

NEWS FROM THE WORLD OF ONCOLOGY

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CHEMOTHERAPY RESISTANCE

I am often asked by veterinarians and by clients why chemotherapy treatments in companion animals rarely cure cancer and why cancer comes back. It turns out there are many mechanisms by which cancer is, or is able to become, resistant to chemotherapy treatments. Some of these mechanisms are present from the beginning of neoplastic development and others develop over time or are selected for as these cells become able to survive treatment after treatment. It appears that these mechanisms are common across many species including dogs, cats and humans.



1. Cancer stem cells that proliferate slowly within a tumour are less susceptible to chemotherapy treatments. It is the most rapidly growing cells that are most likely to be affected by any given chemotherapy protocol. Therefore rapid growth is desirable when it comes to chemotherapy susceptibility.
2. Cells deficient in the protein apaf-1 are resistant to chemotherapy. Apaf-1 is a pro-apoptotic protein, or a protein that encourages cell death. If a cell is lacking the protein telling it to die, it is more likely to keep on proliferating.
3. Most chemotherapy agents mediate apoptosis (programmed cell death) via signalling in the mitochondria. This pathway can be blocked by the protein bcl-2. Therefore tumours able to over express bcl-2 will be able to block initiation of cell death signalling.
4. A commonly used chemotherapy drug is doxorubicin. Tumours that over express fibroblastic growth factor are able to develop resistance to doxorubicin.
5. Alkyltransferase is widely involved in the metabolism and detoxification of many drugs. Tumours able to over express alkyltransferase can more easily repair DNA damage caused by alkylating agents (e.g. Cyclophosphamide).
6. Expression of topoisomerase leads to the development of an immortal phenotype, which will allow for these cells to be resistant to cytotoxic chemotherapy.
7. Expression of the PGP MDR-1 gene (multi-drug resistance gene) gives cells the ability to pump chemotherapy drugs out of the cell before the drug has any cytotoxic effects. Tumours over expressing this gene are able to develop chemotherapy resistance. This is the gene that is up regulated by the use of prednisone and is the reason this drug is typically avoided prior to initiation of chemotherapy.
8. Some drugs have poor absorption or bioavailability. For this reason most chemotherapy drugs are given IV to avoid absorption issues and are given in active forms to help avoid issues related to bioavailability.
9. However some drugs do need to be activated in the body. A good example is cyclophosphamide, which must undergo hepatic activation. Animals with hepatic dysfunction would be resistant to treatments with drugs in need of activation.
10. The glutathione detoxification system is important for detoxifying many drugs. Tumours that have developed an aggressive ability to over produce glutathione are able to quickly detoxify or inactivate the chemotherapy drug and thus resistance will develop.

Clearly there are many ways by which tumours are able to acquire resistance to various chemotherapy drugs. Current research focuses on manipulating these molecular and growth factors or pathways. In the future it is likely that cancer treatments will not only involve the use of chemotherapy drugs but also other treatments to help decrease the probability of the tumour being able to develop or express some of the mechanisms discussed here.

Dr. Kevin Finora is a board certified Oncologist and Small Animal Internist. He sees patients Wednesday (including evenings) to Saturday at VEC/RC South. Please do not hesitate to contact Dr. Finora if you have any cancer related questions.

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