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PREVENTING SIDE EFFECTS
Prevention of chemotherapy-induced side effects begins with appropriate dosing.

ONCOLOGY

Chemotherapy-Induced Side Effects:

Prevention and Treatment

MEET THE AUTHOR

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Emily obtained her associate degree from Vet Tech Institute in December 2008, leading her to her registered veterinary technician license in January 2009.

She moved to Maryland, where she found her place in veterinary medicine, medical oncology. With her passion for helping animals and support from her coworkers, she achieved Veterinary Technician Specialist certification in oncology in 2014.

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Administration of any drug, supplement, or treatment can result in side effects, or adverse events. Chemotherapy is no exception. Although the goal of chemotherapy in veterinary patients is to extend the life of the patient without the harsh side effects seen in human oncology patients, side effects still occur regardless of the precautions taken. Chemotherapy side effects can include anything from drug-specific toxicities (e.g., sterile hemorrhagic cystitis, cardiac toxicity, hepatotoxicity, and hypersensitivity reactions) to more general side effects that fall under the categories of gastrointestinal and hematologic.[1]

GASTROINTESTINAL SIDE EFFECTS

Among the most common side effects of concern to clients when their pet begins chemotherapy are the gastrointestinal side effects (**TABLE 1**). This concern is for good reason because gastrointestinal side effects, which include vomiting, anorexia, diarrhea/soft stool, and ileus, are among the most commonly seen throughout veterinary oncology. Gastrointestinal side effects can occur acutely (during or immediately after treatment) or anywhere from 3 to 5 days post chemotherapy, sometimes as long as 7 to 14 days after (e.g., vinca-alkaloid–induced ileus).

Vomiting

Acute vomiting is caused by the release of certain neurotransmitters and activation of receptors in the chemoreceptor trigger zone and the vomiting center of

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TABLE 1 Drug-Specific Toxicities

Doxorubicin	Cardiotoxicity
Carboplatin, Cisplatin	Renal toxicity
Vincristine	Intestinal ileus
L-asparaginase	Hypersensitivity reaction
Cyclophosphamide	Sterile hemorrhagic cystitis
Rabacfosadine (tanovea)	Dermatologic toxicity, pulmonary fibrosis
CCNU (lomustine)	Hepatotoxicity

the brain. Acute vomiting usually results from rapid administration of a drug or the high emetic potential of certain drugs (**TABLE 2**). The number of acute vomiting episodes can be reduced by proper drug dilution ratios and administration rates.[1]

Before administration of certain drugs (i.e., doxorubicin, cisplatin), pretreatment with antiemetics such as maropitant, ondansetron, and butorphanol is recommended.[2] For patients receiving vincristine, the prokinetic properties of metoclopramide make it a better antiemetic choice than maropitant or ondansetron.[3] Whether to pretreat with antiemetics before drug administration also depends on the patient and client. When vomiting occurs outside of the acute time frame, most patients are treated successfully with medications like maropitant and metoclopramide and with diet change, without the need for a hospital visit. Although humans can experience what is known as "anticipatory vomiting," this phenomenon is uncommon among veterinary patients.

Anorexia

Although nausea, vomiting, and diarrhea tend to be well controlled at home by a number of methods and medications, until recently the same could not be said for anorexia. But in the fall of 2017, the first medication for stimulating appetite in dogs, capromorelin solution, was approved by the US Food and Drug Administration. This drug has been shown to be safe and effective for controlling chemotherapy-induced anorexia.[4,5] It works by mimicking the hunger hormone, ghrelin, binding to receptors on the hypothalamus and causing the feeling of hunger. It has also been shown to increase production of growth hormone from the pituitary gland, which is responsible for growth, metabolism, and body composition. It is supplied as a solution at a concentration of 30 mg/mL; recommended dosing is 3mg/kg PO q24h. For cats with chemotherapy-induced anorexia, there has been limited success with administering the antihistamine cyproheptadine and the antidepressant mirtazapine; these drugs, however, produce their own side effects (e.g., hyperactivity, manic episodes).

Diarrhea/Soft Stool

Vomiting and anorexia are not the only gastrointestinal side effects that affect veterinary oncology patients. Diarrhea and soft stool can occur with many chemotherapy drugs but can also be caused by the cancer itself (e.g., tumors of the intestinal tract, acute tumor lysis syndrome) or by the diet being fed during chemotherapy.

The cells that line the gastrointestinal tract are fully mature crypt cells.[6] Chemotherapy-induced diarrhea is caused by apoptosis (death) of the small intestine crypt cells, causing crypt hypoplasia. In humans, by 1 day

TABLE 2 Emetic Potential of Chemotherapy Drugs

HIGH
Cisplatin
Dacarbazine (DTIC)
Streptozotocin
MODERATE
Actinomycin
Carboplatin
Cytosine
Doxorubicin
Mustargen
Procarbazine
Vinblastine
Vincristine
LOW
Bleomycin
Chlorambucil
Loumustine
Cyclophosphamide
Ifosfamide
L-asparaginase
Melphalan
Mitoxantrone
5-Fluorouracil
Gemcitabine

after chemotherapy, the rate of apoptosis has increased by 7 times. Excoriation of the intestinal lining leads to decline of nutrient absorption and hydration. Patients are susceptible to sepsis from the release of bacteria into the vasculature.

Chemotherapy-induced diarrhea can often be resolved by administration of medications (e.g., metronidazole, tylosin, and loperamide) along with diet changes (e.g., withholding food, offering bland diets, increasing fiber).

Ileus

Ileus is a delayed side effect. Vincristine can cause ileus that doesn't appear until 7 to 14 days after administration. Patients experiencing ileus may exhibit generic side effects (i.e., vomiting, decreased appetite), but they may also exhibit the classic signs of ileus (i.e., infrequent or absent bowel movements, restlessness/discomfort, downward dog stretching).

Patients with severe ileus will require hospitalization and IV administration of fluids and gastroprokinetic drugs. Most episodes, however, are self-limiting and effectively treated by oral medications.[1]

HEMATOLOGIC SIDE EFFECTS

Although clients are typically most concerned about the gastrointestinal side effects of chemotherapy, another dose-limiting toxicity is bone marrow suppression. Traditional chemotherapy relies on administering the maximum tolerated dose. This is the dose that results in apoptosis of not only rapidly dividing cancer cells but also normal rapidly dividing cells (e.g., bone marrow, gastrointestinal tract, hair follicles). Cell precursors in the bone marrow are at a high risk for chemotherapy-induced death, creating a shortage of white blood cells, especially neutrophils. After administration of most chemotherapy drugs, the neutrophil nadir, the point at which this cell line reaches its lowest level during chemotherapy administration, occurs 5 to 10 days (average 7 days) later. Most nadirs progress without incident and without patients exhibiting clinical signs.[7]

When a patient's neutrophil count falls below 1000/µL, the risk for sepsis increases. Febrile neutropenia is a chemotherapy-related emergency. These patients may or may not exhibit clinical signs such as lethargy, vomiting, diarrhea, and anorexia. Management of these patients will require hospitalization, preferably away from other hospitalized patients and in a low-traffic area of the hospital. Treatments usually include intravenous fluids (rates dependent on the patient's health and hydration status), intravenous broad-spectrum antibiotics (e.g., enrofloxacin, ampicillin/sulbactam), and any ancillary medications required by that specific patient (e.g., maropitant, metoclopramide, metronidazole)(**TABLE 3**). The search for the infection source will depend on the patient's admission status and history and often includes thoracic radiography (3 views), along with a complete blood cell count, serum chemistry, and urinalysis and urine culture. Typically, the patient is hospitalized until afebrile and showing signs of improvement and a positive trend in the neutrophil count is documented. At that time, the veterinarian can recommend discharging the patient from the hospital with oral antibiotics and any necessary ancillary medications.[7]

TABLE 3 Commonly Used Ancillary Medications

Metoclopramide
Mirtazapine
Metronidazole
Cyproheptadine
Tylosin
Capromorelin Oral Solution
Loperamide
Maropitant
Ondansetron

CLIENT EDUCATION

Client education is a critical factor in preventing gastrointestinal side effects. Because certain chemotherapy drugs are more likely to result in gastrointestinal side effects, educating clients about gastrointestinal signs will help them identify these earlier and may prevent the need for hospital visits. Nausea is a difficult side effect for clients to recognize; therefore, signs of nausea, such as decreased or finicky appetite, drooling, hiding, or general malaise should be reviewed. Administration of antinausea medications, despite the absence of nausea, is unlikely to harm the patient. The benefits of pre-emptive ancillary medication outweigh the negatives.

An estimated 5% to 10% of patients will experience a side effect severe enough to warrant hospitalization. Fortunately, this subset of oncology patients is very

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small, the hospitalization stays are usually short (24 to 48 hours), and most hospitalizations can be avoided by educating clients on clinical signs and symptoms and proper at-home management.

GENERAL PREVENTION TIPS

Prevention of chemotherapy-induced side effects falls on the shoulders of the veterinary oncology team, beginning with appropriate dosing. Veterinary nurses who are well versed in the manifestations and management of chemotherapy-induced side effects are an integral part of the oncology team.

Most chemotherapy drug dosages are determined by using the m^2 measurement system.[1] However, specific drugs require special dose adjustments because of the size of a patient, and dosing may be based on mg/kg. Along with patient size, other factors that affect dosing include concurrent ailments, patient breed, *MDR1* gene status, and any organ dysfunction.[1] To avoid dose miscalculations, doses should be verified by the oncology staff members (e.g., weight verification, m^2 calculations, dosing calculations) and documented before administration.

After initiating a chemotherapy protocol for a patient, most oncology departments prescribe ancillary medications (e.g., metronidazole, metoclopramide, ondansetron, maropitant, and capromorelin oral solution) at the first treatment. Early administration, or premedication with appropriate ancillary drugs, can successfully decrease the severity of side effects. Having ancillary medications on hand enables clients to manage side effects as soon as they occur, as opposed to having to wait. Educating clients throughout the chemotherapy protocol about each medication's potential side effects and how to handle them will help clients prevent side effects or decrease their severity. The causes of the side effects and the potential for causing side effects vary by drug (e.g., the gastrointestinal side effect potential with cyclophosphamide is low).[1]

Repeat side effects from a specific drug can be prevented in a number of ways, starting with a very detailed-oriented discussion with the client. Discussions should cover what side effects occurred, when they first started, how long they lasted, their severity, and what (if any) treatment was administered. Detailed and accurate record-keeping for each patient, including any side effects, is vital. This information helps the oncologist decide the next course of action to ensure that the patient does not repeat this experience. Knowing when the side effects occurred the first time around will guide the start of early administration of preventive medications. If side effects were severe enough, reduction of future chemotherapy doses may be warranted. Doses can be reduced anywhere from 10% to 25%.

Overall, keeping an open dialogue with clients about the "road map" or plan to decrease side effects, including the pros and cons of dose adjustments and protocol scheduling adjustments, is fundamental. Oncology veterinary nurses can play an important role in this communication. TVN

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