

Chemotherapy of neoplastic diseases

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Cancer therapy

- Conventional methods for cancer therapy in animals are surgery, radiotherapy, and chemotherapy.
- These techniques need not be used in isolation, indeed the combination of surgical management of a primary mass with chemotherapy directed at systemic disease is the most logical and potentially effective way of managing malignant disease.
- Surgery is the most effective form of treatment²

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- The use of radiotherapy in veterinary medicine is limited by the availability of and access to radiotherapy facilities
- The main role of radiotherapy is as a local treatment for malignant tumours, which cannot be controlled by surgery alone.
- Radiotherapy cannot be used to treat widespread disease because of its toxicity, although local lymph nodes may be included in treatment fields

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- The major indication for chemotherapy is in the treatment of systemic malignant disease such as lymphoma and other lymphoproliferative and myeloproliferative diseases.
- The tumour cells in these diseases are reasonably chemosensitive and the widespread nature of the disease necessitates a systemic form of therapy.
- Chemotherapy is not effective against large solid primary tumours of skin, soft tissues, or bone but may have a beneficial role as an adjunct to surgery in the

Cytotoxic drugs

1. Alkylating drugs
2. Antimetabolites
3. Antitumour antibiotics
4. Vinca alkaloids
5. Platinum compounds

Cytotoxic drugs

- Cytotoxic drugs are classified according to their characteristic sites or modes of action.
- Most cytotoxic drugs act upon the processes of cell growth and division.
- These drugs are potent and potentially dangerous and extreme care is required in their use. Careful consideration must be given to the pharmacology and toxicity of the drug, the spectrum of drug activity, and the condition of the patient.

Cont...

- The main indications for cytotoxic drugs in veterinary medicine are management of lymphoproliferative and myeloproliferative disorders including leukaemia, lymphoma (lymphosarcoma), and multiple myeloma.
- Cytotoxic drugs are of little value as sole agents in the management of large solid tumours such as mammary carcinoma or fibrosarcoma.

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- They may have a palliative role as adjuncts to surgery or radiotherapy in the prevention or management of metastatic disease.
- In this role chemotherapy is complementary to surgical excision of the primary tumour with the actions of the drugs directed at microscopic disease residual at the primary site or elsewhere in the body in the form of micrometastases.

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- Generally, the use of cytotoxic drugs in combination protocols is favoured as the most effective approach; by combining different drug classes that have different mechanisms of action greater tumour cell kill may be achieved without increasing normal tissue toxicity.

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- For example, combinations of cyclophosphamide (alkylating agent), vincristine (vinca alkaloid), and prednisolone (corticosteroid) are widely used in the treatment of canine and feline lymphoma.

Alkylating drugs

- In veterinary medicine, alkylating drugs are the most widely used in cancer chemotherapy. They act by interfering with DNA replication.
- **Cyclophosphamide** is widely used in the treatment of lymphoproliferative diseases in cats and dogs. Use in the treatment of multiple myeloma has been reported.
- Cyclophosphamide may also have a role as an adjunct to surgery in the treatment of certain solid carcinomas and sarcomas.

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- Cyclophosphamide is converted to active alkylating metabolites by the liver and primarily excreted by the kidney. One of the metabolites, acrolein, may cause a necrotising haemorrhagic cystitis.
- **Chlorambucil** is the slowest acting and least toxic of the alkylating drugs. It is primarily used for treatment of lymphoma, in the treatment of chronic lymphocytic leukaemia and multiple myeloma.

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- The use of chlorambucil in the treatment of polycythaemia vera has been described.
- Myelosuppression is reversible on discontinuation of the drug.
- chlorambucil is biotransformed in the liver and excreted in the urine as inactive metabolites

Cont...

- **Busulfan** has a selective action against granulocytes and is almost exclusively used in the treatment of chronic granulocytic leukaemia.
- Use in the treatment of polycythaemia vera has been described.
- Myelosuppression is the main side effect although pulmonary fibrosis may occur rarely.
- Busulfan is excreted in the urine as inactive metabolites.

Antimetabolites

- Antimetabolites interfere with DNA and RNA synthesis by interaction with enzymes.
- **Fluorouracil** has been used in the treatment of carcinomas of the mammary gland, gastrointestinal tract, liver, and lung in dogs, but is at best palliative.
- In addition to myelosuppression, fluorouracil causes neurotoxicity, manifest as cerebellar ataxia and seizures. These effects are transitory in dogs *but fatal in cats and fluorouracil is*

Cont...

- Fluorouracil is metabolised in the liver and other tissues. Inactive metabolite are excreted in the urine.
- **Methotrexate** competitively inhibits the enzyme, which is essential for the synthesis of purines and pyrimidines.
- Methotrexate may be used in the treatment of lymphoproliferative and myeloproliferative disorders.
- Its use has also been described in osteosarcoma and other sarcomas.

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- Even at low doses, many dogs will show side-effects of severe diarrhoea.
- Methotrexate is primarily excreted unchanged by the kidney and renal tubular necrosis may occur with high-dose regimens. Myelosuppression and gastro-intestinal ulceration are common side-effects.

Antitumour antibiotics

- These drugs act by forming a stable complex with DNA and interfering with the synthesis of nucleic acids.
- **Doxorubicin** is an anthracycline antibiotic, and is one of the most effective of the cytotoxic drugs.
- In veterinary medicine, doxorubicin is used to treat lymphoproliferative and myeloproliferative disorders.
- It is also a palliative in soft tissue and osteogenic sarcomas and in carcinomas of

Cont...

- **Epirubicin** is a structural analogue of doxorubicin. The tumoricidal activity of both drugs is similar but epirubicin is reported to be less cardiotoxic than doxorubicin.
- The indications for epirubicin are essentially as for doxorubicin.

Vinca alkaloids

- These drugs are plant alkaloids. They bind to microtubular proteins, causing metaphase arrest thus inhibiting mitosis. They may also cause enzyme inhibition.

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- **Vincristine** is the most widely used vinca alkaloid in veterinary medicine.
- The main indications are in the treatment of lymphoproliferative disorders. And also in the treatment of soft tissue sarcomas and carcinomas.
- Vincristine causes virtually no myelosuppression, Constipation may result from long-term therapy.

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- **Vinblastine** is less frequently used than vincristine. Its uses include treatment of lymphoproliferative disorders and mast cell tumours.
- Unlike vincristine, vinblastine causes myelosuppression, and will also cause severe perivascular reactions.
- vincristine and vinblastine undergo hepatic metabolism and biliary excretion.

Platinum compounds

- Platinum compounds inhibit protein synthesis by cross linking strands of DNA.
- These are potent drugs with a broad spectrum of activity
- They may cause severe toxicity which limits their use in veterinary medicine
- **Cisplatin** has been used, by intravenous infusion, in the treatment of osteosarcoma, soft tissue sarcoma, and various carcinomas.

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- Cisplatin is nephrotoxic, causing acute proximal tubular necrosis. Vomiting and myelosuppression also occur.
- Pretreatment hydration recommended.
- Treatment with this drug should be supervised by specialists familiar with its use.
- ***Cisplatin*** can cause severe pulmonary reactions in cats and its use is contra-indicated in this species.

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- **Carboplatin** is a second generation platinum analogue with a spectrum of antineoplastic activity similar to cisplatin.
- Carboplatin has a much shorter elimination half-life than cisplatin and is significantly less nephrotoxic however, myelosuppression can be severe.
- Carboplatin has been used in the treatment of canine osteosarcoma and some carcinomas. It