Side Effects of Chemotherapy
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Clients of pets with cancer have recently begun to expect the same level of care for their pets as they receive from their physicians and oncologists. This predicates that veterinarians treating pets with cancer have an increased understanding of the possible complications of cancer therapy. This review will concentrate on developing an increased understanding of the side effects of chemotherapy in order to best prevent and treat these side effects, thereby leading to an increased quality of life for those pets.

Most chemotherapy agents have a “BAG” (Bone marrow suppression, Alopecia, and Gastrointestinal) of side effects. The reason why these side effects are so common after chemotherapy administration is because these tissues contain cells that are rapidly growing and therefore inherently sensitive to chemotherapy. Therefore, cells such as those found in the bone marrow, as well as gastrointestinal epithelial cells and hair follicle cells that rapidly turnover are quite sensitive to chemotherapy, whereas cells that slowly turnover, or do not turnover (e.g. spinal cord, muscle, etc.) are generally extremely resistant to most chemotherapy agents.

The “B” in a “BAG” of side effects stands for bone marrow suppression, or myelosuppression. Almost all chemotherapy agents are myelosuppressive, however, at standard doses, corticosteroids, L-asparaginase, vincristine and bleomycin are not myelosuppressive. After a myelosuppressive chemotherapy agent is administered, the neutrophil count and platelet count may decrease, and the low point of the count for either of these types of cells is called the “nadir.” The neutrophil and platelet nadir for most myelosuppressive chemotherapy agents is ~7 days, and this can be predicted based on the half-lives of neutrophils and platelets. The half life of neutrophils, platelets and red blood cells is 6 hours, 6 days, and ~120 days, respectively. Therefore, after myelosuppressive chemotherapy administration, neutropenia is the first to occur, and then thrombocytopenia, whereas anemia due to chemotherapy is extremely rare, because of the longer half-life of red blood cells. There are exceptions to this ~7 day nadir rule, which include cisplatin in the dog (days 7 & 17), carboplatin in dogs (day 10-14) and cats (day 21; and such is why an every 28 day therapy cycle is recommended in cats), as well as those chemotherapy agents that are orally administered on a somewhat continual basis such as melphalan, chlorambucil and others.

In order to ensure that the nadir does not drop below safe levels, a pre-treatment cbc/platelet count is required within 12-24 hours before EVERY myelosuppressive chemotherapy administration. For most myelosuppressive agents, a good rule of thumb is the presence of > 3,000 neutrophils and > 75,000 platelets. Similarly, after the first administration of a myelosuppressive chemotherapy agent, a “nadir” cbc/platelet count is performed ~7-10 days after the drug is administered. If the neutrophil count is 1500-3000, this is to be expected and subsequent doses of this drug should continue at the same level. If the “nadir” neutrophil count is < 1500 but the pet is not sick and does not have a fever, prophylactic broad spectrum antibiotics (Clavamox, TMP-S, etc.) are instituted for 5-7 days and considerations are made for a 10% decrease in the next dosing of that chemotherapy agent. If the pet has < 1500 neutrophils, has a fever and/or is sick (vomiting, diarrhea, etc.), then this represents an oncologic emergency, and hospitalization, blood/urine cultures, emergency fluid support and IV antibiotics are indicated. In addition, the dose of that chemotherapy agent upon the next administration will
typically be reduced by ~ 25-30% to reduce the chance of subsequent severe neutropenia. The astute clinician will also remember that neutrophils are necessary for the production of a fever, therefore, a lack of a fever does not rule out sepsis.

The “A” in a “BAG” of side effects stands for alopecia or hair loss. This is a rare side effect of chemotherapy, however, it can occur in any breed of dog. Chemotherapy-associated alopecia is primarily seen in breeds with continuously growing haircoats such as Old English Sheepdogs, Terriers, and Poodles. More commonly, dogs tend to have partial alopecia with hair loss over exposed areas such as the face, shoulders, and the back. It is important to remember that shaved areas are particularly slow to regrow while on chemotherapy, and therefore these areas should be minimal and squarely shaved. Cats do not generally experience alopecia while on chemotherapy; however, loss of whiskers is extremely common. The hair/whiskers begins to regrow over the course of weeks to months once chemotherapy is discontinued, and it is generally more coarse and of a slightly different color than originally seen.

The “G” in a “BAG” of side effects stands for gastrointestinal. While gastrointestinal side effects of chemotherapy are not very common, when they occur it can be a serious side effect for the patient and client alike. Gastroenteritis manifesting as vomiting and or small bowel diarrhea is seen in ~ 15-20% of dogs and cats receiving most chemotherapy protocols (because the small bowel enterocyte is so rapidly turning over), whereas nausea is thought to be seen in ~ 50-75%. This side effect is generally seen 3-4 days after chemotherapy administration and lasts for 2-4 days. Chemotherapy-associated colitis is extremely rare because of the slower turnover of large bowel epithelial cells, however, 25-40% of dogs experience colitis after administration of Doxorubicin.

This author routinely sends home metoclopramide (Reglan) for all patients receiving chemotherapy, however, the client is instructed to use it on an as needed basis. In addition, dogs receiving Doxorubicin are sent home with sulfasalazine (potent anti-colitis medication) to also be used on an as needed basis. The clients are also educated to be better able to delineate when their pet is experiencing nausea, as this can be very difficult to discern when compared to overt vomiting or diarrhea. The table included below compares and contrasts the presently available anti-nausea/anti-emetic products, including the new Cerenia product from Pfizer Animal Health.

In addition to the more common “BAG” of side effects discussed above, there are unique side effects to certain organ systems that are generally chemotherapy-agent dependent. This includes Doxorubicin cardiotoxicity, the nephrotoxicity of platinum agents (cisplatin & carboplatin), cyclophosphamide sterile hemorrhagic cystitis, neurotoxicity of vinca alkaloids and platinum agents, allergic and hypersensitivity reactions to L-asparaginase and other drugs, dermatotoxicity of Doxil (liposome-encapsulated doxorubicin), prevention of doxorubicin-related extravasation injury with a new drug called Zinecard, and lastly the hepatotoxicity of CCNU (Lomustine) and occasionally other chemotherapy agents. These will be covered in more detail in the oral discussion, as will the rarely seen syndromes of acute tumor lysis and cranial vena cava syndrome.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Antagonism</th>
<th>Dose &amp; Route</th>
<th>DVM Cost 40# dog per day</th>
<th>Efficacy for Delayed Nausea/Emesis</th>
<th>Efficacy for Acute Nausea/Emesis</th>
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<tbody>
<tr>
<td>Cerenia (Maropitant)</td>
<td>Neurokinin-1</td>
<td>2 mg/kg PO or 1mg/kg SQ q 24 hours</td>
<td>~ $ 4-6 (oral)</td>
<td>+++/??</td>
<td>+++</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>~ $10-12 (inj)</td>
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<tr>
<td>Zofran (Ondansetron)</td>
<td>Serotonin Re</td>
<td>~ 0.5 mg/kg BID-TID PO or IV</td>
<td>~ $50-75</td>
<td>+++/??</td>
<td>??</td>
</tr>
<tr>
<td>Anzemet (Dolasetron)</td>
<td>Serotonin Re</td>
<td>~ 0.5 mg/kg q 24hrs PO, SQ, IV</td>
<td>~ $25-35</td>
<td>+++/??</td>
<td>??</td>
</tr>
<tr>
<td>Reglan Metoclopramide</td>
<td>Dopaminergic &amp; Weak Serotonin Re</td>
<td>0.2-0.4 mg/kg BID-TID PO or Inj</td>
<td>~ $1-2</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Thorazine/Compazine</td>
<td>Histaminergic Adrenergic</td>
<td>Variable</td>
<td>Variable Inexpensive</td>
<td>+/-</td>
<td>??</td>
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<tr>
<td>Butorphanol</td>
<td>Opiate Re</td>
<td>0.4 mg/kg IM 30 mins prior</td>
<td>Variable</td>
<td>--/??</td>
<td>++</td>
</tr>
<tr>
<td>Steroids</td>
<td>??</td>
<td>Variable</td>
<td>Generally Inexpensive</td>
<td>--/??</td>
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CE Questions by Dr. P. Bergman

1. When discussing with a client the side effects of chemotherapy, it is easy for the client to understand and remember the acronym a “BAG” of side effects, which stands for bone marrow, alopecia and gastrointestinal. Why are these cell types inherently so sensitive to chemotherapy?
   a. Their DNA is less resistant to the chemotherapy
   b. They come into more contact with the chemotherapy
   c. They break down the chemotherapy making them more sensitive
   d. They are rapidly dividing and growing cells

2. Which one of the following chemotherapy agents is myelosuppressive at standard dosages?
   a. L-asparaginase
   b. Vincristine
   c. Carboplatin
   d. Bleomycin

3. The lowest point that a neutrophil and/or platelet count reaches after administration of a chemotherapy agent is generally:
   a. 12 hours
   b. 24 hours
   c. 2 days
   d. 5-7 days
   e. 14 days

4. The neutrophil nadir for cats treated with carboplatin is X days and the recommended time between carboplatin treatments in cats is Y days (please answer X / Y).
5. The recommended minimum number of neutrophils and platelets prior to administration of a myelosuppressive chemotherapy agent is:
   a. 5,000 neutrophils & 125,000 platelets
   b. 3,000 neutrophils & 125,000 platelets
   c. 3,000 neutrophils & 75,000 platelets
   d. 2,500 neutrophils & 50,000 platelets

6. Which one of the following breeds of dogs would be most expected to experience significant chemotherapy-associated alopecia?
   a. Rottweiler
   b. Standard Poodle
   c. Golden Retriever
   d. German Shepherd
   e. Cocker Spaniel

7. What drug should be sent home with clients to be used on an as needed basis for possible colitis from Doxorubicin administration in dogs?
   a. Tylosin
   b. Sucralfate
   c. Metronidazole
   d. Sulfasalazine

8. Doxorubicin can cause dilated cardiomyopathy after any number of administrations in dogs, however, it is seen more commonly after what cumulative dose?
   a. 100-140 mg/m2
   b. 180-240 mg/m2
   c. 300-340 mg/m2
   d. > 500 mg/m2

9. What drug can be given IV just after IV cyclophosphamide (Cytoxan) in dogs to prevent or decrease the chance of sterile hemorrhagic cystitis?
   a. Furosemide
   b. Dexamethasone
   c. Normosaline (0.9%)
   d. Thiosulfate

10. A cat represents to your clinic 7 days after administration of a chemotherapy agent for constipation, and on workup you find the cat to have GI ileus. Which of the following chemotherapy agents most likely has caused this??
    a. Carboplatin
    b. Vincristine
    c. Doxorubicin
    d. Cyclophosphamide

Answers:
1. d
2. c
3. d
4. a
5. c
6. b
7. d
8. b
9. a
10. b