Cancer Treatment Options: Chemo, Surgery & Radiation Therapy

Abstract
These lectures are two part series taking a detailed look at veterinary cancer treatment options.

Learning outcomes
- Knowledge and understanding of different treatment options for cancer patients in veterinary practice.

Course Notes

Introduction:
Cancer is the most common cause of death in older dogs and cats. Despite this, there are a number of treatments available that can offer pets a good quality of life. Recent advances in veterinary oncology have increased owner awareness and the readiness of many veterinary practitioners to treat cancer patients. This means that greater numbers of pets with cancer are being managed long-term. The veterinary team should be prepared to provide advice and current information concerning cancer, to enable owners to make informed decisions about their pets’ well-being. Cancer can be a painful and debilitating disease, therefore those involved in the care of these patients should always consider the importance of treating the patient as a whole - not just medically, but also ethically and humanely. A trained and dedicated veterinary team is essential to compassionately care for cancer patients and their owners. Cancer is also a serious health concern of people and many owners of cancer-bearing pets will have had personal experience of the disease, or had a close relative or friend with cancer. Because of this, we should treat the subject with particular sensitivity and make open acknowledgement of the human-animal bond, which has elevated the importance of pets to that of family members for many owners. Owner circumstances will vary – some may decide to euthanase pets as soon as the diagnosis of cancer is made, others will want to pursue every treatment option available. Whatever the owners’ decision, they should be made aware, from the outset that the goal of treatment in the majority of cases is to maintain optimum quality of life for their pet, as opposed to quantity.

Treatment Options:
The three most important treatment options used in veterinary oncology are surgery and/or radiotherapy and/or chemotherapy and/or other (e.g. palliative care, tyrosine kinase inhibitors, immune therapy, etc.).

- Surgery may be diagnostic (collection of biopsy samples) or therapeutic (removal or debulking localised tumours).
- Radiotherapy can be used alone or in conjunction with surgery and chemotherapy, to treat local disease. Radiation may be used with palliative (analgesia for bone pain) or therapeutic intent. It is a specialist treatment, which may take the form of brachytherapy (e.g. iodine $^{131}$, for hyperthyroid cats) or as electron or photon beams, delivered via a linear accelerator. It most often used to treat smaller or debulked localised tumours.
- Chemotherapy is used treat systemic cancer or as an adjunct to surgery or radiation, to treat microscopic disease.
**Chemotherapy:**

In human cancer therapy, chemotherapy is often very aggressive, with severe debilitating side effects, including immune suppression, vomiting and diarrhoea, weight loss and total hair loss. Therefore many owners’ first reaction to learning their pet needs chemotherapy is “I don’t want to put my pet through that”. In veterinary oncology quality of life is paramount and chemotherapy protocols are used which are less aggressive than those used for humans - in general the doses used are one third of those used in human medicine, with lesser intensity (i.e. weekly treatments, rather than daily). The payback for this is often limited life-expectancy. Adequate time should be spent with owners to counsel them on what to expect during their pet’s chemotherapy, the anticipated chances and duration of remission, potential side-effects and estimated cost of treatment, so that they an informed decision can be made.

Chemotherapy is most successfully used for systemic/diffuse tumours such as lymphoma, multiple myelomas, leukaemia and some mast cell tumours. It can of certain benefit as an adjunct to surgery and/or radiation therapy for other solid tumours (e.g. certain sarcomas and carcinomas) or as palliation. However, not all tumours are chemotherapy-sensitive. Glucocorticoids or non-steroidal anti-inflammatory drugs are often used as adjuncts or palliative therapy.

**Mechanism of Action and Basic Concepts of Chemotherapy:**

The goal of chemotherapy is to inhibit the growth of cancer cells with minimum effect on normal cells. Most chemotherapeutic agents either bind directly to genetic material in the cell nucleus or affect a cell’s ability to synthesise protein. This may also damage growth and reproduction of the patient’s normal cells, as both healthy cells and cancer cells go through the same cell division cycle. However, most tumour cell populations are characterised by genetic instability, on which chemotherapy drugs can have an impact. For instance, individual tumour cells can mutate and produce variant cells, which are genetically distinct from the tumour cell of origin. This genetic instability is an important concept because it can be linked to chemotherapy-resistant cells.

Treatment dose and schedule depends on the type of cancer and chemotherapy method. In some cases periodic chemotherapy will be necessary to control the cancer for the rest of the pet’s life. For maximum therapeutic effect, a drug should be used with a dose that causes minimal toxicity with maximal effectiveness. The most effective dose of chemotherapeutic agents is often very close to the toxic dose.

Chemotherapeutic agents are classified according to their pharmacologic action and the point in the cell cycle at which they interfere with cellular reproduction. The mechanism of action of a chemotherapy drug may be either cell cycle specific or cell cycle non-specific. Both normal and neoplastic populations of cells contain cells that are actively proliferating cells and cells that are resting. The use of cell cycle non-specific drugs appears to result in the death of both resting cells and cycling cells. Following cell death, resting cells are ‘awakened’ into the reproduction cycle and are then more susceptible to chemotherapeutic agents. Regardless of the specific mechanism of the intracellular disruption, the cell will die as it attempts cell division if it is not capable of repairing itself. The cell kill rate of various drugs is related to the concentration of the drug and to the degree of tumour cell exposure over time.
Combining cytotoxic drugs is an important, effective strategy in chemotherapy, designed to target different parts of the cell cycle to increase the proportion of total tumour cells that are killed at any one treatment time. When drugs are used in combination, they often enhance the activities of each other. Drugs are also combined to minimise their dose-limiting toxicities and help reduce the development of tumour resistance - cells resistant to one drug may be sensitive to another within that regimen.

The factors governing tumour chemosensitivity include the growth fraction (proportion of actively dividing cells), the inherent sensitivity of the tumours and acquired drug resistance. Cells which were originally susceptible to chemotherapy drugs may develop resistance by multi-drug resistance (MDR). This is thought to be the reason for chemotherapeutic failure in all canine lymphoma patients. The drugs may be in different classes and unrelated to the drugs which have previously been used. Drugs commonly used that are known to be affected by MDR include doxorubicin, vinblastine and vincristine.

**Commonly Used Antineoplastic Drugs, Their Actions and Side Effects:**

- **Vincristine** (Oncovin ®) - vinca alkaloid; mitotic spindle inhibitor inhibits cell division. Commonly used in the treatment of lymphoid tumours, e.g. lymphoma. May be used alone or in multi-drug combinations. This drug must be injected through a carefully placed intravenous catheter - if it leaks into perivascular tissue, extreme irritation occurs, causing wounds which may be slow to heal and difficult to manage. Side effects include vomiting and/or diarrhoea, constipation or abdominal cramps due to altered bowel motility or occasionally, neurological side effects, especially in cats. Vincristine is less likely to severely suppress bone marrow function than many cytotoxic drugs and, in some cases, is used to boost platelet production.

- **Vinblastine** (Velbee ®) - vinca alkaloid; mitotic spindle inhibitor, similar to vincristine. Commonly used in the treatment of round cell tumours, e.g. mast cell tumours. Side effects are similar to vincristine, but more profound myelosuppression may occur. It is also vesicant and must be injected through a well-placed intra-venous catheter.

- **Cyclophosphamide** (Cytoxan ®, Endoxana ®) - alkylating agent; nitrogen mustard derivative - it is cell cycle non-specific and interferes with DNA replication. It is most commonly used to treat bone marrow and lymphoid cancers and certain solid tumours (e.g. mammary). It may be used alone or in multi-drug combinations. In common with other cytotoxic drugs, side effects include myelosuppression and gastrointestinal signs. A serious potential side-effect of cyclophosphamide is sterile haemorrhagic cystitis, which is caused by excretion of irritant drug metabolites. Frequent urine sampling should be performed to
avoid/prevent problems and adequate hydration should be maintained, with diuresis encouraged (e.g. pre-treatment with furosemide).

- **Doxorubicin** (Adriamycin ®) - an anthracycline anti-tumour antibiotic - inhibits DNA, RNA and protein synthesis. It is an intravenous injectable, given as a slow infusion. Commonly used in the treatment of lymphoma, osteosarcoma and other solid tumours. Doxorubicin must be given intravenously - if it leaks into perivascular tissue, an extreme reaction occurs, causing severe tissue damage. For safety reasons, doxorubicin is bright red (patients' urine may be orange post-administration). In common with many cytotoxic drugs, doxorubicin may induce gastrointestinal side effects (mild → severe) and myelosuppression. Breeds of dogs which are predisposed to dilated cardiomyopathy should be carefully screened and monitored throughout their treatment. Heart muscle toxicity is cumulative and there is a maximum dose which can be given in a patient's lifetime. In cats, doxorubicin may be nephrotoxic and blood test monitoring is needed throughout treatment.

- **Mitoxantrone** (Novantrone ®) - an anthracycline anti-tumour antibiotic, similar to doxorubicin. Mitoxantrone has similar uses to doxorubicin. Gastrointestinal side effects are usually less profound, but myelosuppression may be more so. It is deep blue and may produce a blue tinge to the urine or whites of patient’s eyes.

- **Lomustine** (CCNU) - alkylating agent - binds to cellular DNA preventing replication. It is most commonly used to treat lymphoma, mast cell tumours and brain tumours. Lomustine comes in capsule form and is given by orally, being absorbed within 30-60 minutes. Side effects are predominantly related to myelosuppression, which may be profound and cumulative - increased risk of infection and bruising or bleeding. Lower doses of lomustine should be used in cats as bone marrow effects are more pronounced. Lomustine is metabolised by the liver and hepatotoxicity may also occur. However, compared with other cytotoxics, lomustine is relatively gentle on body systems such as the gastro-intestinal tract.

- **L-Asparaginase** (Elspar ®) - This drug exploits the high requirement that some tumour cells have for an amino acid called asparagine. L-asparaginase is an enzyme that destroys asparagine outside the cell. Normal cells are able to make the asparagine they need, whereas some lymphoid tumour cells become depleted and die. L-asparaginase is primarily used to treat acute lymphoid leukaemia and lymphoma. It is given as an intramuscular or subcutaneous injection, used as a single agent or in conjunction with other drugs. Unlike many other chemotherapy agents, bone marrow suppression is not a side-effect of asparaginase. L-asparaginase is a foreign protein and may produce an anaphylactic reaction - whilst this is uncommon, pre-treatment with anti-histamines should be given to reduce the risk.

- **Carboplatin** (Paraplatin ®) - a platinum compound that binds to DNA and prevents normal function. It used either alone or in combination with surgical intervention and/or other drug regimes. It is particularly indicated for solid tumours, such as sarcomas and carcinomas. Carboplatin is given intravenously, usually with intravenous fluid support during administration. It is now generally used in preference to cisplatin, which is highly emetic and nephrotoxic and cannot be used in cats. However, carboplatin may induce nausea and vomiting in the first 48 hours after treatment and patients should be pre-medicated with anti-emetics to reduce or prevent this potential side effect. Carboplatin is excreted by the kidney, so reduced renal function may result in toxicity - frequent blood and urine monitoring is required.

- **Chlorambucil** (Leukeran ®) - alkylating agent. Used orally in the treatment of leukaemia, lymphoid and mast cell tumours, as well as other immune-mediated disorders.

- **Melphalan** (Alkeran ®) - alkylating agent. Used mainly for treating multiple myelomas. Side effects relate to myelosuppression. Given orally or parenterally.
- **Cytosine arabinoside/Cytarabine** (*Cytosar ®*) - injectable; inhibits DNA synthesis. Used to treat lymphoma (especially with CNS involvement) and other lymphoproliferative disorders. Side effects: bone marrow and gastrointestinal.

- **Methotrexate** - anti-metabolite; affects DNA replication. Used in combination protocols to treat lymphoma, myeloproliferative disorders, osteosarcoma, transitional venereal tumours and Sertoli cell tumours. Side effects: bone marrow and gastrointestinal. Given orally or parenterally.

- **Corticosteroids (i.e. glucocorticoids) e.g. dexamethasone, prednisolone** - in addition to anti-inflammatory effect, bind to receptors in tumour cell nucleus and inhibit DNA synthesis. Produced naturally in the body and used in veterinary medicine to treat a variety of conditions. Many chemotherapy protocols include corticosteroids, which can be effective in treating some cancers (usually alongside other cytotoxic agents). Treatment often begins with relatively high doses, slowly decreasing the amount given. This gradual tapering allows the body to adapt to steroid withdrawal. Side effects include polydipsia, polyuria, polyphagia, iatrogenic hyperadrenocorticism, hepatomegaly, muscle wasting, gastrointestinal signs and panting. Most oncologists advocate not using steroids in patients suspected of having lymphoma - i.e. before a definitive diagnosis is made. This is because, unless lymph nodes aspirates or biopsy samples have been obtained, the rapid lymphocytolytic effects of corticosteroids may obscure the diagnosis. Also, it is thought that prior treatment with steroids may induce multi-drug resistance. Steroids are often started after obtaining diagnostic samples in patients whose clinical signs are unmanageable or which are hypercalcaemic due to the potential renal toxicity of hypercalcaemia, but ideally they are introduced at the beginning of a chemotherapy protocol.

- **NSAIDs, e.g. Meloxicam, Piroxicam** - anti-inflammatory and anti-tumour effects. They are often used as adjunctive/palliative therapy, particularly in the management of carcinomas (e.g. transitional cell and squamous cell carcinomas). Gastrointestinal side effects may be severe with piroxicam and gastroprotectants are recommended. Renal function should be monitored throughout treatment. Meloxicam is licensed for use in dogs and cats, whereas piroxicam is not. These drugs should never be administered concurrently with glucocorticoids.

Of the drugs used in small animal chemotherapy, none are licensed for veterinary use – there are no alternatives.

Chemotherapy safety should be discussed with owners prior to discharge of the patient. While it is important to point out potential hazards associated with human exposure to these drugs, it is equally important not to frighten people. Explain that excretions from chemotherapy patients may be hazardous, but assure them that the pet is safe to be around all family members – interaction with family members is important to both pets and owners. Owners should be provided with an information sheet about how to prevent exposure to chemotherapeutic agents.
**Surgery**

- "A chance to cut is a chance to cure"
  - Complete surgical excision cures more cancer patients than other modalities
  - Indicated if function & cosmetic outcome not compromised to a point which impinges on welfare/QOL
- Careful planning required – think ahead when embarking on lumpectomies +/- biopsy procedures – all may not be as it appears!
  - Involves aspects of soft tissue, orthopaedic & neuro surgery
  - Requires comprehensive knowledge of anatomy & reconstructive procedures for tissue deficits.

**Nursing:**

- Preparing the patient
  - Clip widely
  - Avoid vigorous palpation/handling of tumours when scrubbing
  - Infection rates are higher with oncological surgery
- Post operative care
  - Analgesia +++ (depending on extent)
  - Fluid therapy & nutrition
    - More is often more

Think ahead with feeding tubes, etc

**Surgery Pitfalls:**

- MCT can degranulate if not handled carefully
  - Premedicate with H₁ & H₂ agonists
- Poorly planned surgery +/- incomplete excision of tumours, e.g. sarcomas, MCT, can lead to
  - Local recurrence +/- systemic spread
  - Poor wound healing
  - Undue patient suffering
- If in doubt, refer!

**Radiotherapy**

- Medical use of ionising radiation to control malignant disease
- Usually palliative therapy
- May be used alone, with surgery &/or chemo
- Produces damaging ionisation within cells → affects cell survival
- Ideal RT dose would cause high tumour cell kill, but spare normal cells
- Side effects broadly divided into acute & late reactions
- Acute = immediately after treatment
- Late = weeks, months or years after tx
- Approximately half of human patients with serious cancer will receive RT
- RT is an effective treatment modality for animals but availability has been limited
- Local treatment for solid tumours
- No systemic side effects
- Local side effects are limited to tissue in the treatment field
When is Radiation Therapy Used?

- Local disease
- Theoretically any solid tumour +/- local LN
- Pre- or post- operative
- Palliation of pain
- Temporary local tumour control

Summary

- Used alone or in conjunction with surgery & chemo
- Specialist treatment using linear accelerator
- Lin acc – photons for deep tissues, electrons for surface
- Imaging first
- Prevent adverse effects through good collimation & accurate planning
- Palliative or therapeutic intent
  - Treat localised or debulked tumours
  - Analgesia for bone pain
- Be pre-emptive with analgesia & nursing care
- Good knowledge of modality & owner liason

Alternative Treatment Options:

Owners frequently ask about alternative treatment options they have heard or read about. Whilst many “alternative” or “complementary” may seem attractive to owners of cancer-bearing pets, few have been assessed or subjected to clinical trials. Dosing usually needs to be extrapolated from human literature and efficacy is difficult to assess. Homeopathy may help to alleviate certain clinical signs and is unlikely to harm the patient, unless given in place of conventional therapy. Although “natural” remedies may be thought of as harmless, we are generally unaware of their effects on chemotherapy, analgesic or adjunctive drugs or on the patient’s health status. Consequently, unless trained in such therapies, it is best to avoid offering advice on many of these treatments.

Knowing When to Let Go:

With advances in veterinary medicine, decisions on when to let go have actually become more difficult than in the past, when all that could be done was to make a terminally ill pet as comfortable as possible for as long as possible. Now, many of the options of human medicine are available for pets, making it easy to persist with treatment when letting go is too difficult. If a cure is not achievable, the increased level of care we can offer cancer-bearing pets is designed to prolong quality of life, as well as quantity, but the former should take precedence. Pets are part of the family.

When living with a terminally ill pet, it is common for owners be stressed and to wonder if they are doing the right thing. When it comes to decision making, how and when to let go is often the hardest for owners. Whilst they have to make the decisions for their pets, the veterinary team can help owners through this process – veterinary nurses may be able to give time and empathy.
Although difficult, sometimes planning a euthanasia can take away a lot of stress from owners – i.e. owners may wish to consider when and where they would like to have their pet put to sleep, which vet they would like to be present and what they would like done with their remains, e.g. cremation with ashes to scatter or quiet burial in the garden.

Following euthanasia, many owners are surprised by the emotions that surface after losing a pet. In some cases the animal is their sole companion, or the grief is not only for the lost pet, but for a time in the person’s life the animal represented and/or connections with other people. It is important to recognise this need to grieve and offer support, but in some circumstances it may be appropriate to advise professional counselling.

References/Further Reading:

- Small Animal Clinical Oncology, Ed. Withrow and MacEwen
- Royal Canin Encyclopaedia of Canine Clinical Nutrition
- Pain Management in Animals, Ed. Flecknell and Waterman-Pearson
- The Safe Use of Cytotoxic Drugs in Companion Animal Practice, N. Bexfield, EJCAP - Vol. 16 - Issue 1 - April 2006