

## Recommendations for management of the common side effects of chemotherapy

### Neutropenia

Mild neutropenia is a common side effect of chemotherapy and can often be self limiting and require no treatment. However, at the other end of the spectrum severe neutropenia can be complicated by sepsis and may be life threatening. The neutrophil nadir (or trough) usually occurs after 7–10 days for most drugs, although there will be variability between patients and chemotherapy agents and some drugs can have a bimodal nadir (e.g. CCNU, carboplatin). The effects on the patient are related to the drug used in many cases. For example; a dog with severe neutropenia ( $<0.2 \times 10^9/L$ ) after receiving CCNU can have no clinical signs at all while other dogs with a milder neutropenia ( $0.9 \times 10^9/L$ ) 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 after at least the first treatment and after any dose changes.

#### ***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. We recommend broad spectrum antibiotics such as potentiated penicillin (Clavulox 12.5mg/kg bid). We commonly use trimethoprim-sulphonamide (15mg/kg bid) as studies have shown there may be less effect on the normal gastrointestinal flora, and this can be considered the drug of choice. A repeat haemogram five to seven days later generally reveals marrow recovery.

#### ***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 potentiated amoxicillin (12.5–25mg/kg bid) and enrofloxacin (5–10mg/kg orally or IV sid to bid); or metronidazole (10mg/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 there is often colitis.

#### ***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 fluids and close observation and monitoring. Lactated solutions (such as Hartmanns) should be avoided in dogs and cats with lymphoma, as these patients tend to have high serum lactate concentrations. It may be prudent to keep them in an isolated area and practise good hygiene and biosecurity (reverse isolation) as they are at risk of exposure to pathogens from other hospitalised patients. A hunt for a possible source of infection (i.e. urinary tract infection, occult pneumonia, sepsis) may be

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indicated, particularly if clinical signs do not normalise rapidly with treatment; or an infectious cause of the pyrexia is suspected.

### ***Dose reductions***

Dose reductions of 20% should be considered if the neutrophil count falls below  $0.5 \times 10^9/L$  at nadir or below  $1.5 \times 10^9/L$  at the time of the next scheduled treatment. 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 dose reduction. Patients need to have recovered from neutropenia before their next treatment, but in some cases treatment can be given at levels of  $1.5\text{--}2.5 \times 10^9/L$  depending on the drug.

In patients where the tumour is the primary cause of the neutropenia, these rules no longer apply. But knowledge of the case and aggressive supportive care is needed.

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.

## **Recommendations for management of the common side effects of chemotherapy**

### **Gastroenteritis**

Gastrointestinal toxicity is seen commonly as a side effect of chemotherapy. It can occur secondary to direct damage to intestinal epithelial cells or by means of efferent nervous stimulation of the chemoreceptor trigger zone (CRTZ). 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 responsible, vomiting is maximal on the day of therapy. If an animal has experienced significant GI events after a particular chemotherapy drug, several options are available to reduce further complications after subsequent treatments including: dose reductions or alterations, pre-emptive anti-emetics or non-specific gastric protectants (i.e. peptosyl), and/or the patient can be given 3–5 days of prophylactic antibiotics. We routinely use trimethoprim-sulphonamide (15mg/kg po bid) or metronidazole (10mg/kg po bid).

### ***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 vomiting. We typically prescribed metoclopramide (maxolon) for mild nausea/vomiting. A bland diet can be offered in small amounts every 3–4 hours once 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 pet has repeated bouts of vomiting and/or diarrhoea or symptoms have lasted for more than 24 hours veterinary intervention is indicated. When the signs are delayed and are the result of mucosal damage the treatment is symptomatic. This should involve:

**Intravenous fluids** For rehydration, replacing continued losses and correction of electrolyte abnormalities. When used early we typically see a better response and a shorter period of illness. The type of fluid is dependent on the needs of the patients and ideally is based on

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electrolyte monitoring. Lactated solutions (such as Hartmanns) should be avoided in dogs and cats with lymphoma, as these patients tend to have high serum lactate concentrations.

Monitoring the **haemogram (CBC) and serum biochemistry** - particularly for severely ill patients to monitor for neutropenia and/or sepsis that may occur concurrently.

**Anti-emetics** Vomiting can be persistent and severe. When this is a direct result of the drug (as seen with cisplatin or others), then the use of butorphanol and 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 where vomiting has been induced by gastroenteric irritation or ileus.

1. Serotonin antagonists: These are very effective anti-emetics that work centrally and peripherally. They can be expensive but are often worth the cost to decrease hospitalisation and improve quality of life.
  - a. **Ondansetron** (Zofran®) 0.1–0.5mg/kg slow IV (diluted in 0.9% saline) or 0.5–1mg/kg orally sid-bid. CRI- Loading dose 0.5mg/kg/hour for 6 hour infusion.
  - b. **Dolasetron** (Anzemet®)—0.6–1mg/kg IV or PO sid.
2. Butorphanol—0.1–0.4mg/kg IM, IV or SC. Can be given prior to chemotherapy treatment to reduce nausea and vomiting.
3. Metoclopramide—0.5–1mg/kg q 8–24 hours IV, IM, SC or orally; can also be given as a continuous rate infusion for protracted vomiting at 1–2mg/kg/day. Can be used orally as a pre-emptive treatment for vomiting. Centrally acting (in the CRTZ as a dopamine agonist) and peripheral (increases lower oesophageal sphincter tone and relaxes the pylorus).
4. Chlorpromazine—0.5mg/kg IM or SC tid-qid. Used for mild nausea, it works centrally in the CRTZ. A suppository form is also available.

**H<sub>2</sub> antagonists** Cimetidine (Dogs - 5-10mg/kg IV, IM, PO tid-qid; Cats - 2.5-5mg/kg IV, IM, PO bid-tid), ranitidine - may also have a gastric prokinetic effect - (Dogs 2mg/kg slow IV, SC, PO bid-tid; Cats - 2mg/kg/day CRI, 2.5mg/kg slow IV bid, or 3.5mg/kg PO bid; or famotidine (0.5-1.0mg/kg sid-bid).

**Bismuth subsalicylate** a gastric cytoprotectant, it has activity against spiral bacteria, stimulates mucosal prostaglandin and bicarbonate secretion. It is often used in conjunction with an H<sub>2</sub> receptor antagonist and appropriate antibacterial therapy (if necessary). Pepto-bismol: 1-2ml/kg PO tid-qid.

**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 always give antibiotics, especially if there 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 (15mg/kg po bid) for mild cases (studies have shown it may interfere less with normal flora), amoxicillin-clavulanic acid (12.5mg/kg bid) and/or enrofloxacin (5-10mg/kg SID). If there is evidence of colitis (particularly associated with doxorubicin) then metronidazole (10mg/kg po bid) can be of benefit.

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## **Dose reductions**

Dose reductions of 20% are recommended for severe GI toxicity. Dose reductions should not be considered lightly, because dose intensity is extremely important for anti-tumour response. An alternative to dose reductions is to substitute the offending drug with another chemotherapeutic drug (i.e. 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.

## **Recommendations for management of the common side effects of chemotherapy**

### **Platelet disorders**

Platelet disorders occur with some frequency in cancer patients. The most common is a reduction in platelet number (thrombocytopenia), but we also see increases in numbers (thrombocytosis) or dysfunction of platelets (thrombocytopathy).

**Thrombocytopenia** associated with chemotherapy is rarely clinically significant and does not often result in bleeding. It may be caused by decreased production (usually from myelophthetic 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, the neoplasia must be treated to resolve the low cell count. We will provide supportive care and close monitoring in these cases. Immunotherapy is indicated if the thrombocytopenia is confirmed to be secondary to auto-immune destruction. A repeat haemogram is necessary 5-7 days later or prior to the next scheduled treatment.

**Thrombocytosis** is less well understood. It is most often associated with primary bone marrow diseases such as leukaemia but also myelofibrosis and other causes of damage. We also see a rebound thrombocytosis in some patients after myelosuppression with chemotherapy and also with the use of glucocorticoids.

**Thrombocytopathy** is the least common and often occurs when the platelets get 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.

### **Clinical signs**

The signs of thrombocytopenia and thrombocytopathy 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 usually not seen. 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 be hypercoagulable and be at risk of thrombotic disease or DIC.

### **Treatment**

There are few effective treatments for platelet disorders other than removing the underlying cause and immune suppression in the case of immune-mediated destruction. General

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supportive care for these patients includes cage rest, prevention of trauma, and minimisation of injections (use oral or intravenous route 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 extremely limited availability and a very short half life, they are almost always not an option. If platelets numbers are severely low, the patient is showing clinical signs of thrombocytopenia, or 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 (the latter two are often not available) can be used for transfusion. 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 20kg dog by as much as  $30\text{-}40 \times 10^9/\text{L}$ . However, in patients with thrombocytopenia due to accelerated platelet destruction or utilisation (IMT, DIC), 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.

### Recommendations for management of the common side effects of chemotherapy

## Cyclophosphamide induced sterile haemorrhagic cystitis

Sterile haemorrhagic cystitis (SHS) is a potential side of effect of cyclophosphamide in the dog and rarely in the cat. It is also almost always seen with ifosfamide treatment if preventative measures are not taken (Mesna – see later). SHS typically occurs with chronic cyclophosphamide use but can also less commonly occur acutely after one dose. Cystitis associated with cyclophosphamide is caused by a metabolite of cyclophosphamide, acrolein, which 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** and sensitivity should be performed in all cases on a urine sample collected by cystocentesis.

### **Treatment**

Firstly discontinue the cyclophosphamide and ensure it is not given to this patient again.

There is no single effective treatment for sterile haemorrhagic cystitis and many will resolve without treatment. The time to resolution varies widely and can be days to months. If 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.

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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 signs consistent with gastrointestinal upset or uncontrolled lymphoma, glucocorticoids are preferred. Glucocorticoids can be given at anti-inflammatory doses (i.e. 0.5–1.0mg/kg sid-bid prednisolone).

Spasmolytics or anticholinergics, i.e. Oxybutynin (Ditropan).

Tricyclic antidepressants, i.e. amitriptyline.

## **Prevention**

We advise giving cyclophosphamide with a diuretic (frusemide 1–2mg/kg) 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 administer Mesna when ifosfamide is used to mitigate the cystitis normally seen when this drug is given alone.

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