General Recommendations for Management of the Common Side Effects of Chemotherapy

Dr Maureen Cooper and Dr Laura Brockley
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Dr Maureen Cooper  
DVM, MACVSc (Small Animal Medicine), FACVSc (Veterinary Oncology)  
Dr Maureen Cooper, originally from Canada, obtained her veterinary training at the Western College of Veterinary Medicine in Saskatoon, Saskatchewan, Canada. After completing a combined Medicine/Surgery internship at Purdue University (Indiana), USA, Dr Cooper spent time in a mixture of general and referral practice in New York. Dr Cooper completed her residency in Veterinary Oncology at the Melbourne Veterinary Specialist Centre. She became a Fellow in the Australian College of Veterinary Scientists in Oncology in 2010.

Dr Laura Brockley  
BVSc (Hons), MACVSc (Small Animal Medicine)  
Dr Laura Brockley graduated from The University of Melbourne with a Bachelor in Veterinary Science with honours in 2001. Dr Brockley has worked in a variety of small and mixed practices in Victoria and the UK. She joined Melbourne Veterinary Specialist Centre in 2008 as an Oncology Intern. Dr Brockley achieved membership of the Small Animal Medicine chapter of the ACVS (Australian College of Veterinary Scientists) in 2009. She is currently in the second year of her oncology residency at the Melbourne Veterinary Specialist Centre.
General Recommendations for Management of the Common Side Effects of Chemotherapy

The use of effective chemotherapy protocols in animals with sensitive cancers can lead to a good quality of life and extended survival. However, we need to consider the potential for adverse effects in these patients that may impact on quality of life. To make the experience for owners and their pets a positive one, it is important to educate clients as to the type and likelihood of adverse effects. Additionally, a plan for prevention and management of these events should be discussed in advance. Most chemotherapy agents and protocols routinely used in veterinary oncology are well tolerated by animals. In general, approximately 80% of patients experience minimal to no side effects; and when they occur they tend to be mild and self-limiting. Veterinary oncology protocols are generally designed to result in less than a 5% hospitalisation rate for chemotherapy toxicity. With appropriate intervention, the risk of a treatment-associated fatality is <0.5-1%.

Most current chemotherapeutic drugs work by damaging or destroying cells with a high turn-over rate. This will target the cancer, but can also damage normal tissue whose cells are actively dividing. This can be thought of as “collateral damage”. Most cells in the body are in a quiescent state, however, normal cells which are susceptible to damage due to increased cell turnover are those of the gastrointestinal tract, blood and bone marrow, skin and reproductive organs. It has been shown in human oncology that prevention of these adverse effects is more effective than managing the events after they have occurred. In the case of serious side effects which impact significantly on quality of life and are not alleviated by pre-emptive measures, dose reductions or drug alterations can be considered. Included are some guidelines for managing the patients that do experience adverse effects.
Individual and Breed Predisposition to Adverse Effects

Individual and breed variations can be seen in both the response to chemotherapy and the potential associated toxicity. In humans, pharmacogenetic testing has started to determine variations between individual patients in regards to pharmacokinetics and pharmacodynamics, however, this is not yet underway for animal patients. Certain breeds, particularly Collies, are known to be at risk from chemotherapeutic agents which are actively transported by the P-glycoprotein pump (P-gp). Some examples of drugs which are P-gp substrates include vincristine and the other vinca alkaloids, doxorubicin and anthracyclines, dactinomycin and the taxanes. P-gp acts as an efflux pump that actively extrudes drugs from tumour cells, preventing these drugs from reaching cellular sites of action. P-gp is under control of the multidrug resistance (MDR) gene. Certain breeds have been shown to have a high frequency of a germline mutation of the MDR1 allele (ABCB1-1Δ polymorphism). This mutation can lead to increased drug toxicity to the patient by diminishing the excretion of P-gp substrate drugs. If the patient is homozygous for the mutant allele, they will be affected and at risk for toxicity. If the patient is heterozygous they are a carrier and whilst the risk may be increased, it is unlikely to have a clinical impact.

**Pharmacogenetic**
Pharmacogenetics refers to genetic differences in metabolic pathways which can affect individual responses to drugs, both in terms of therapeutic effect as well as adverse effects.

**Pharmacokinetics**
The effect the body has on the drug.

**Pharmacodynamics**
The pharmacological effects the drug has on the body.

An assay for the gene mutation is available via Gribbles Veterinary Pathology and is recommended for at risk breeds. In Australia, the homozygous mutation has been reported in 24% of Collies and 21% of Australia shepherds. The heterozygous mutation has been reported in 64% of Collies, 43% of Australian shepherds and 43% of Shelties. The results of the MDR1 gene test are usually available within one week. In the meantime, another non-P-gp substrate drug can be substituted until the results are received. P-gp drugs should be avoided if possible in dogs homozygous for the mutant allele. If their use is unavoidable, significant dose reductions should be used, however there are no published recommendations on the degree to which these drugs should be reduced. Some veterinary oncologists suggest a 40% dose reduction for MDR1 homozygous patients. If the dose reduced drug is tolerated well in a homozygous patient, gradual increasing doses can be trialled.
Specific Toxicities

I. Bone Marrow

Myelosuppression occurs secondary to damage to the rapidly dividing bone marrow stem cells. Cells with the shortest circulating life span are the most susceptible, hence myelosuppression often manifests as neutropenia or thrombocytopenia or possibly both.

A. Neutropenia

Some degree of neutropenia is an expected side effect of chemotherapy and the risk of secondary infections is low if the neutrophil count remains greater than $1 \times 10^9/L$. Mild neutropenia is often self-limiting and often requires no treatment. However, at the other end of the spectrum, severe neutropenia can be complicated by sepsis and may be life threatening. If the timing of neutropenia coincides with gastrointestinal damage from chemotherapy the consequences can be more serious. Micro-ulcers in the gastrointestinal tract along with loss of the protective layer of desquamated cells, saliva and mucous, can create a favourable environment for bacterial overgrowth, invasion and translocation.

Assessing for neutropenia
Febrile Neutropenia

Febrile neutropenia is defined as neutropenia induced by chemotherapy, in combination with fever. The neutrophil nadir or trough usually occurs after 7-10 days for most drugs, although there will be variability between patients and chemotherapy agents. Some drugs can have a bimodal nadir (e.g. carboplatin), and others can cause neutropenia as early as 4-5 days post chemotherapy (e.g. vinblastine) or as late as 2-3 weeks post chemotherapy (e.g. carboplatin). The effects on the patient are related to the drug used in many cases. For example; a dog with severe neutropenia after receiving CCNU can have no clinical signs, while another dog with a milder neutropenia after doxorubicin can be very unwell. Monitoring patients with a complete blood count (CBC) is mandatory prior to each chemotherapy treatment. It is also essential to perform a CBC at the expected nadir for each chemotherapeutic drug administered. This should at least be done after the first treatment and after any dose changes.

Standardised recommendations for the prevention and management of chemotherapy induced febrile neutropenia exist in human oncology. In veterinary oncology standardised recommendations have not been developed thus decisions are based on the current literature and experience of the oncologist.

Neutropenia without Pyrexia or Clinical Signs

A neutrophil count of $1 \times 10^9/L$ or less in an otherwise clinically normal animal can usually be managed with prophylactic oral antibiotics and monitoring of body temperature on an outpatient basis. The risk of nosocomial infection probably outweighs the benefit associated with hospitalisation. We recommend broad spectrum antibiotics that spare normal anaerobic gastrointestinal flora such as trimethoprim-sulphonamide (7.5-15 mg/kg bid) or a fluoroquinolone (enrofloxacin 5-10 mg/kg sid), prescribed for a seven day course. Anaerobe sparing antibiotics are preferred as they help prevent overgrowth of aerobic Gram-negative bacilli and Gram-positive cocci and their invasion across the potentially weakened gastrointestinal tract. A repeat haemogram five to seven days later generally reveals marrow recovery. Non-febrile, clinically well patients with mild neutropenia ($>1 \times 10^9/L$) generally require no treatment.

Neutropenia with Mild Clinical Signs

If the patient has neutropenia and is unwell we recommend using combination antibiotics to cover a broad spectrum of bacteria. The combinations of clavulanic acid and amoxicillin (12.5-25 mg/kg bid) and enrofloxacin (5-10 mg/kg orally or IV sid to bid); or metronidazole (10-15 mg/kg bid) and enrofloxacin are two options we use commonly in these situations. Metronidazole is commonly used in the combination if doxorubicin has been administered as colitis may be present with this drug.
Neutropenia with Pyrexia and Moderate to Severe Clinical Signs

Patients with neutropenia who have pyrexia and moderate to severe systemic signs of illness (general malaise, anorexia, vomiting or diarrhoea) should be hospitalised for parenteral administration of broad spectrum antibiotics, intravenous crystalloid therapy and close observation and monitoring. Septic patients are usually febrile, however some patients with a severe neutropenia may be unable to produce a fever due to inadequate cytokine production. These patients will often show other signs of sepsis such as tachycardia, injected mucous membranes, weak pulses and prolonged capillary refill times. An initial minimal database should include a complete blood count, serum biochemistry profile and urinalysis.

Urinalysis may reveal an inactive sediment, however a urinary tract infection cannot be ruled out as neutropenia can result in the absence of white blood cells in the urine. A urine culture could be considered in any patient with neutropenia. Thoracic radiographs to search for a nidus of infection are indicated in patients presenting with coughing, or a history of vomiting prior to presentation. It may be prudent to keep the patient in an isolated area and practise good hygiene and biosecurity as they are at risk of exposure to pathogens from other hospitalised patients.

Lactated solutions (such as Hartmanns) should be avoided in dogs and cats with cancer. This is particularly important with lymphoma patients as these patients tend to have high serum lactate concentrations. Lactate is not in a useable energy form for patients and thus must be converted to glucose at a net energy expense to the host. This is part of the futile energy cycles that can contribute to cancer cachexia in oncology patients. Often a 0.9% saline solution will be a suitable choice for fluid therapy. A fluid rate of 1.5 times maintenance is reasonable after correction of any existing fluid deficits. It is common for fever and clinical signs to improve dramatically after several hours of fluid therapy. Intravenous antibiotics which cover both Gram-positive and Gram-negative organisms should be administered.
We typically use a combination of amoxicillin (22 mg/kg tid) and enrofloxacin (5-10 mg/kg IV sid) or cephalexin (20-30 mg/kg tid) and enrofloxacin (5-10 mg/kg IV sid). Anti-pyretics, such as non-steroidal anti-inflammatories, are almost never necessary and may make interpretation of the patient’s response to therapy difficult.

The majority of patients respond quickly to therapy, and neutrophil counts often rise rapidly. Most are afebrile within 12-24 hours. Patients are generally discharged when they are eating, drinking, afebrile and their neutrophil count is rising (but it does not have to normalise prior to discharge). In patients that do not respond clinically within the first 12-24 hours, a search for a potential nidus of infection is indicated. Further diagnostics include aseptic collection of urine (cystocentesis) for culture and sensitivity; thoracic radiographs, abdominal ultrasound and echocardiography and blood cultures. It may be prudent to contact your local laboratory in regards to blood cultures. We recommend at least two sets of cultures be submitted. Because the majority of patients respond to symptomatic treatment, the inclusion of these diagnostics at presentation may not be warranted, particularly in regards to a cost benefit ratio. In those patients not responding to therapy, antibiotic coverage can be broadened to include anaerobic coverage (metronidazole 10-15 mg/kg IV bid). If protracted neutropenia occurs (>72 hours) a bone marrow evaluation (aspirate or core biopsy) may be useful. This is particularly helpful in patients with haematopoietic neoplasia, to rule out neutropenia secondary to bone marrow infiltration (myelophthisis) versus myelotoxicity.

**Prophylaxis for Chemotherapy Induced Neutropenia**

Dose reductions of 20% should be considered if the neutrophil count falls below 0.5 x 10⁹/L at nadir. Dose reductions should not be considered lightly because dose intensity is extremely important for anti-tumour response. In many cases prophylactic antibiotic therapy is used in preference to a dose reduction.

Patients need to have recovered from the neutropenia before their next treatment, but in some cases treatment can be given at levels of 1.5-2.5 x 10⁹/L, depending on which drug you next plan to use. In patients where the tumour is the primary cause of the neutropenia, often these rules no longer apply! In these patients, detailed knowledge of their situation is needed to select the appropriate chemotherapy drug or protocol along with aggressive supportive care afterwards.

Human haematopoietic growth factors for animal species are not routinely recommended in veterinary oncology. Their use is controversial as their utility in decreasing morbidity and mortality for animals in a clinical setting has not been established. Availability of canine and feline recombinant granulocyte colony stimulating factor (G-CSF) is limited and often a human product is used. This is an expensive option and due to species differences cross reactive antibody production may occur, exacerbating the neutropenia. These products can also have an undesirable pro-growth effect on haematopoietic neoplasia. In people the only setting in which their use has translated into clinically relevant gains (in morbidity and mortality) is for patients in which the risk of febrile neutropenia is >20%. This is rarely, if ever, the case for veterinary oncology protocols.

Reduction in other white cell lines, such as lymphocytes and eosinophils are rarely recognised as being clinically significant. There is no specific treatment known at this time for these findings and there is no clinical reason to attempt to correct them.
B. Platelet Disorders

Platelet disorders occur with some frequency in cancer patients. The most common is thrombocytopenia, but we can also see thrombocytosis and thrombocytopathy or a dysfunction of platelets.

Thrombocytopenia associated with chemotherapy is rarely clinically significant and often does not result in bleeding. It may be caused by decreased production (usually from myelophthletic disease); increased destruction (usually immune-mediated); increased utilisation (blood loss or disseminated intravascular coagulation or DIC) or sequestration (within large vascular tumours). Chemotherapy treatment should be delayed if the platelet count is $50 \times 10^9/L$ or less. The exception to this rule is if the cytopenia is believed to have arisen secondary to the tumour, as a paraneoplastic syndrome or from myelophthisis. In these cases, we often consider a less myelosuppressive drug such as vincristine or L-asparaginase. Sometimes cancer must be treated in the face of cytopenias to resolve the low cell count. We provide supportive care and close monitoring for these cases. Immunosuppressive therapy is indicated if the thrombocytopenia is confirmed or suspected to be secondary to auto-immune destruction. A repeat haemogram is necessary 5-7 days later and/or prior to the next scheduled treatment.

Thrombocytosis is not well understood. It is most often associated with primary bone marrow diseases such as leukaemia but also myelofibrosis and other causes of marrow damage. Additionally a rebound thrombocytosis is noted in some patients after myelosuppression due to chemotherapy and also with the use of glucocorticoids.

Thrombocytopathy is the least common and often occurs when the platelets are coated with proteins which reduce their ability to adhere to damaged blood vessels. The plasma cell tumours (plasmacytoma and multiple myeloma) are most commonly associated with a clinically relevant thrombocytopathy.

Assessing Mucous Membranes
Clinical Signs
The signs of thrombocytopenia and thrombocytopathia are similar. The defect in primary haemostasis leads to bleeding, usually from mucosal surfaces. The most common signs are epistaxis, oral bleeding, gastrointestinal bleeding and haematuria. Bleeding into internal body cavities is not common. The amount of blood loss is variable, but can be severe. Thrombocytosis is generally not associated with clinical signs, but if marked it is theoretically possible for the patient to become hypercoagulable and be at risk of thrombotic disease or disseminated intravascular coagulation (DIC).

Treatment
There are few effective treatments for platelet disorders other than treating the underlying cause and immune suppression in cases of immune-mediated destruction. General supportive care for these patients includes cage rest, prevention of trauma, and minimisation of injections. For example, consider using oral or intravenous routes into a pre-existing catheter when possible. If thrombocytopenia is induced by a chemotherapeutic drug, often all that is required is a delay in treatment until the platelet count rises. Platelet transfusions have a very short half life and with their extremely limited availability, they are almost always not an option. If platelets numbers are severely low, if the patient is showing clinical signs of thrombocytopenia, or if there is concurrent anaemia; fresh whole blood can be transfused and may temporarily alleviate clinical signs. Fresh whole blood or platelet components such as platelet rich plasma or platelet concentrate can be used for transfusion. The latter two are often not available in Australia. These products must be fresh as platelets become non-functional if they are frozen or stored for prolonged periods. Administration of a single unit of any of these products has the potential to increase the platelet count of a 20 kg dog by as much as 30-40 x 10^9/L. However, in patients with thrombocytopenia due to accelerated platelet destruction or utilisation (immune mediated thrombocytopenia, disseminated intravascular coagulation), the platelets have dramatically reduced circulating life spans (minutes to hours) and transfused platelets are destroyed rapidly. In these cases multiple units are required which is both impractical and cost prohibitive in most situations. The administration of a single unit of these products to these patients is often ineffective.
2. Gastroenteritis

Gastrointestinal toxicity secondary to chemotherapy can be mild and self-limiting, moderate or severe. It may occur secondary to direct damage to intestinal epithelial cells or by means of efferent nervous stimulation of the chemoreceptor trigger zone (CRTZ) and other higher brain centres (i.e. the emetic centre). It typically manifests as inappetence, nausea, vomiting and/or diarrhoea, usually beginning 3 to 5 days after therapy. When direct stimulation of the CRTZ is the aetiology, vomiting is maximal on the day of therapy. Acute vomiting is defined as that occurring within 24 hours of treatment, this is most commonly associated with dogs receiving cisplatin. Chronic gastrointestinal upset (3-5 days post treatment) is much more common and is a result of irritation or inflammation of the gastric and intestinal mucosa. The consequences of significant gastrointestinal side effects include: dehydration, decreased quality of life, nutritional deficiencies, delays in therapy or dose reductions, increased financial burden (associated with hospitalisation) and in general, a decreased enthusiasm in clients to continue therapy. Therefore, judicious use of anti-emetics and anti-diarrhoeals is recommended.

Chemotherapy induced diarrhoea is believed to be due to cytotoxicity to highly proliferative intestinal crypt cells along with alterations in intestinal enzyme balance. As previously discussed, patients with diarrhoea are at higher risk for sepsis secondary to bacterial translocation secondary to mucosal damage, particularly if there is a concurrent neutropenia. The mechanisms involved in the emetic pathway are complex and no single agent can be expected to provide complete protection for every chemotherapy protocol or patient. The most effective class of anti-emetic to date in people for vomiting associated with chemotherapy are the NK-1 receptor antagonists. They have been shown to be superior to other classes of anti-emetics and their use is recommended in human cancer guidelines. Maropitant (Cerenia®), an NK-1 receptor antagonist has been approved by the Australian Pesticides and Veterinary Medicines Authority (APVMA) in Australia for use in dogs. It has been shown to be a highly effective anti-emetic in dogs, including superior activity for prevention and treatment of acute vomiting associated with cisplatin administration. Maropitant is not yet approved for use in cats, however, studies in this species have found it to be safe and efficacious at a recommended dose of 1 mg/kg by either oral or subcutaneous routes.
It has been shown in people that prevention of nausea and vomiting is much easier than treatment once the event(s) has occurred. This is likely to be true for veterinary patients. For patients that have experienced significant gastrointestinal toxicity after a particular chemotherapy drug, or for a protocol with an anticipated moderate to high risk of gastrointestinal events we typically pre-treat with maropitant and/or dispense a four day course of oral therapy (2 mg/kg once daily).

Metoclopramide is a less costly option and is generally effective for mild, or even moderate vomiting. It has both central and peripheral activity. Centrally it acts as a dopamine antagonist at the CRTZ. Peripherally it increases lower oesophageal sphincter tone and relaxes the pylorus. It also has a pro-kinetic effect and can also be useful in cats experiencing ileus secondary to vincristine.

If maropitant and metoclopramide are ineffective, the 5-HT₃ receptor antagonists can be used, these include ondansetron and dolasetron. These are very effective anti-emetics that work centrally and peripherally. Peripherally 5HT₃ receptors are located on vagal nerve terminals. When gut is insulted, serotonin is released, and binds to receptors on the vagal afferents, thus initiating the vomiting reflex. These receptor antagonists block this pathway. Centrally they act on the CRTZ and emetic centre. They can be costly but are often worth the expense as their use can decrease hospitalisation and improve quality of life.

If a patient is refractory to symptomatic therapy, further investigation should be considered to rule out other causes of gastrointestinal upset, such as pancreatitis, obstruction, GI involvement of neoplasia, etc.

**Treatment for Chemotherapy Related Gastroenteritis**

**Mild**
These can usually be managed at home by offering small amounts of water and providing an anti-emetic if the patient is vomiting. We typically prescribe maropitant (CERENIA®) or metoclopramide for mild nausea/vomiting. A bland diet can be offered in small amounts every 3-4 hours once the vomiting has stopped. In cases of mild diarrhoea keep water available at all times and feed a bland diet until diarrhoea ceases. If symptoms persist for more than 24 hours veterinary intervention is indicated.

**Moderate to Severe**
If the patient has repeated bouts of vomiting and/or diarrhoea or symptoms have lasted for more than 24 hours veterinary intervention is indicated. It is important to submit a haematology and serum biochemistry panel for severely ill patients to monitor for renal or hepatic insufficiency, or neutropenia and/or sepsis that may occur concurrently. When the signs are delayed and presumed to be due to mucosal damage the treatment is symptomatic.
This includes:

**Intravenous Fluids**

For rehydration, replacing continued losses and correction of electrolyte and acid-base abnormalities. When used early we typically see a better response and a shorter duration of illness. The type of fluid is dependent on the needs of the patients and ideally is based on electrolyte monitoring. Lactated solutions such as Hartmanns, should be avoided in cancer patients. As previously mentioned, this is more important in lymphoma patients as they tend to have elevated serum lactate concentrations.

**Anti-emetics**

Vomiting can be persistent and severe. When this is a direct result of the drug (as seen with cisplatin), the use of maropitant, butorphanol or ondansetron appear to be the most effective. Metoclopramide is less effective but is still of some use, especially when used as a constant rate infusion. Metoclopramide is useful in patients whose vomiting has been induced by gastroenteric irritation or ileus.

- **Maropitant (CERENIA®):** 1 mg/kg SC or 2 mg/kg PO. Given for a maximum of five consecutive days, after which a break of at least 48 hours is required.
- **5-HT\textsubscript{3} Receptor Antagonists:**
  - Ondansetron (ZOFRAN®): 0.1-0.5 mg/kg (dog)\textsuperscript{5} slow IV (diluted in 0.9% saline); 0.1-1 mg/kg (cat) or 0.5-1 mg/kg PO sid-bid.
  - Dolasetron (ANZEMET®): 0.6-1 mg/kg IV or PO sid (dogs and cats).\textsuperscript{6}
- **Butorphanol:** 0.4 mg/kg IM or SC.\textsuperscript{7} Can be given prior to chemotherapy treatment to reduce nausea and vomiting.
- **Metoclopramide:** 0.5-1 mg/kg q 8-24 hours IV, IM, SC or orally; metclopramide can also be given as a continuous rate infusion for protracted vomiting at 1-2 mg/kg/day. Metoclopramide can be used orally as a pre-emptive treatment for vomiting.
- **Chlorpromazine:** 0.5 mg/kg IM or SC tid-qid.\textsuperscript{5} Used for mild nausea, it works centrally in the CRTZ.

**H2 Antagonists**

- **Cimetidine (TAGAMET®):** Dogs – 5-10 mg/kg IV, IM, PO tid-qid; Cats – 2.5-5 mg/kg IV, IM, PO bid-tid.
- **Ranitidine (ZANTAC®):** May also have a gastric prokinetic effect – Dogs 2 mg/kg slow IV, SC, PO bid-tid; Cats – 2 mg/kg/day CRI, 2.5 mg/kg slow IV bid, or 3.5 mg/kg PO bid.
- **Famotidine (PEPCIDINE®):** 0.5-1.0 mg/kg IV, PO sid-bid.
**Antibiotic Therapy**

If severe gastrointestinal toxicity is present, bacterial translocation and sepsis are possible sequelae due to the loss of the normal mucosal integrity. We do not routinely prescribe antibiotics, especially if the patient is vomiting only, as the gastrointestinal barrier may be intact. Indications for antibiotic use include: pyrexia, melaena or haematochezia, severe diarrhoea and colitis.

We routinely use trimethoprim-sulphonamide (7.5-15 mg/kg PO bid) for mild cases as studies have shown it may interfere less with normal flora. Other choices to consider are amoxicillin-clavulanic acid (12.5 mg/kg PO bid) and/or enrofloxacin (5-10 mg/kg PO, IV sid). If there is evidence of colitis then metronidazole (10-15 mg/kg PO bid) can be of benefit.

As most cases of diarrhoea are self-resolving and the products listed below have variable efficacy we rarely find their use necessary.

**Anti-diarrhoeals**

Loperamide (0.08 mg/kg PO tid) can be used in select cases if other treatments are ineffective and diarrhoea is persistent.

Sulphasalazine (6.5-12 mg/kg PO qid) has been used anecdotally for chemotherapy induced colitis in dogs and has had mixed results.

**Bismuth Subsalicylate**

This is a gastric cytoprotectant with activity against spiral bacteria. It simulates mucosal prostaglandin and bicarbonate secretion and may be used in conjunction with an H$_2$ receptor antagonist and appropriate antibacterial therapy if necessary.

**Pepto-bismol**

1-2 ml/kg PO tid-qid. The use of theorised intestinal protectants and probiotics has mixed results in human oncology reports and have not been fully evaluated in animals.

**Dose Reductions**

Dose reductions of 20% are recommended for severe gastrointestinal toxicity. Dose reductions should not be considered lightly because dose intensity is very important for anti-tumour response. Dose intensity should be at the highest tolerated dose with minimal toxicity, as most often the higher the dose intensity the greater the outcome with chemotherapy. An alternative to dose reductions is to substitute the offending drug with another chemotherapeutic drug. For example, substitute vinblastine for vincristine or mitoxantrone for doxorubicin. Symptomatic treatments (anti-emetics, anti-diarrhoeals) should be attempted to abrogate adverse effects before dose reduction is considered if side effects are mild.

**Dose intensity:** the amount of drug given per unit time, usually in mg/m$^2$/week.
3. Cyclophosphamide Induced Sterile Haemorrhagic Cystitis

Sterile haemorrhagic cystitis (SHS) is a potential side effect of cyclophosphamide. It is seen uncommonly in the dog and rarely in the cat. It is almost always seen with ifosfamide treatment if preventative measures are not taken. SHS can occur with chronic cyclophosphamide use, but can also occur after one dose. Cystitis associated with cyclophosphamide is caused by a breakdown product of cyclophosphamide called acrolein. Acrolein has a toxic effect on the bladder mucosa or lining.

Clinical Signs
Clinical signs include haematuria, dysuria and pollakiuria.

Diagnosis
Sterile haemorrhagic cystitis must be differentiated from other causes of lower urinary tract signs before treatment is instituted. This includes bacterial cystitis, primary bladder neoplasia (i.e. transitional cell carcinoma), and relapse or involvement of the current neoplasia within the bladder or lower urinary tract. Rarely, transitional cell carcinoma of the bladder has been associated with chronic cyclophosphamide use. Urinalysis and bacterial culture with sensitivity should be performed in all cases on a urine sample collected by cystocentesis, ideally ultrasound guided.
Treatment
Firstly discontinue the cyclophosphamide and ensure it is not given to this patient again. There is no single effective treatment for SHC and many will resolve without treatment. The time to resolution varies widely and can be days to months. If clinical signs are severe or persistent, trial therapy can be instituted. The response to treatment is variable and it can be very difficult to ease the symptoms.

Trial therapy may include:
- Anti-inflammatory therapy: This may involve non-steroidal or glucocorticoid therapy and will depend on the patient. There is evidence to suggest that non-steroidal anti-inflammatories may be more effective. However, if there are clinical signs consistent with uncontrolled lymphoma, glucocorticoids are preferred. Glucocorticoids can be given at anti-inflammatory doses (i.e. 0.5-1.0 mg/kg sid-bid prednisolone).
- Spasmolytics or anticholinergics, i.e. oxybutynin (DITROPAN®): 0.2-0.3 mg/kg PO bid-tid.¹
- Tricyclic antidepressants, i.e. amitryptyline.

Prevention
We advise giving cyclophosphamide with a diuretic (frusemide 1-2.2 mg/kg) and to give the medication in the morning. We ask that owners allow free access to fresh drinking water and frequent bladder emptying throughout the day. This can decrease the likelihood of SHS occurring. Another preventative strategy used in humans is the concurrent administration of 2-mercaptoethanesulphonate or MESNA®. This works by binding acrolein and inactivating its toxic effects on the bladder mucosa. It is mandatory to administered Mesna with ifosfamide in an effort to mitigate the cystitis normally seen when this drug is given alone.

4. Alopecia
Alopecia or hair loss that is commonly seen in humans is uncommon in dogs. It is seen most often in breeds that have continuously growing hair coats (i.e. Poodles, Old English Sheepdogs). Cats generally do not lose body hair, but can lose their guard hairs and whiskers. Chemotherapy can also slow regrowth of hair. The hair generally regrows, however it may vary in colour or texture in some patients.

5. Cardiotoxicity
Doxorubicin is the drug most commonly associated with cardiotoxicity and there are both acute and chronic forms. The acute form manifests as arrhythmias that occur during or soon after administration; these are transient. The chronic and more common form of toxicity results in a dilated cardiomyopathy and possible congestive heart failure. This is not reversible. In the dog, cumulative doses between 180-240 mg/m² are considered safe, although toxicity has been reported in a small number of cases at lower doses. Dilated cardiomyopathy can even occur after a single dose. The mechanism of cardiac damage is likely to be due to the formation of free radicals and the oxidative damage that subsequently occurs. Treatment is the same as that which is used for any other type of cardiomyopathy.
Prevention:

- Increasing the infusion time of doxorubicin decreases the peak plasma level of doxorubicin which is directly associated with both the acute and chronic forms of cardiotoxicity. Increasing infusion time will also increase the area under the curve which will increase efficacy.
- Use caution in susceptible breeds, such as Boxers and Dobermans. A pre-treatment echocardiography is recommended in susceptible breeds, however this does not eliminate the risk of developing cardiotoxicity. If fractional shortening is decreased prior to treatment, an alternative drug can be substituted (i.e. mitoxantrone).
- Using liposome-encapsulated formulations of doxorubicin (DOXIL®) significantly reduces the cardiotoxic effects, however these formulations can be cost prohibitive.
- Substitute other drugs in dogs with underlying heart disease.
- Concurrent use of dexrazoxane (ZINACARD®). This is an iron chelator which binds reactive oxygen species, however this drug is not available in Australia and is often cost prohibitive. Other anti-oxidants studied have not been promising.

6. Anaphylactic or Allergic Reactions

This is an uncommon to rare, but serious side effect which can be seen with any drug, and has been reported after doxorubicin, paclitaxel (the non-cremaphor free formulation) and L-asparaginase. Dogs and cats may develop immediate, histamine-mediated side effects that manifest as allergic reactions and possibly shock. Affected animals may show vomiting, diarrhoea, urticaria, oedema, pruritis, dyspnoea, restlessness, hypotension and rarely collapse. In the dog it typically manifests in the gastrointestinal tract and skin. In the cats, the lungs are more likely to be affected. If adverse acute drug reactions occur whilst administering chemotherapy, stop the infusion immediately, administer anti-histamine (chlorpheniramine 0.35-0.5 mg/kg IM) and dexamethasone (0.5-1 mg/kg IV), and wait for the reaction to subside before restarting the doxorubicin infusion at a slower rate. Intravenous fluids can be administered and if the reaction is severe, adrenaline is recommended. If animals have had allergic reactions before, a different drug could be substituted or the patient should be premedicated with chlorpheniramine and dexamethasone 15-20 minutes before subsequent treatments. The former should be considered after severe allergic reactions. With L-asparaginase the likelihood of allergic reactions increases with subsequent doses.

7. Extravasation

Severe perivascular tissue reaction and necrosis, leading to sloughing can be seen with extravasation of any chemotherapeutic agent. Doxorubicin and the vinca alkaloids (vincristine, vinblastine) are potent vesicants and are considered more toxic to tissues than other routinely used chemotherapeutic drugs. However all chemotherapeutic agents should be considered as potential vesicants. These drugs can be extremely damaging if extravasated and therefore clean venipuncture and catheter placement is mandatory. Hyaluronidase and dexrazoxane may decrease tissue damage after extravasation. The latter needs to be given immediately and as previously mentioned, it can be difficult to obtain and may be cost prohibitive. Sometimes
surgical treatment is required, including debridement of the extravasated tissue or in severe cases, amputation.

If a catheter is not cleanly placed it should not be used and an alternative site should be attempted. It is better to send a patient home without treatment than to give chemotherapy through a catheter which is not cleanly placed. Alternatively we occasionally place subcutaneous vascular access ports (SVAP) in patients with consistently poor venous access.

Venipuncture

8. Other Less Common Side Effects

**Palmar Plantar Erythrodysesthesia**

Is associated in dogs and humans with cutaneous toxicity syndrome known as palmar plantar erythrodysesthesia (PPES). This syndrome is reported in humans treated with prolonged infusions of various chemotherapeutic drugs, in particular DOXIL® (liposome encapsulated doxorubicin). Dogs may develop irritation, alopecia, and ulceration in the axilla, inguinal region, and skin around the footpads. It is self-limiting, but treatments need to be delayed or discontinued to allow resolution of the affected areas.

Renal insufficiency or failure can be seen with any chemotherapeutic agent, but is more commonly associated with the platinoid drugs, particularly cisplatin. In cats, doxorubicin has been uncommonly associated with renal toxicity.

**Hepatotoxicity**

A potentially fatal hepatotoxicity may occur uncommonly to rarely in association with CCNU. Greater numbers of treatments are more likely to be associated with hepatopathy. Monitoring of liver parameters is recommended during therapy and discontinuation is recommended if moderate ALT elevation occurs and is persistent. Any chemotherapy drug also has the potential to cause hepatotoxicity, as many drugs are metabolised to either active or inactive forms in the liver.
Peripheral Neuropathy
This toxicity is more relevant in people treated with vincristine. It can occur with any vinca alkaloid but is more commonly seen with vincristine. It can occur rarely in animals with prolonged administration. Dogs usually show signs of hindquarter weakness, but may also present with generalised pain and may lick and chew at their feet or legs, consistent with paraesthesia. Drug substitution is recommended if this rare side effect is seen. 5-fluorouracil (5-FU) can cause fatal neurotoxicity in cats and should be avoided in this species.

Pulmonary Oedema
Fatal pulmonary oedema has been associated with cisplatin use in cats, consequently this drug should never be used in felines.

9. Small Molecule Inhibitors
Although these drugs are not true chemotherapy or cytotoxic products, they are often used in cancer patients and thus their potential side effects must be considered. The two main drugs that fall into this category are toceranib (PALLADIA®) and masitinib (MASIVET®, KINAVET®). Imantinib (GLEEVAC®) is another example but is not registered for use in animals and tends to be cost prohibitive. Interestingly, these drugs are given orally and tend to work at very low concentrations; their activity is not based on maximum tolerated dose.

The mechanism of action of small molecule inhibitors is through the disruption or blocking of cellular signalling pathways. This mainly occurs via targeting protein kinases, such as tyrosine kinase receptors, on the cell surface. The toxicities seen with these products are thought to occur as a result of blocking normal cellular pathways.

The spectrum of toxicities seen is influenced by the stage of the disease within the patients, the type of cancer being treated, any pre-existing conditions in the patient and whether the patient is receiving additional medications. More common side effects include anorexia, lethargy, diarrhoea, gastrointestinal bleeding, vomiting and neutropenia. Less commonly, muscle cramping, hepatotoxicity, pancreatitis and protein losing nephropathies have been reported. Management of these toxicities tends to be supportive, including H2-blockers, sucralfate, possibly protein pump inhibitors and traditional anti-nausea and anti-diarrheal products.

However, as these are very new products in the veterinary field with very little published information regarding recommended dosing and expected toxicity, we recommend reviewing current literature or speaking with an oncologist prior to administration.
References


8. London C. Personal communication presented at the 2010 Veterinary Cancer Society Annual Meeting, San Diego, USA.