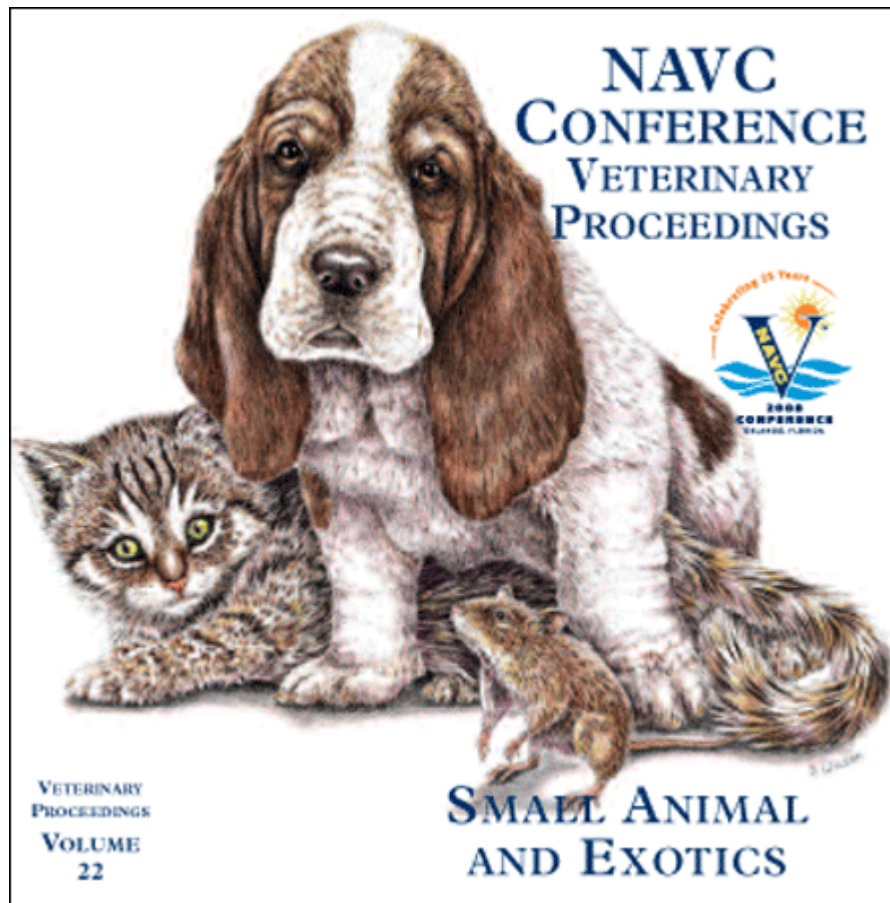


Proceeding of the NAVC
North American Veterinary Conference
Jan. 19-23, 2008, Orlando, Florida



www.tnavc.org

DEALING WITH COMPLICATIONS FROM CHEMOTHERAPY

Michael S. Kent, MAS, DVM, Diplomate ACVIM
(Oncology) and ACVR (Radiation Oncology)
School of Veterinary Medicine
University of California, Davis, CA

Chemotherapy agents carry the risk of complication. Complications can be broken down into those associated with administration such as anaphylaxis and extravasation reactions and those associated with toxicity of the drug itself. The most common toxicities associated with chemotherapy drugs relate to their effects on rapidly dividing cells, leading to bone marrow suppression (myelosuppression and thrombocytopenia) and gastrointestinal side effects (vomiting and diarrhea). There are, however, other toxicities found with some commonly used drugs including cardiac, renal, liver, and bladder toxicities.

ALLERGIC/ANAPHYLACTIC REACTIONS

Certain chemotherapy agents are known to produce allergic or anaphylactic reactions in some or even a majority of patients. L-asparaginase and doxorubicin are the two commonly used agents that can result in these reactions. Other drugs that are used less frequently such as paclitaxel (Taxol) are known to cause severe allergic-type reactions.

Doxorubicin reactions often are seen during administration and are secondary to the degranulation of mast cells. Dogs will often shake their heads and on occasion salivate when having a reaction. The infusion should be stopped. Administration of dexamethasone (0.2 mg/kg IV) and diphenhydramine (2 mg/kg IM) can be helpful. Blood pressure should also be monitored. If the reaction was not severe, the infusion can be restarted but should be given at a slower rate. The next time a patient is to receive the drug they should be premedicated with dexamethasone and diphenhydramine before the drug is given and monitored closely.

L-asparaginase has also been associated with anaphylactic reactions either soon after or as late as several hours after administration. As L-asparaginase is a protein, which the immune system can react to anaphylaxis is more likely to happen when the drug is used multiple times. Owners should be advised of the possibility of a reaction if the patient is released soon after administration. Patients should be treated symptomatically based on the severity of signs. If the drug is to be given multiple times, then premedication with dexamethasone and diphenhydramine is advised.

BONE MARROW SUPPRESSION

As most chemotherapy agents hit rapidly dividing cells, we see bone marrow toxicity commonly in our patients; however for the most part they remain non-symptomatic. The toxicities seen relate to the circulating half-life of the cells the marrow produces. While neutrophils stay in circulation only for hours, platelets

can stay in circulation for about a week and red blood cells stay in circulation for 3 to 4 months. This explains why we see neutropenia most commonly followed by thrombocytopenia and anemia is rare.

The nadir refers to the time point when the agent has the most effect on circulating cell counts. For most chemotherapeutic agents the nadir for neutrophils is about 7 to 10 days. This is why it is recommended to repeat a CBC at that time. There are some exceptions to this rule. For example, carboplatin in dogs has a nadir of 10 to 14 days, cisplatin has a double nadir of about 7 and 17 days, and CCNU is less predictable and can nadir at 7 days but also later over the 3-week period. For drugs like chlorambucil and melphalan, which are administered several times a week to daily, CBCs should be checked monthly.

A CBC must be checked before giving any myelosuppressive drugs. If the absolute neutrophil count is less than 2,000 cell/ μ L and the nadir CBC revealed a neutrophil count less than 1,500 cells/ μ L then it is advisable to consider reducing the dose on the next administration by 10% to 20%. While dose reductions may be necessary it is important to remember that you are also decreasing the intensity of the cancer therapy and are also sparing the tumor.

If the neutrophil count is less than 2,000 to 2,500 cells/ μ L then the dosing should be delayed until the neutrophil count recovers; generally this will happen within 5 to 7 days. If the patient has a nadir neutrophil count of less than 1,500 cells/ μ L, is not ill, and does not have a fever then prophylactic oral antibiotics should be started for a 5- to 7-day course. Clavamox and enrofloxacin at standard dosing are good choices. Some clinicians also like to use trimethoprim-sulfamethoxazole (TMS). If the patient appears ill, even if they do not have a fever (without neutrophils the body may not be able to mount a fever), the patient should be treated aggressively with IV fluids, IV antibiotics (eg, ticarcillin/clavulanate 50 mg/kg IV TID), blood and urine cultures, and supportive care. Often these patients will recover rapidly with this high level of care. Subsequent chemotherapy treatments should also be dose reduced by at least 20% and the patient should be monitored closely. The owner can monitor body temperature at home and the CBC values should be closely watched.

Platelets counts can also be affected and chemotherapy should be delayed and dose reductions considered if the platelet count falls below 75,000. It is particularly important to watch platelet counts carefully when using CCNU. Permanent progressive thrombocytopenia is possible. If platelet counts decrease between treatments, even if they are still in the normal range, a dose reduction or increased time between administrations is necessary. If the platelet counts do not recover then the drug should be discontinued.

GASTROINTESTINAL COMPLICATIONS OF CHEMOTHERAPY

One of the major complications of chemotherapy and probably the thing that causes the most owner concern is gastrointestinal toxicity, which includes nausea,

anorexia, vomiting, and diarrhea. Different agents have different probabilities of causing differing degrees gastrointestinal signs. Some of the agents used with a high likelihood of causing GI signs are cisplatin, dacarbazine, mustargen, and streptozotocin. Agents with a moderate chance of causing GI signs include carboplatin, cyclophosphamide, cytosine arabinoside, doxorubicin, methotrexate, and 5-fluorouracil. The time to onset of signs also varies ranging from during the infusion until 3 to 5 days after treatment. In either case if vomiting is not well controlled it is important that the patient be provided with good supportive care early on. Clinical signs can become very severe and the patient can decompensate either leading to longer hospital stays or death or euthanasia if treatment is not started promptly. Besides starting antiemetics, IV fluids are essential if the patient cannot drink water without vomiting. In less severe cases subcutaneous (SQ) fluids and oral antiemetics as outlined below may be sufficient.

As many of our oncology patients are older, they may be on additional medications for concurrent disease that may predispose them to increased side effects. The use of NSAIDs and corticosteroids can exacerbate chemotherapy related gastrointestinal toxicity. Of course these other drugs may be necessary for the patient's quality of life, but it may be possible to limit their use right at the time chemotherapy is given.

It is important to rule out other causes of gastrointestinal signs, such as obstruction, progression of the patient's tumor, renal failure, diet change, pancreatitis and infectious causes. Physical examination, CBC, chemistry panel, abdominal ultrasound, radiographs, fecal examination and history can be helpful in ruling out these causes.

ACUTE CHEMOTHERAPY-RELATED NAUSEA AND VOMITING

Acute vomiting is most associated with drugs of high emetogenic potential and occurs within 24 hours of drug administration. Cisplatin is the drug most commonly associated with acute vomiting. Cisplatin-induced vomiting can often be avoided by pretreatment with butorphanol used in addition to maropitant or ondansetron. Doxorubicin is more often associated with anorexia in the acute phase of treatment. This is likely related to nausea. Concurrent or even pretreatment with oral metoclopramide or maropitant can be effective in treating patients who become anorexic after treatment. In reviewing the toxicity of doxorubicin in a protocol for the treatment of osteosarcoma we found that there were 2 reported episodes of inappetence and 4 patients experienced vomiting out of the 82 doses given. Most of the occurrences were self-limiting and required only symptomatic treatment. No dogs were hospitalized.

DELAYED CHEMOTHERAPY-RELATED NAUSEA, VOMITING, AND DIARRHEA

Although the incidence rate is low many chemotherapeutic agents can cause delayed vomiting. Most often clinical signs start between 2 and 5 days after drug administration. Many chemotherapeutic drugs have

cytotoxic effects directly on mucosal and crypt cells of the small intestine. Chemotherapeutic drugs that are commonly used in veterinary patients that can lead to an ulcerative enteritis include actinomycin D, cytosine arabinoside, doxorubicin, DTIC, methotrexate, and vincristine. The clinical features include pain, bleeding, vomiting, ileus, and diarrhea. Many cases can be treated on an outpatient basis with oral antiemetics but with severe cases supportive care with IV fluids, antiemetics, potassium supplementation, and pain medication started soon after the start of clinical signs often results in a positive result. With therapy clinical signs usually resolve in 2 to 4 days as the mucosa and crypt cells are replaced.

Chemotherapy induces diarrhea by disrupting the normal processes that regulate fluid absorption and secretion, by altering GI defense mechanisms, and by damaging the mucosa of the small and large intestine. Diarrhea associated with chemotherapy is often self-limiting, but on occasion can be severe. Supportive care is the cornerstone of therapy. Ensure that the patient has adequate fluid intake so as not to become dehydrated. If melena is seen GI protectants (H₂ blockers and sucralfate) are indicated. In cases where colitis is suspected metronidazole at 30 mg/kg PO divided BID or Sulfasalazine (10–25 mg/kg PO TID-QID) can be very effective.

Vincristine use has been associated with paralytic ileus. This is thought to be part of the toxicity, which is also manifested as a peripheral neuropathy that is sometimes seen with use of this drug. Paralytic ileus can be associated with the first use of the drug or after it has been used multiple times in a patient. Once a patient has shown gastrointestinal signs after the use of vincristine, care should be taken with using this drug again as the clinical signs tend to progress with subsequent dosing. The onset of clinical signs can be from several days after administration to as long as two to three weeks after the drug was given.

Diagnosis is made based on clinical signs, abdominal radiographs, which reveal dilated gas filled bowel loops and ultrasound, where a lack of peristalsis can be identified. Ultrasound of these patients may be difficult if there is a large amount of gas in the intestines. It is important to rule out intestinal obstruction, as the signs are similar and treatment markedly different.

Treatment is based on supportive care and depending on severity, can take several weeks for resolution of signs. Hydration should be maintained with the use of IV fluids. After an obstruction is ruled out a metoclopramide CRI (1.1–2.2 mg/kg/24 hr) can be helpful. As paralytic ileus can be painful analgesics should be used. If the patient has constipation and no vomiting then a laxative such as laxatone can be administered. If there is fecal impaction then enemas may be helpful. If the patient is not able to eat for more than several days then nutritional support is essential. In a review of lymphoma cases treated at UC Davis with a multi-drug protocol 3 dogs out of a total of 39, developed paralytic ileus during the course of their treatment.

Small Animal – Oncology

Table 1. Antiemetics

| Drug | Dose | Mechanism of Action |
|----------------------|--|---|
| Metoclopramide | Oral, IV, SQ, IM: 0.2–0.4 mg/kg CRI: 1 mg/kg/24hrs | Dopamine antagonist at the CRTZ. At higher doses may be a 5-HT ₃ receptor antagonist. Also increases lower esophageal sphincter tone and increases GI motility |
| Ondansetron (Zofran) | Oral: 0.5–1 mg/kg BID to TID IV: 0.1–0.5 mg/kg IV over 15 minutes TID or 30 minutes before cisplatin infusion | Serotonin Antagonists (5-HT ₃ receptor antagonists) Peripherally: Serotonin is released from enterochromaffin cells in GI tract. Centrally blocks chemoreceptor trigger zone |
| Dolasetron (Anzamet) | Oral, IV: 0.5–1.0 mg/kg PO There are anecdotal reports of using the IV formulation orally to decrease costs | Serotonin Antagonists (5-HT ₃ receptor antagonists) Peripherally: Serotonin is released from enterochromaffin cells in GI tract. Centrally blocks chemoreceptor trigger zone |
| Maropitant (Cerenia) | IV: 1–2 mg/kg IV PO: 2 mg/kg | NK-1 inhibitor acts by competitively inhibiting substance P binding in emetic center |
| Butorphanol | For cisplatin premedication: 0.4 mg/kg IM ½ hour before infusion SQ, IM: 0.2 mg/kg TID-QID | Opioid/narcotic. Mechanism of action is unknown, but there are opioid receptors in the chemoreceptor trigger zone and it may work through use of these receptors. |

MISCELLANEOUS TOXICITIES

Doxorubicin is known to have cardiotoxicity. While it can happen at lower doses, with cumulative doses of >180 to 240 mg/m² many dogs will develop dilated cardiomyopathy. An echocardiogram can be done prior to starting therapy with doxorubicin to evaluate for pre-existing heart disease. A tachyarrhythmia is one of the early signs. To help protect the heart from this toxicity if using the drug at a high cumulative dose or if using this drug in dogs with preexisting heart disease, dexrazoxane (10 times the doxorubicin mg/m² dose) can be given 15 minutes before the infusion. The problem is that this drug is quite expensive.

Cyclophosphamide has been associated with sterile hemorrhagic cystitis. This is caused by the accumulation of the metabolites of cyclophosphamide in the bladder. Frequent walks after administration are advised to avoid the animal holding its urine. Many oncologists also prescribe furosemide (2-4 mg/kg PO BID for 3 doses) to help avoid this problem. If a patient does develop hemorrhagic cystitis it can be very difficult to treat. Clinical signs include stanguria, polakiuria and hematuria. We generally culture the urine to look for secondary infections. Prescribing a short course of

prednisone (0.5 mg/kg PO once daily) or NSAIDs may help with inflammation and discomfort. This can take weeks to months to resolve. In severe cases the bladder can be infused with DMSO, but this can be very uncomfortable so the patient will need to be sedated or anesthetized. It is important to note that once a patient shows signs hemorrhagic cystitis not to give the drug again as signs will progress.

Cisplatin is associated with nephrotoxicity. To help avoid this saline diuresis is necessary. The recommended saline infusion rates are 18.3 mL/kg/hr for 4hrs before, during and for 2 hours after the cisplatin administration. Creatinine levels should also be monitored and the drug not used if they are elevated.

CCNU has been associated with liver toxicity and liver values should be monitored for increases in ALKP and ALT. Remember that we will see some increase in ALKP if the patient is also on prednisone as part of their protocol. If the liver values continue to increase you may have to discontinue the drug.

References are available from the author upon request.