TEXTBOOK OF SMALL ANIMAL MEDICINE

Edited by

John K. Dunn MA, MVetSc, BVM&S, DSAM, DipECVIM, MRCVS

Department of Clinical Veterinary Medicine
University of Cambridge, UK

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used in the management of human cancers but veterinary experience of this technique is limited. The main problem with this combination is that irradiated soft tissues have poor tolerance of surgical manipulation and complications with wound healing may lead to dehiscence and necrosis.

Radiation may also be applied to unresectable tumours at the time of surgery. Surgical exposure of the tumour site and removal of sensitive tissues from the treatment field allows the application of high doses of radiation to tumours which are otherwise difficult to treat by radiation. Intraoperative radiation requires close proximity of surgical and radiation facilities and is not commonly practised in the veterinary field although the technique has been used in the treatment of a number of tumours including canine bladder carcinomas (Walker and Breider, 1987; Withrow *et al.*, 1989).

PRINCIPLES OF ANTICANCER CHEMOTHERAPY

The use of cytotoxic or anticancer drugs in the treatment of cancer is a relatively new branch of veterinary medicine. In contrast to surgery and radiation which are only effective against local neoplastic disease, chemotherapy has the potential to act against systemic disease which is a major problem in oncology. Many cytotoxic drugs are now available for the treatment of human cancers and some of the major advances in human cancer therapy, for example in the treatment of childhood leukaemias and testicular cancers, have been achieved through the use of such drugs. In animals, chemotherapy has become established as the treatment of choice for lymphoproliferative and myeloproliferative diseases and significant increases in life expectancy can now be achieved in many of these conditions. The use of cytotoxic drugs in the treatment of other animal cancers is constantly being explored and as more drugs become available for veterinary use so the indications for chemotherapy in animals are likely to expand.

Cytotoxic drugs are highly potent agents and extreme care is required in all aspects of their use. Not only do they pose a danger to the patient but staff and owners should be aware of the potential hazards of exposure to these agents. Guidelines for safe handling of cytotoxic drugs are given later in this chapter. The therapeutic margin of most cytotoxic agents is extremely narrow and toxicity is the main dose-limiting factor. In humans, intensive medical care is often necessary to support the patient through periods of severe toxicity resulting from aggressive chemotherapy. Such intensive care is not routinely available or feasible in veterinary medicine and aggressive therapy which would result in serious toxicity to the patient also raises ethical questions. In veterinary practice treatment regimes and dosages are therefore a compromise between efficacy and toxicity. Careful consideration must always be given to the pharmacology and toxicity of the drug, the spectrum of its activity and the condition of the patient.

Mechanisms of action of cytotoxic drugs

Most cytotoxic drugs act on the processes of cell growth and division (Fig. 50.20); it therefore follows that the growth kinetics of a tumour are a major factor governing response to chemotherapy. Tumours with a high growth fraction are more likely to respond favourably to chemotherapy than those with a low growth fraction. The proportion of resting (G_0) cells is also important as these cells are resistant to the actions of cytotoxic drugs and therefore govern the ultimate response to therapy. Normal tissue toxicity follows a similar pattern: organs containing a high

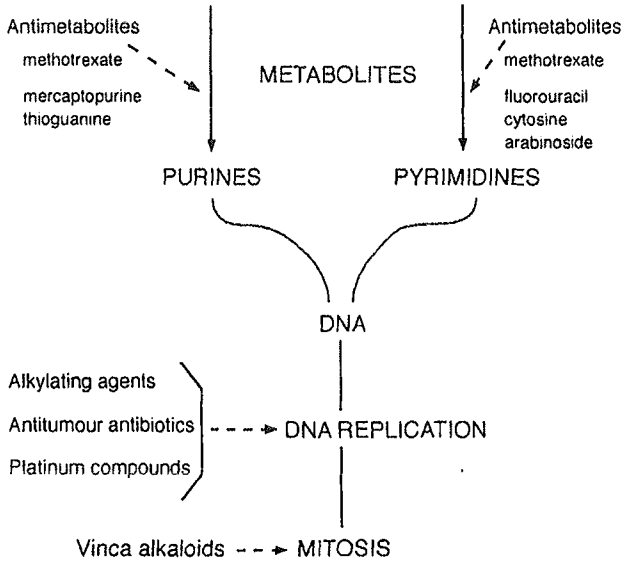

Figure 50.20 Summary of the mechanisms and sites of action of cytotoxic drugs.

proportion of dividing cells, e.g. bone marrow and the gastrointestinal epithelium, are most susceptible to drug-induced toxicity. The resting stem cell populations in these tissues are, however, relatively resistant to the actions of cytotoxic drugs and most cytotoxic drug toxicity is reversible.

Cytotoxic drugs are commonly divided into a number of classes each with characteristic sites or modes of action, antitumour activity and toxicity (see also Table 50.12 and Fig. 50.20).

Table 50.12 Anticancer drugs by group

Alkylating agents	
Nitrogen mustard derivatives	Cyclophosphamide
	Chlorambucil
	Melphalan
Ethenimine derivatives	Thiotepa
Alkyl sulphonates	Busulphan
Triazine derivatives	Dacarbazine
Nitrosureas	Carmustine
	Lomustine
Antimetabolites	
Antifolates	Methotrexate
Pyrimidine analogues	Cytosine arabinoside
	Fluorouracil
Purine analogues	Mercaptopurine
	Thioguanine
Antitumour antibiotics	
	Actinomycin D
	Bleomycin
	Daunorubicin
	Doxorubicin
	Epirubicin
	Mitoxantrone
	Mithramycin
	Mitomycin C
	Streptozotocin
Vinca alkaloids	
	Vincristine
	Vinblastine
Corticosteroids	
	Prednisolone
	Prednisone
Miscellaneous agents	
	L-Asparaginase/ cristantaspase
	Cisplatin
	Hydroxyurea

Alkylating agents

Alkylating agents are the most widely used cytotoxic agents in veterinary medicine. These drugs act by interfering with DNA replication and RNA transcription. They substitute alkyl radicals ($R\text{-}CH_2\text{-}CH_2$) for hydrogen atoms in the DNA molecule. Alkylation of nucleotide bases (e.g. the N^7 guanine of DNA) causes breaks, cross-linkages and abnormal base pairing in DNA. Alkylating agents also react with sulphydryl, phosphate and amino groups causing inhibition of enzymes involved in protein and nucleic acid synthesis. These actions of the alkylating agents are not cell cycle specific. Myelosuppression is the major side effect of these drugs, they may affect the gastrointestinal tract and can cause anorexia, vomiting and diarrhoea. Alkylating agents may also affect gametogenesis and cause alopecia in some breeds of dog.

Antimetabolites

Antimetabolites are a group of drugs which interfere with the normal metabolism of the cell. They are generally structural analogues of metabolites required for purine and pyrimidine synthesis and thus interfere with DNA and RNA synthesis by enzyme inhibition or by causing synthesis of non-functional molecules. Antimetabolites are cell cycle specific, acting during the S phase of the cell cycle. These agents all cause myelosuppression and may also affect the gastrointestinal tract causing anorexia, vomiting and diarrhoea. Renal and neurological toxicity are features of individual drugs (see individual agents).

Antitumour antibiotics

Antitumour antibiotics are derived from soil fungi, e.g. *Streptomyces*. These agents act by forming stable complexes with DNA thus inhibiting DNA synthesis and transcription. These actions are not cell cycle specific. Antitumour antibiotics have a particularly wide spectrum of antitumour activity. With the exception of bleomycin, antitumour antibiotics are myelosuppressive but they also cause a diverse range of selective toxicities (see individual agents).

Vinca alkaloids

The vinca alkaloids are plant alkaloids extracted from the periwinkle (*Vinca rosea* Linn). They bind to microtubular proteins (tubulin) and inhibit formation of the mitotic spindle, causing a metaphase arrest. These agents are thus cell cycle

specific, acting during the M phase. Vinca alkaloids may have other cytotoxic effects on the cell which are less well documented, for example they may cause enzyme inhibition. Tubulin microtubules are also important in neurotransmission therefore neurological toxicity can occur.

Hormones

Hormonal manipulation has an important role in the management of breast, prostatic and endometrial carcinomas in humans. Although hormones clearly play a role in the development and growth of similar tumours in animals, the therapeutic value of hormonal manipulation has yet to be clearly demonstrated. Oestrogens and androgen antagonists may be of value in the management of certain hyperplastic or benign neoplastic conditions of the prostate and perianal hepatoid glands in the dog.

The corticosteroids prednisone and prednisolone are widely used in oncology. They have a cytotoxic action on haematological malignancies, particularly lymphomas. Their immunosuppressive activity is valuable in the management of certain tumour-related complications and finally, they have a role in the palliation of advanced disease.

Miscellaneous agents

There are a number of other agents with antitumour activity which do not fit into the previous groups. These include L-asparaginase (Cristantaspase) and platinum coordination compounds.

Doses of cytotoxic drugs are usually calculated as a function of body surface area (in M_2) rather than body weight because the blood supply to the organs responsible for detoxification and excretion (liver and kidneys) is more closely related to surface area than body weight. The calculation of body surface area from body weight and conversion tables for cats and dogs are provided in Appendix I. Details of all cytotoxic drugs included in the following text and tables are provided in an easy reference format in Appendix II. The dose rates, indications and side effects for these agents are only intended as an approximate guide to the use of these agents and more detailed information should be sought prior to their use. In the individual patient, the severity of the disease, haematological or metabolic complications and the presence of concurrent health problems must be fully addressed since all may influence the prognosis and the ability of the patient to tolerate cytotoxic drug therapy. Care must be taken in patients with compromised renal or hepatic function as impaired metabolism and excretion of the drug may result in increased toxicity.

The rationale of cytotoxic drug administration

The theoretical basis for cytotoxic drug regimes used in clinical practice has been established through years of laboratory and clinical research concerning the interaction of cytotoxic drugs and cancer cells *in vitro* and *in vivo*. Such work has led to the realization that the successful clinical application of cytotoxic drugs demands a different approach to that governing the administration of antibiotics and other pharmacological agents commonly used in practice.

The cell kill hypothesis

One of the most important and basic principles of anticancer chemotherapy is described by the 'Cell Kill Hypothesis' (Skipper *et al.*, 1964). This states that cytotoxic drugs kill tumour cells by first-order kinetics: that is to say that a given dose of a cytotoxic drug kills a fixed percentage of the total tumour population as opposed to a set number of tumour cells. For example, if a given dose of a drug A kills 90% of tumour cells then it will reduce a tumour cell population of 100 million to 10 million, but if there are only 100 cells in a tumour the same dose of drug A will only reduce the number of tumour cells from 100 to 10. This theory therefore infers that, even a highly effective drug acting on a highly sensitive tumour cell population is unlikely to eradicate the tumour cell population in a single dose. In most clinical situations where tumours are known to be chemosensitive, a single treatment will achieve a log kill of 2 to 4.

The Cell Kill Hypothesis is essentially a theoretical model, it assumes a constant rate of growth for all tumour cells, that all tumour cells are equally chemosensitive and that the drug is equally distributed to all tumour cells. In the clinical setting these assumptions are not entirely accurate for reasons discussed earlier in this chapter. Furthermore, the toxicity of the drug to the patient is a major factor governing the dose of drug which can be administered. Nevertheless the Cell Kill Hypothesis does form the basis of two important principles of chemotherapy:

1. Maximum doses of anticancer drugs should always be used where possible.

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