

Problems with Chemotherapy of Lymphoma--How to Cope

**Laura Blackwood, BVMS (Hons), MVM, PhD, CertVR, DECVIM-CA (Oncology), MRCVS
Small Animal Teaching Hospital, University of Liverpool, Leahurst Campus
Neston, Merseyside, UK**

The main problems encountered in chemotherapy of lymphoma are adverse effects of therapy and emergence of resistance resulting in relapse.

Adverse Effects of Chemotherapy

Cytotoxic drugs have a lower therapeutic index than most other drugs. As cytotoxic drugs kill dividing cells, the normal tissues adversely affected by these drugs are those which are rapidly dividing: the bone marrow and the gastrointestinal tract. Some agents have other organ specific toxicities. Additionally, some drugs are associated with immediate adverse reactions which are a result of their biochemical nature rather than their action against tumours. Both you and the client must be aware of the potential side effects of the drugs you are using.

The most commonly used drugs in lymphoma are vincristine, cyclophosphamide and prednisolone in COP regimens; and, in addition to these drugs, doxorubicin/epirubicin, (L-asparaginase) and antimetabolites in multidrug regimens like the Madison Wisconsin protocols.

Vincristine

Vincristine is a severe perivascular irritant. In the event of suspected extravasation, a hot compress should be applied immediately. Hyaluronidase (300 units diluted in 6ml of 0.9% saline, administered circumferentially to site, immediately then weekly) may limit tissue necrosis and promote recovery. Topical DMSO may be applied by the owner at home.

Vincristine is generally not very myelosuppressive, though dogs receiving the higher end of the dose range (0.7-0.75 mg/m²) may occasionally become neutropenic 4-7 days after administration. Gastrointestinal side effects are generally uncommon, though some animals may not eat their food on the evening of drug administration.

Vincristine has its effects against tubulin, and neuropathies (mainly sensory) are reported in people. In dogs, the autonomic nervous system may be affected and constipation or ileus is occasionally seen.

Some collie dogs have a mutation in the MDR1 gene which makes them sensitive to vincristine, and it is sensible to start at the lower end of the dose range and establish the maximum tolerated dose on an individual basis.

Cyclophosphamide

Cyclophosphamide can cause gastrointestinal side effects such as vomiting or diarrhoea 1-3 days after treatment. It may cause myelosuppression (neutrophil nadir 5-7 days after bolus administration).

A particularly troublesome side effect of cyclophosphamide is haemorrhagic cystitis. Urinalysis should be carried out every 2-3 weeks on low dose regimes, and prior to every bolus on high dose COP/multidrug regimens. If blood is detected in the urine, or the dog develops any signs of cystitis, cyclophosphamide should be stopped (and replaced with melphalan or chlorambucil). Haemorrhagic cystitis is debilitating and may take weeks to resolve. Anti-inflammatories are of benefit, but the role of n-acetyl glucosamine is unproven. In persistent cases, DMSO flush is of benefit: 10 ml of medical

grade 50% DMSO is diluted with 10 ml of water instilled into the bladder and removed after 20 minutes.

In cats, cyclophosphamide can cause reduced appetite, thought to be due to altered taste and/or subclinical stomatitis. It is also associated with whisker loss, though this tends to occur gradually and patients adapt. Haemorrhagic cystitis is rare in cats and is not generally closely monitored for, but owners should be aware and monitor for clinical signs.

Prednisolone

Prednisolone has a number of problematic effects in lymphoma patients. Iatrogenic hyperadrenocorticism is potentially very problematic. Dogs with marked polyphagia may cause problems in everyday management and may grow obese. Polyuric dogs may get owners up during the night. Prednisolone can also cause gastrointestinal ulceration, and has rarely been associated with pancreatitis. Multidrug regimens often cease steroid therapy after the first few weeks.

L-asparaginase

L-asparaginase is an enzyme, and so is a foreign protein. To reduce the risk of an anaphylactic reaction, the drug is given intramuscularly rather than intravenously. It has also been associated with diverse effects on protein synthesis including coagulation disturbances in humans. It has rarely been associated with pancreatitis.

Doxorubicin and Epirubicin

Doxorubicin or epirubicin are used interchangeably in treatment of lymphoma. Epirubicin is a structural analogue of doxorubicin, but is much less cardiotoxic in dogs. Both are very severe perivascular irritants, and the complications of extravasation can be disastrous (limb amputation or euthanasia). In the event of suspected extravasation, a cold compress should be applied immediately. Hyaluronidase may reduce the risk of severe tissue injury as above, and topical DMSO may then be applied by the owner at home.

Hypersensitivity reactions have been rarely reported--it is recommended that patients receiving doxorubicin are premedicated with an antihistamine (usually chlorpheniramine).

Another potential problem during drug administration is cardiac dysrhythmia: pulse should be monitored throughout infusion and ECG must be available.

Animals that vomit or are off food post treatment should be treated with antiemetics (metoclopramide or maropitant), ideally on the day of treatment and for three further days.

Myelosuppression may occur and the nadir is generally 5-10 days after administration.

Doxorubicin and epirubicin may cause an irreversible dose dependent chronic/cumulative cardiotoxicity in dogs. The maximum cumulative dose of doxorubicin for dogs is 240 mg/m² (8 standard doses) but many dogs will show changes in myocardial function at lower doses. Echocardiographic evaluation prior to the first treatment and then at the third and each alternate treatment is recommended as a minimum. Epirubicin is less cardiotoxic: patients are still monitored in the same stringent manner. Dogs that develop cardiomyopathy do not respond to traditional medical management.

Cytosine Arabinoside/Methotrexate

The main adverse effects of these S phase specific agents are on the rapidly dividing cells in the gastrointestinal tract and bone marrow. Gastrointestinal side effects and/or myelosuppression are relatively common.

Common Side Effects

Gastrointestinal Toxicity

The direct effects of cytotoxic drugs on the dividing cells of GI tract may cause adverse effects, usually 1-5d (uncommonly up to 10d) after treatment. The pattern is most often anorexia on day 1, then vomiting/diarrhoea at day 2-3. Symptomatic treatment is required: intravenous fluids, electrolytes, antiemetics, gut protectants, acidity regulators and antibiotics. If GI toxicity results in epithelial damage then there is a greater risk of sepsis should neutropenia develop, as the gut mucosa is a less effective barrier to bacterial translocation.

Myelosuppression

Haematological monitoring is vital in all cases receiving potentially myelosuppressive drugs. Haematology must be carried out prior to every bolus dose of myelosuppressive agents and at appropriate intervals depending on the regime.

Clinically significant effects of myelosuppression are:

Neutropenia (a neutrophil count of less than $3 \times 10^9/l$ in a dog, $2.5 \times 10^9/l$ in a cat)

Thrombocytopenia (a platelet count of less than $70 \times 10^9/l$)

Anaemia is rarely clinically significant and often indistinguishable from anaemia associated with chronic disease. Chronic GI haemorrhage is a potential cause of iron deficiency anaemia in patients on long-term steroid therapy.

Neutropenic Patients

Asymptomatic, Afebrile, Neutropenic Animals

If the neutrophil count is less than $1 \times 10^9/l$, the animal may be treated as follows:

Trimethoprim sulphonamide combinations (TMP:S)

Discontinuation of the offending drug until neutrophil numbers recover

If possible, the owner should check the animal's temperature 2 or 3 times a day

If the neutrophil count is $2-3 \times 10^9/l$ then discontinuation of the drug until the count recovers will suffice. If it is $1-2 \times 10^9/l$ then antibiotics may be given at the discretion of the clinician e.g., if there is a pre-existing focus of infection.

TMP:S combinations are recommended for prophylaxis as although they affect the aerobic intestinal flora, the anaerobes remain, and these bacteria are involved in local defence in the intestines. TMP:S combinations also have broad spectrum bactericidal activity, and do not have the resistance issues

associated with enrofloxacin. Some oncologists prefer to use clavulanate-potentiated amoxicillin as their first line drug because of the potential toxicities associated with TMP:S combinations.

Pyretic, Neutropenic Patients

These patients are a medical emergency, but in most cases, pyrexia resolves within hours and circulating neutrophil numbers normalise within 24-48 hours. Patients must be supported appropriately as well as treated with antibiotics. In most cases, bacteria responsible for septicaemia are gram-negative Enterobacteriaceae (often from the patient's own intestinal tract) or Staphylococci. In addition:

All cytotoxic drugs except corticosteroids should be immediately discontinued.

The patient should be barrier nursed, and all sampling, catheter placements etc. carried out aseptically.

Supportive therapy: intravenous fluids, electrolytes, glucose as indicated.

Bactericidal antibiotics: TMP:S, fluoroquinolones (enrofloxacin) (can alter later based on sensitivity). (Avoid gentamicin (historically recommended) due to the nephrotoxicity.)

5-7 days of antibiotic therapy after clinical recovery and restoration of neutrophil numbers.

In neutropenic patients, lack of neutrophils will considerably reduce the inflammatory response and it may be difficult to identify foci of infection should culture and sensitivity be required.

What Happens Next Time?

When re-introducing a previously myelosuppressive drug, a reduced dose rate is often required. However, all drug dose reductions reduce tumour cell kill and a 20% reduction in drug dosage can result in up to 50% reduction in tumour cell kill. Dose reduction should be discussed with the owner: approaches include trying a 10% reduction at the next dose, or reducing by 20% or 25%, then next time increasing to 90% of initial dose if there is no toxicity. In some cases the original planned dose will be tolerated by the patient once in remission.

When drugs associated with previous GI toxicity are given again, supportive therapy should be increased. Where there has been vomiting, should be treated with antiemetics (metoclopramide or maropitant) ideally on the day of treatment and for three further days. Where there has been severe GI upset, a dose reduction might be required.

Some individual animals do not cope well with particular drugs or dosage regimens, and protocols should be tailored to suit. A dog on high dose COP that has problems after bolus doses of cyclophosphamide may do better on low dose oral treatment at home, and a cat that is inappetent after cyclophosphamide treatment may do better on chlorambucil or melphalan.

Resistance and Relapse

You must check that the animal achieves and maintains remission. Complete remission (CR) means no detectable disease. Lymph nodes should be normal or subnormal in size, and of normal texture. Extranodal disease should be undetectable. Even in complete remission many tumour cells remain.

Partial remission (PR) refers to a reduction in tumour volume of more than 50%. In PR there is a

huge population of resistant cells. If your patient is not in CR, your chemo is not working.

When relapse occurs, it is often possible to achieve a second remission. However, this remission is usually shorter than the first.

Re-induction: for modern non-continuous regimens (e.g., Madison Wisconsin 24 week), simply starting at the beginning again is the usual approach.

Re-induction plus additional drugs cytosine arabinoside, L-asparaginase (taking care to avoid additive toxicities).

Alter regime completely using drugs which have not been used before e.g., doxorubicin/epirubicin instead of COP; lomustine after other protocols, D-MAC (dexamethasone, melphalan, actinomycin D), etc.

Radiation therapy.

Eventually, most dogs and cats develop multidrug resistance and will cease to respond to any drugs.

Other Problems in Chemotherapy of Lymphoma

Alimentary Lymphoma

Where there is a mass lesion that is amenable to surgery this should be resected. Where there is extensive intestinal infiltrate, chemotherapy should be initiated in a staggered manner to reduce the risk of tumour lysis resulting in intestinal perforation, e.g., for COP give vincristine therapy on day one, then give cyclophosphamide on the third day and start prednisolone on the fifth. Absorption of orally administered drugs may be poor.

Cutaneous Lymphoma

Standard chemotherapy regimes have poor response rates in cutaneous lymphoma, and recent studies suggest lomustine is more effective. Alpha interferons show promise for cutaneous lymphomas, but only human recombinants are available. The role of retinoids (isotretinoin/etretinate) in the treatment of cutaneous lymphoma remains controversial but they may ameliorate clinical signs (pruritus) rather than producing true remission.

Tumour Lysis Syndrome

Rarely, where there is a large tumour burden, sudden lysis of the neoplastic lymphoid cells produces a hyperkalaemia and hyperphosphataemia (with resultant hypocalcaemia) which can cause fatal cardiac dysrhythmias, or fatal renal failure.

CNS/Renal Lymphoma

It may be beneficial to include cytosine arabinoside in induction.

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