Easy Ways to Improve Chemotherapy Treatment in Your Practice

Sue Ettinger, DVM, DACVIM
Dr. Sue Cancer Vet
Tarrytown, NY

"Cancer" is a scary word that is often equated with death. There is often a visceral fear of cancer, and pet owners think cancer equals pain and suffering. There are many myths and misconceptions about chemotherapy in pets. Owners think cancer treatment will just make the patient sicker.

But cancer is not a death sentence. With treatment, many cancer patients are not only living longer, but living well. Chemotherapy is well tolerated in the majority of dogs and cats undergoing treatment. Whether you are directly managing chemotherapy patients or sharing cases with an oncologist, there are simple tips and tricks to improve quality of life and minimize side effects in chemotherapy patients.

Chemotherapy

Conventional chemotherapy

Conventional chemotherapy is typically given at high dosages, known as maximum tolerated dose, or MTD. The goal is to kill the rapidly dividing cancer cells. But some normal cells that also have high turnover often can be temporarily damaged by MTD chemotherapy. The normal tissues that typically are most sensitive to chemotherapy are the bone marrow, hair follicles (alopecia), and the gastrointestinal lining. This is often referred to as "BAG". As a result there is a break period to allow these cell populations to recover. MTD is typically given weekly to every 3 weeks.

The overall toxicity rate is very low in veterinary chemotherapy patients. In my experience, only 15-20% experience side effects, and this is even less common in cats than dogs. The primary goal is to provide the best quality of life possible for as long as possible. As I say**, live longer, live well.** Most side effects are mild and medically manageable.

Metronomic chemotherapy

In contrast to MTD chemotherapy, metronomic chemotherapy is pulse or low-dose continuous chemotherapy. This is typically administered daily or every other day. The target is endothelial cells in that line tumor blood vessel. The goal may be tumor is stabilized, but this prevents further growth and spread. Common chemotherapy drugs include Palladia, cyclophosphamide, and chlorambucil and also with NSAIDS. There is still much to be learned including best drugs, dose, schedule, tumor types, and toxicity. This can be considered for some dogs and cats with advanced metastatic disease.

Side effects

Alopecia

Alopecia (hair loss) is due to damaging the rapidly dividing hair follicle. In dogs, potentially affected breeds have continuously growing coats and include Poodles, Scottish Terriers, and Westies. In cats, alopecia is rare, but shaved areas tend to grow back more slowly (limb catheters, abdominal ultrasounds). Cats more commonly lose their whiskers. The good news is that hair and whiskers will re-grow once the treatments have completed. Occasionally, hair will grow back a different texture or color. In cats it is typically softer, aka the "chemo coat". It is important to remember pets do not care about this cosmetic side effect, and it does not impact the quality of life. However, pet owners like to be advised about the whiskers and coat so they are not surprised.

Gastrointestinal (GI) toxicity

Gastrointestinal (GI) toxicity includes vomiting, diarrhea, decreased appetite, nausea. It typically 1 to 5 days after chemotherapy and is self-limiting – lasting on average 2-3 days. These side effects are less common in feline chemotherapy patients than dogs. I recommend being very proactive with nausea/anti-emetic drugs.

I often will use Cerenia or mirtazapine preventatively and as needed. I recommend giving Cerenia at administration with the following drugs: doxorubicin, vincristine, vinblastine, carboplatin, mitoxantrone, dacarbazine, and the MOPP protocol. If the pet has nausea/vomiting event within 24 hours of administration, I will add Cerenia SQ or IV at the time of administration at the subsequent treatment. For oral chemotherapy being given at home, I advise the owner give oral Cerenia 1 hour before chemotherapy pill dosing.

I always recommend oral Cerenia for 4 days after doxorubicin in dogs to prevent nausea and vomiting. If there are side effects with other chemotherapeutics, I also typically will add prophylactic medications to prevent side effects like nausea, vomiting or diarrhea as indicated. If the GI side effects are more severe in a patient, the drug type or dosage may be adjusted at subsequent treatments to minimize the chance of side effects recurring.

Unlike dogs, I do not routinely use GI medications unless the cat had issues with a prior treatment or had GI clinical signs prior to treatment (i.e. GI lymphoma)

For diarrhea, I typically send my patients home with metronidazole and a probiotic. Metronidazole is a synthetic nitroimidazole with antibacterial, anti-protozoal and anti-inflammatory properties and is commonly prescribed for acute and chronic diarrhea. It is

metabolized and excreted by the liver, so take care with patients with impaired liver function. Neurotoxicity is associated with higher doses and chronic use, so I do not recommend chronic use. Dose: 15 mg/kg PO BID for 5 days

Rx Clay is a good option for chronic diarrhea and patients needing multiple courses of metronidazole. Rx Clay is a calcium aluminosilicate (CAS), which is geological nanomaterial that adsorbs bacterial enterotoxins and increases reabsorption of intraluminal water in GIT

Vomiting and diarrhea

Acute vomiting is typically associated with cisplatin, doxorubicin (Adriamycin), dacarbazine (DTIC), cyclophosphamide, actinomycin, 5-FU streptozoticin. This can typically be prevented with pre-treatment

Delayed vomiting is more common in our patients. This is due to direct damage to rapidly dividing GIT cells (crypt cells) or via the centrally mediated CRTZ stimulated via gut vagal efferents. Delayed vomiting is most commonly 2 to 5 days post-chemo and seen with doxorubicin and the vinca alkaloids. Clinical signs include vomiting, diarrhea, anorexia, lethargy, weakness, ± dehydration.

For work up, I recommend CBC, chemistry panel, UA, +/- fecal floatation and cultures. If abdominal pain is present, consider AXR or AUS to rule out foreign body, obstruction, and intussusception. For patients with GI neoplasia, it can be challenging to differentiate chemotherapy side effects vs. disease, and a good history can be key.

For outpatient treatment, I recommend NPO, food & water trial, bland diet, anti-emetics, antibiotics with severe diarrhea and a probiotic. Do not forget to discontinue oral chemotherapy or delay chemotherapy treatment. In addition, I recommend prophylactic therapy with the next chemotherapy.

For inpatient, I add injectable antiemetics, IV fluid therapy, and IV antibiotics. An important note, I strongly encourage owners to NOT EUTHANIZE at this time. It is amazing with 1 to 2 days of good supportive care how quickly these patients improve. And with prophylactic therapy and a dose reduction, these patients can tolerate the same chemotherapy drug.

Myelosuppression and neutropenia

Bone marrow suppression most commonly results in a neutropenia but cats seem to be more tolerant than dogs. Neutrophils and platelets are at greatest risk due to the shorter circulating lifespan and shorter bone marrow transit times. Neutropenia is the dose-limiting toxicity in veterinary oncology.

How Myelosuppressive?	Chemotherapy Drug
Mildly to not	corticosteroids, Elspar, cisplatin, chlorambucil, bleomycin, vincristine
Moderately	vincristine, vinblastine, cyclophosphamide, melphalan
Highly	doxorubicin, Lomustine, mitoxantrone, carboplatin, combination protocols

In addition to the chemotherapy targeting rapidly dividing bone marrow stem cells, other mechanisms for neutropenia includes bone marrow infiltration with neoplastic cells (leukemia, advanced stage lymphoma, multiple myeloma) and increased consumption due to infection.

When a chemotherapy drug is used that is known to have a high potential for bone marrow suppression (like doxorubicin, carboplatin and Lomustine), a complete blood count (CBC) is often checked after the treatment to check the expected nadir (low neutrophil count) and see if antibiotics and/or a dose reduction are needed. I recommend a nadir be checked with all chemotherapy drugs except L-aspariginase.

The nadir typically occurs 7 days after chemotherapy administration. Pay attention to the neutrophil count, not the total white blood cell count. For some chemotherapy drugs the nadir is more variable such as carboplatin and Lomustine. For cats, the nadir is can occur 7 to 28 days after treatment. In dogs the nadir for carboplatin in day 10-14. Chlorambucil tends to cause delayed neutropenias and thrombocytopenias after chronic use. Subsequent doses of chemotherapy are adjusted based on the results of the CBC.

Antibiotics may be prescribed as a preventive measure but its use is controversial. Common antibiotics are TMS and Clavamox. I recommend prophylactic use with the more myelosuprressive drugs (doxorubicin, carboplatin and Lomustine) or if the previous nadir was <1500 neutrophils. Unlike dogs, I do not routinely use prophylactic antibiotics unless the cat had issues with a prior treatment.

In my experience, there is less than a 5% chance that a patient will need hospitalization. If this does occur, these patients are usually hospitalized for typically 24-48 hours with supportive care including IV fluids and antibiotics. In my experience most chemotherapy patients can successfully receive that drug again with a dose reduction.

What to do at the nadir visit?

In addition to running a CBC, it is important to get a good history, TPR (fever is so important in neutropenic patients), and a complete physical examination. I am always interested in knowing how the patient handled chemotherapy –did she eat well, any vomiting/diarrhea, did the owner use any nausea or diarrheal medications? For the exam, did he lose weight, was she febrile? The nadir CBC should not be a technician appointment to just pull the blood sample. The history and exam are very important.

Pay attention to the *neutrophil* count, not the total white blood cell count. The nadir typically occurs 7 days after chemotherapy administration, but can vary (see above). I recommend antibiotics if the neutrophil count is <1500. If the patient has <1500

neutrophils and is afebrile and feeling well, I recommend managing as an outpatient. However, if the patient has <1500 neutrophils and is febrile and sick, I recommend admitting for supportive care. Remember a febrile neutropenic is an oncologic emergency.

Also, I prefer that we get blood samples from the jugular veins for patients getting IV chemotherapy (unless thrombocytopenic). Save those peripheral veins for treatment please. Finally many times the oncologist has run a recent chemistry panel, so check with the oncologist, and try not to repeat unneeded blood work to keep costs down.

Neutrophil count (per uL)	**Fever, Systemic Signs**	**Plan**
1500-2500	No	Monitor +/- treatment delay 2 to 4 days
<1500	No	Oral antibiotics treatment delay Consider dose change
<1500	Yes	ATH for IVF & IV antibiotics treatment delay Dose reduction

Sepsis

Sepsis in chemotherapy patients is typically due to patient's own flora - Gram negative from GI bacteria: *E. coli, Klebsiella, Pseudomona;* Gram positive from skin bacteria: *Staphylococcus epidermitidis and aureus*, Anaerobes from oral bacteria. Predisposing factors include neutropenia (infection risk well correlated with degree and duration), cellular immune dysfunction, humoral immune dysfunction, prolonged hospitalizations, indwelling catheters, and poor nutrition.

History and clinical signs are typically straightforward - cytotoxic chemotherapy was administered typically 5 to 7 days ago. Remember, the **febrile neutropenic patient is an oncologic emergency!!!** In addition the patient may have an inability to mount an inflammatory response, so the lack of fever, pyuria, or radiographic changes of pneumonia does not rule out sepsis. Signs of illness are unrelated to absolute neutrophil count, but are related to an increased susceptibility to local and systemic infections when neutropenic. Gastrointestinal, urogenital, and respiratory infections are most common. Shock is also possible

The sepsis work up includes: CBC, Chemistry panel, UA & UCS (if >50,000 platelets). If respiratory signs are present, chest radiographs are recommended, and TTW should be considered. Blood cultures may be needed, but uncommon in my experience. Culture any catheters suspected as the infection source.

Treatment for sepsis includes: IVF and broad-spectrum IV antibiotics. Neupogen is human recombinant G-CSF. The MOA is stimulation of proliferation & maturation of neutrophil precursors, and monocyte precursors to a lesser extent. It also primes neutrophil for cell killing & neutrophil migration. The benefit for the febrile & febrile neutropenic patient is contradictory, and in my experience, Neupogen is rarely needed. The recommended dose is 5 ug/kg SQ SID until neutrophil >1000.

When should I lower chemotherapy dose?

Dose Intensity is chemotherapy given at MTD & shortest possible interval. It is important to remember than small dose changes can have significant impact on cancer control. Dose reductions as small as 20% can decrease drug efficacy up to 50%. *Dose reductions should not be considered lightly.*

Don't treat cats like small dogs when it comes to chemotherapy

Some chemotherapy drugs are dosed differently in cats. In dogs, weight and body surface area are used to determine the carboplatin dose. In cats there is now a more accurate method to dose carboplatin in cats based on glomerular filtration rate, which is determined with an Iohexol clearance test.

Side effects in cats are also different. Cardiotoxicity is a well-described adverse effect in dogs treated with doxorubicin, but it has not been reported in cats. Sterile hemorrhagic cystitis (SHC) is a relatively uncommon complication of cyclophosphamide in dogs and ifosfamide therapy in dogs and cats. SHC is typically associated with long-term use, but possible after single dose, and can progress to bladder fibrosis. The incidence with cyclophosphamide has been reported to be 9% in dogs (7-24%), 3% in cats, and 24% in humans. Unlike dogs, concurrent administration of furosemide with cyclophosphamide is not recommended in cats. Mesna, which binds the SHC-inducing acrolein, is recommended for cats and dogs when administering ifosfamide.

Chemotherapy safety

Chemotherapy requires careful prescription preparation, drug dispensing, drug administration, client education, and safe handing of patients by ALL staff. Chemotherapy exposure has been documented in nurses and pharmacy workers. It is important to protect your team, our clients, & follow protocols.

To protect your staff, the following are recommended a hood, closed system transfer device, dedicated counting equipment, dedicated chemo fridge, and Personal protective equipment (PPE) including gloves, gowns, chemo mat, and eye protection. Closed system transfer device such as PhaSeal® are leak-proof and airtight closed system transfer devices. Studies show closed systems reduce contamination and should be combined with other safe handling practices

Active drug & metabolites are excreted in urine & feces, and there is some in saliva but research six limited. In the hospital identify patients after chemotherapy and dispose of wastes separately. Spill kits should be on hand and stocked.

Protect your entire staff and make sure staff is aware patient is getting chemotherapy. Special precautions are recommended for staff and clients that are pregnant, trying to become pregnant, breast-feeding, immunosuppressed, ir taking immunosuppressive medication. Recommend they talk to their physician.

Protect your client and discuss safety tips including common sense precautions, good basic hygiene, and provide an information sheet. Recommend they wear gloves when handling urine, feces, or vomit for at least 72 hours after treatment and when cleaning litter box. Wash soiled bedding separately & 2 wash cycles before use again, use detergent to clean floors, carpets, or countertops, and wear gloves when cleaning

It is safe to be around pets undergoing chemotherapy. Metabolites are far less active than original drug. Being around family members – human and other pets in the home - is an important part of a pet's life. Normal activities are safe, but owners need to be careful with excretions.

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