be done in a separate, designated area. A disposable gown with closed-cuff sleeves and latex (not vinyl) gloves should be worn. Ideally a vertical laminar flow biological safety cabinet should be used to prepare all chemotherapy drugs. If this is not available, protective eyewear and a respirator-mask should be used in addition. These are usually available through chemotherapy drug distributors. Breaking or splitting of capsules or pills results in both inaccurate dosing and excessive personnel exposure. To adjust dosage of oral agents, compounding pharmacies should be used (below). During preparation and administration of injectable drugs, Luer-lok syringes decrease the risk of drug leakage or spills. Hydrophobic filters that insert into chemotherapy drug vials help prevent aerosolisation of drugs during preparation for dosing. We use Chemo Dispensing Pin (CE 0123, B. Braun Medical Inc, Bethlehem PA 18018 USA; available from Braun). This doesn't allow pressure to build up in the vial, and can be used as a multi-dispensing pin on larger vials that you store. If a filter is not used, alcohol moistened gauze should be wrapped around the vial top and needle when the needle is withdrawn to protect from aerosolized drug. We have recently begun using a system that is very popular in human oncology at the moment called PhaSeal from Intensive Care Products, and it has just been approved for marketing in Australia. It is moderately expensive, but very safe, being a double-membrane, individual component system.

When administering drugs to the patient, both parenterally and orally, latex gloves should be worn. If owners are administering drugs orally at home, gloves and a resealable plastic waste bag should be provided.

For drugs that are excreted in the urine (such as cyclophosphamide metabolites), the pet should be encouraged to urinate on soil where urine will drain quickly, and any urine in other areas should be handled and disposed of as chemotherapy. These precautions should be followed for approximately 48 - 72 hours following administration.

Premixed chemotherapy drugs: In some areas, certain suppliers will prepare individual doses of chemotherapy drugs and / or compound specific formulations. These services can be invaluable to veterinarians treating pets with cancer by limiting veterinary staff exposure in preparing injectable chemotherapy and providing accurate and less stressful dosing of oral drugs; and may even be more economical for those using chemotherapy infrequently. It is of course important to be sure of the reliability, safety and efficiency of the supplier.

There are some minor problems with this system. One is, if the pet is unable to receive chemotherapy on the scheduled day, it may not be able to be stored in the syringe, so lost to you and the client. The other is, if a dosage adjustment is needed this needs to be anticipated. Usually this is not a problem as most dose adjustments needed can be foreseen by at least a few days.

Compounding pharmacies can also be extremely helpful in providing drugs at nonstandard dosages or formulations, by prescription. This is particularly important for cats and small dogs needing oral chemotherapeutics as the available tablet and capsule sizes must not be split in the veterinary facility. Another alternative is a local hospital that may be willing to help, as they would have the safety equipment in place.