A PRACTICAL GUIDE TO FELINE CANCER FOR THE CARING CAT OWNER

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PART II: CANCER CHEMOTHERAPY

In Part I of this article, the major types of cancer and their various forms of treatment were presented. While surgical excision of cancerous tissue remains the major treatment for most types of cancer in cats, two types of cancer benefit from drug therapy. These include many of the various forms of lymphosarcoma as well as the separate cancer, mastocytoma. In this article, the strategy of chemotherapy will be explained, followed by a descriptive list of the major drugs used in veterinary medicine to fight cancers. All of these drugs are also used in human medicine and the doses and programs described have been tailored by research veterinarians to the needs of cats. The drugs emphasized here will be those that are most readily available to veterinarians in private practice through their local hospital pharmacies.

It should be realized that ALL drugs that are used to fight cancer in man were first tested in animals and are now also used to treat cancer in animals. Nevertheless, some have extreme side effects in both animals and humans, and these would primarily be used only in veterinary colleges or research institutions such as the Animal Medical Center or Angell Memorial hospital which are affiliated with major human medical facilities like the Sloan- Kettering Institute. These facilities are impressive; on any given weekday, as many as 90 to 150 animals are hospitalized for cancer therapy at the Animal Medical Center. Highly toxic drugs can be administered under carefully controlled conditions, both for the benefit of the animals as well as for the benefit of researchers who work to cure cancer not only for animals, but for man as well.

It would be impossible in one article to present all the available treatments for all the existing cancers in animals. Thus, discussion will focus on drugs used by many veterinarians in private practice who are not researchists, but do have a special interest in treating cancer patients. The drugs and protocols presented here can be done on a local level. You do not have to drive to a major research institution to obtain safe and effective chemotherapy for an afflicted pet!

BASIC CELLULAR PHYSIOLOGY AND THE RATIONALE FOR MULTIPLE DRUG COMBINATIONS

Every cell, whether normal or cancerous, must undergo the same process to divide and increase its numbers. This explains why anti-cancer drugs are so toxic; they destroy the capability to divide in ALL cells, both cancerous and normal. We depend on the constant division of cells to keep our skin in one piece, the lining of our intestines and stomach intact, and our blood's population of red blood cells and disease-fighting cells high. Thus, side effects from anti-cancer drugs often cause open sores, bleeding and bruising, stomach or intenstinal ulcers, colonic bleeding, anemia, and poor resistance to infection. Anyone who has had chemotherapy or known a loved one who has had chemotherapy may have experienced the pain of witnessing such side effects.

However, as I detailed in Part I of this article, veterinarians do not attempt complete cure of cancer. Doses of chemotherapeutic drugs are kept much lower in animals than they are in man. Thus, few animals ever experience a complete remission. But, at the same time, few animals experience pain and illness from the drugs that they are taking. Instead, the goal is to extend a quality life with a minimum of discomfort due to the drugs. The drugs are given at doses that inhibit cell division greatly, but do not stop it entirely.

To divide, every cell goes through the same cycle of events. First, it must gather food material from the environment to go about its daily needs. To begin to prepare for division, it must produce extra proteins and RNA strands to get the machinery ready to create a second cell. This is called the First Gap or G1 stage. Next, it doubles its DNA amount, thickening its chromosomes; this synthesis of DNA is called the Synthesis or S phase. Then there is a brief Gap again (G2) where final proteins and RNA are made before mitosis (M) can occur

Many anti-cancer drugs are termed "phase-specific", that is, they attack division at either Gap 1, Synthesis, Gap 2, or Mitosis and at no other time. Thus, combinations of drugs that act at different phases of the cell cycle can often be used for a double- or triple- kill effect. Low doses of several drugs administered at very specific times, depending on the tumor, can have a better tumor-kill effect than using one drug alone at very high doses. Thus, combination therapy helps to avoid side- effects of high doses while increasing cure rates. Combination therapy is the cornerstone of drug therapy for cancer in man and is also used in animals with cancer

A PRACTICAL PHARMACOPEIA OF ANTI-CANCER DRUGS

GLUCOCORTICOID

These drugs are the most commonly used drugs against cancer. In the case of mastocytoma, they are generally the only anti- cancer drugs needed. In the case of lymphosarcoma, it is frequently possible to maintain remission with a glucocorticoid alone for a significant period of time. Moreover, they are readily available at all veterinary hospitals because they have far more uses than simply cancer therapy. At low doses, corticosteroids are prescribed for allergic eruptions and the vertigo associated with

middle ear infections. In injectable forms, they are used as the primary drug to combat shock after traumatic events such as automobile accidents, high falls, and massive bee and wasp stings.

Glucocorticoids and mineralocorticoids are the two subsets of the family of natural hormones called corticosteroids; these are produced in the cortex of the adrenal glands. Every mammal, including ourselves, depends on natural levels of many different corticosteroids for proper health. Cortisone, a glucocorticoid, is one of the most important of these natural chemicals working to keep the body's internal systems in balance. Corticosteroids should not be called simply "steroids" since many other hormones in the body are also types of steroids, including the sex hormones estrogen and testosterone

From cortisone, pharmacologists have synthesized different glucocorticoids that emphasize only one or two of the many different characteristics of the natural parent compound. As an example, prednisone and prednisolone have roughly five times the anti-cancer effects than cortisone, the natural hormone. Other synthetic corticosteroids include triamcinolone, dexamethasone, flucortisone, and betamethasone. Each has its own spectrum of beneficial effects as well as unwanted side-effects that have to be managed in cancer therapy since the drugs are used at high doses and generally for the life of the patient

One side-effect that will be discussed below will also be presented here, ironically, as a use. Since corticosteroids may stimulate the appetite and may decrease inflammatory redness, pain, and swelling, many veterinarians will prescribe corticosteroids for tumors that are not lymphatic in origin. This is valid, since the drug frequently makes the animal more comfortable and keeps its appetite up, but it is not a direct treatment for the cancer per se. Only mastocytomas and lymphosarcomas and leukemias have been shown to experience a direct kill effect from glucocorticoids.

MODE OF ANTI-CANCER ACTION:

In nature, corticosteroids balance the immune-system; they help to dampen the body's reaction against foreign invaders such as bacteria, viruses, and external proteins. Examples of the body's immune system over-reaction to invaders would include severe poison ivy, bee sting reaction, or asthmatic attack requiring hospitalization; physicians administer large doses of potent corticosteroids to quiet the body's reaction, to suppress the immune system. Corticosteroids attach to cell membranes, stabilizing them; thus, tiny blood vessels don't swell and leak serum, relieving the puffy, red face from the bee sting or poison ivy or the air-choking fluid in the lungs of the asthmatic.

Corticosteroids also directly effect the numbers and performance of all the white blood cells that are orchestrated in the immune response. Most specifically, they dramatically decrease numbers of lymphocytes; thus, these drugs become the foundation for all therapies against lymphosarcoma, the cancer of the lymphocytes, whether these lymphocytes are multiplying in lymph nodes, free in the bloodstream (lymphocytic leukemia), or in selected sites in other organs (renal lymphosarcoma in the kidneys, hepatic lymphosarcoma in the liver, neurologic lymphosarcoma in the brain or spinal

cord, or intestinal lymphosarcoma, generally in the small intestine). Prednisolone and prednisone are five times more potent than cortisone in decreasing lymphocyte numbers.

Finally, since cortisone is a natural hormone, it has its own natural rhythm in the body. In man and the dog, the values are high in the morning and low at night. In a nocturnal animal, such as the cat, it is low in the morning but high in the evening. Whenever possible, physicians and veterinarians try to use corticosteroids in accordance with this natural rhythm in three ways. Firstly, prednisolone or prednisone are most similar to the natural hormone, cortisone; thus, they are the first drugs used in most therapies since they can usually be eliminated by the body within 24 hours. Secondly, after an animal is stabilized and it is clearly benefitting from the drug therapy chosen, it is given only in the evenings to cats or only in the mornings to dogs. Finally, it is then given only every 48 hours; this gives the body a rest from the artificial drug and keeps the body making its own cortisone on the 'off' day. This 'alternate day therapy' is very important for the long-term health of the patient. If the cancer cannot be maintained on alternate day glucocorticoid therapy, then a multiple drug, combination chemotherapy will be recommended

SIDE-EFFECTS:

Cortisone is involved in balancing many bodily functions besides those of the immune system. One of these is sugar metabolism. Our body's blood sugar values are changing all the time; at any given moment, our blood sugar responds to what we are eating, how much we are exercising, or even if we are angry, upset, or happy. Cortisone acts to raise blood sugar values; thus, if a patient is on continuous prednisone for a long period of time, there is a risk of diabetes developing. Moreover, these higher blood sugar levels are achieved by breakdown of body muscle and fat; thus, the pet on cortisone will have an increased appetite to try and balance this tissue breakdown, yet may still look as if muscling over the back is decreasing. These risks are decreased if the drug is only give on alternate days, timed with the body's natural rhythms.

Cortisone also helps to balance blood pressure, primarily by affecting salt retention. Thus, an animal on high doses of corticosteroids for a prolonged period of time will not only eat more than usual, but will also drink more than usual. These effects are sometimes less pronounced when dexamethasone or triamcinolone is used, compared to prednisone or prednisolone. In selected cases, those drugs would be chosen instead of the shorter-acting ones.

Other side-effects can include bone weakness, gastric ulcers, bruising, poor wound healing, and increased susceptibility to infection. All these effects are diminished if the drug is given at the lowest effective dose and only every other evening (cats) or morning (dogs). Luckily, the cat is very resistant to side-effects from corticosteroids when compared to man or the dog. Still, the less drug the better, and, generally speaking, low dose corticosteroid therapy can only be accomplished if other drugs are used as well. Total dependence on prednisone alone generally requires very high doses of that drug, compared to the use of cortisone along with one or two other immune-suppressive drugs some of which will be discussed below

OTHER IMMUNOSUPPRESSIVE DRUGS: AN INTRODUCTION

These drugs, like the glucocorticoids, are used to depress the immune system in many situations, not just against lymphosarcoma. This would include kidney, heart and liver transplant recipients as well as victims of diseases as diverse as Rheumatoid Arthritis, Multiple Sclerosis, and other less common immune-mediated diseases with bizarre names such as Pemphigus, Systemic Erythemic Myelosis, and Autoimmune-Mediated Hemolytic Anemia. Like lymphosarcoma, treatment for these diseases involves combinations of corticosteroids and/or some of the drugs to be presented below. Emphasis will be placed on those drugs most readily available to the practicing veterinarian, rather than those available at research institutions.

THE ALKYLATING AGENTS

The two drugs cyclophosphamide (Cytoxan -- Mead Johnson) and chlorambucil (Leukeran -- Burroughs Wellcome) derive from the nitrogen mustard group and have proven very helpful in veterinary medicine. Their prescription is common, particularly since they are relatively inexpensive and easily procured through local pharmacists. More importantly, they are one of only a few effective anti-cancer drugs available in pill form that can be given at home. Many others are limited to injectable preparations that must be administered by the veterinarian at the clinic.

MODE OF ANTI-CANCER ACTION:

These drugs are not phase-specific, that is, they act to kill cells throughout the G1, S, G2, and M phases of the cycle. They do this by binding to DNA strands and then linking with neighboring strands. By this cross-linking, effective duplication of the DNA, and thus actual division of the cell, is impossible. Multiplication of dividing cells is blocked at the DNA level.

SIDE-EFFECTS:

These relate primarily to the drugs' very potent anti-cell division effects. Since this drug, unlike the glucocorticoids, is not very specific for lymphocytes, it effectively blocks multiplication in most rapidly dividing cells, including the cells lining the intestinal tract and, more importantly, cells in the bone marrow that produce the white blood cells and platelets that fight infections and prevent bleeding tendencies. Thus, the owner and the veterinarian must watch for signs of stomach ulcers such as vomiting, blood in the stool, or black or tarry stools.

Luckily, the cat is very tolerant of these drugs, but monitoring is still very important. Monitoring is accomplished by taking a small blood sample every 7 to 30 days, depending on the dose and protocol being followed. The veterinarian will then measure the numbers of different white blood cells and platelets in the blood stream. Since these are affected more easily than are the intestinal cells, doses can easily be reduced to a very safe level by doing this simple test.

One last side-effect that occurs only with cyclophosphamide is a bleeding cystitis. This occurs in man and the dog much more frequently than in the cat where it is reported relatively rarely. However, it is still important to check the litter box for signs of blood in the urine as well as in the stool. If these effects occur with cyclophosphamide, then chlorambucil would be substituted in its place. This is a slightly newer drug and not as commonly used in the cat as is cyclophosphamide. Blood samples for monitoring of the bone marrow would also be necessary to regulate the dose of this drug, just as it is for cyclophosphamide.

ALKALOIDS

MODE OF ANTI-CANCER ACTION:

The primary drug in this group is the vinca alkaloid called vincristine (Oncovin) which is extracted from a plant. This drug is very phase-specific, acting only at mitosis (M) by interfering with the protein spindle. The spindle is the structure which pulls doubled chromosomes apart to the opposite ends of the cell just before two separate cells are formed. Despite its very potent effect on division, the drug has little side effects and blood sample monitoring is not generally required.

SIDE-EFFECTS:

Unfortunately, it is only available as an injection which must be administered directly into a vein by a veterinarian. Moreover, if any of the drug leaks outside of the vein, it causes a very nasty chemical burn in the area. If your cat is difficult to restrain and handle, this drug would not be selected for use in a cancer chemotherapy protocol. Taking a blood sample on a fractious cat can be done from a pinprick of an ear vein while the cat is wrapped in a towel or zipped into a restraint bag. But an intravenous injection of vincristine demands cooperation from the patient since a large vein, like that running on the inside of the hind leg or along the top of the front leg, is needed to assure that none of the drug is injected into tissue.

However, if your cat is easy-going and tractable, vincristine is definitely a very good option. The stability of the drug has been greatly improved over the past five years, greatly extending its shelf-life and decreasing its cost. Thus, many veterinarians now keep the drug on hand since it is so safe, very effective, and now affordable. For those clinics that do not keep the drug in stock, it is readily available through any human hospital pharmacy. It is a very commonly used drug in human medicine.

ANTIMETABOLITES

Methotrexate (Methotrexate -- Lederle), azathioprine (Imuran -- Burroughs Wellcome), and cytarabine (Cytosar -- Upjohn) are the three major antimetabolite drugs used in veterinary medicine. Methotrexate and azathioprine are major drugs for human organ transplant patients and are readily available in pill form. Cytarabine is only available as an injection, but is likely to become a very important drug for the cat in the near future.

MODE OF ANTI-CANCER ACTIONS

These drugs mimic natural compounds vitally needed for cell division, acting specifically at the Synthesis phase of the cell cycle. Basically, the biochemical machinery of the cell continues to operate, using these false-compounds, until the gears are jammed and division grinds to a halt. Methotrexate imitates the compound folate, one of the B vitamins needed for a certain enzyme to function properly. Azathioprine imitates a purine while cytarabine imitates a specific nucleoside, both fundamental building blocks of the DNA ladder.

SIDE-EFFECTS:

The cat has a very high tolerance to methotrexate pills, although 20% of patients will be nauseous, even at low doses. These individuals are changed to the injectable form of the drug or are simply taken off it completely. In dogs, the rate of nausea is close to 50% and many veterinarians who treat cancer patients regularly do not use protocols that include methotrexate. However, the cat tolerates the drug fairly well, so it is often prescribed for the cat. Moreover, it is one of the few anti-cancer drugs that has an antidote if signs of long- term toxicity appear. These signs are essentially an anemia due to vitamin-B deficiency and would be recognized by the veterinarian through regular blood tests and examinations. The antidote is simply high levels of the B-vitamin folate. Unfortunately, no such antidote exists for cytarabine or azathioprine since the false compounds bind permanently to DNA.

Azathioprine is not regularly used in feline anti-cancer protocols. Rather, its most common usage is in some of the unusual immune-medicated diseases such as the rheumatoid, lupus, and pemphigoid complexes. In cancer therapy, it is generally used only as a substitute for stronger drugs (e.g. methotrexate or cyclophosphamide) that are not being tolerated by a specific individual. Azathioprine has relatively low toxicity and few side-efects.

Cytarabine has two special applications in the treatment of feline lymphosarcoma. It is one of the few drugs that can penetrate into the brain and spinal cord; thus, it is one of the drugs of choice in treating lymphosarcoma of the central nervous system. Moreover, recent studies have demonstrated nearly a 50% incidence of invasion of the central nervous system by malignant lymphocytes in cases of relapse of renal (kidney) lymphosarcoma. In otherwords, if a cat is treated successfully for renal lymphosarcoma and is in remission, but later relapses, there is a 50% probability that the relapse will occur in the brain or spinal cord where treatment can be very difficult. Now, with the new evidence linking relapse of renal lymphosarcoma to invasion of the nervous system, many protocols encourage the use of cytarabine in renal lymphosarcoma to help prevent later invasion of the nervous system by malignant cells.

Unfortunately, this drug is only available as an injection, necessitating trips to the clinic. However, the injection does not have to be given in the vein like vincristine (the alkaloid Oncovin: Eli Lilly). Cytarabine is simply given under the skin, just like most vaccinations. However, it is a relatively new drug, and not particularly stable once it is opened. Thus, it is fairly expensive to use this drug. For the near future, cytarabine is

likely to be reserved for cases involving the nervous system or the kidneys; vincristine will continue to be the most important injectable cancer-fighting drug.

"RESCUE" DRUGS

Several other drugs are finding increasing use in veterinary medicine, primarily at veterinary colleges and research hospitals, but also by regional specialists and referral clinics. They are frequently employed when relapse has occurred and the more commonly used products are no longer effective in maintaining remission. For this reason, they are called "rescue drugs". In some cases, their mode of action is not yet fully understood, but most can be classified as the older compounds. The following is a summary of some of these drugs.

Doxorubicin (Adriamycin -- Adria Laboratories) is derived from a fungus and was originally researched as a possible antibiotic. It acts only on the Synthesis phase of the cell cycle, actually uncoiling the DNA strands, making coordinated division impossible. It is truly a miracle drug that will have increasing importance in the future. However, it must be administered as an injection directly into a vein, has very serious effects on the heart, and must be administered with extreme care by a clinician thoroughly familiar with its use. An electrocardiogram is frequently performed prior to each dose.

Asparaginase is an enzyme that can break down the amino acid asparagine, depleting the entire body of its supply. However, normal cells can make their own asparagine while most tumor cells cannot, so the drug is fairly specific for tumor cells. Side effects occur as an allergic reaction; since asparaginase is a protein, life-threatening anaphylactic reactions can occur after injection. Antihistamines are generally given at the same time that asparaginase is administered; this helps to decrease the risk of anaphylactic shock.

Cisplatin (Platinol -- Bristol Myers Oncology) is a phase non-specific alkylating drug that essentially produces a controlled case of heavy metal poisoning with the metal platinum. Vomiting is very common and the drug must be given intravenously through a catheter over a several hour period while kidney function is carefully monitored. This drug is generally limited for use at colleges of veterinary medicine or research institutions

NEW HORIZONS FOR CANCER THERAPY

Research in cancer is on-going, benefiting both man and animals. The most important treatments are developed in response to a deepening understanding of each disease. For example, certain breast cancers in women have estrogen receptors on the cell membrane, making these particular tumors susceptible to manipulations of different female hormones. In dogs and cats, these receptors have not been shown to exist, but basic research in other aspects of cellular physiology may reveal a different characteristic that could be exploited in treatment protocols.

The most encouraging work may come from research on the immune system. We know that the body has millions of cells dividing every day and that some divide abnormally. A healthy immune system finds these abnormal dividers and destroys them,

preventing cancer. This may explain why transfusions from normal cats have frequently extended the lives and shrunk the tumors of some cats dying of Feline Leukemia.

Much research in human and veterinary medicine is being devoted to helping the body's own immune system fight cancer. Some drugs that are available include levamisole (used as a wormer and shown incidentally to stimulate the immune sytem), Immunoregulin, and vaccines of either Corynebacterium parvum or Calmette-Guerin bacillus (BCG). Unfortunately, there is no consistent body of research that can recommend these therapies at this time; they remain experimental only, although some veterinarians have found them useful. Surgery and the chemotherapeutic drugs detailed in Part II of this article remain the most accepted and consistent route of treatment of cancer in our pets.

CONCLUSION

Many different drugs have been presented and discussed in this article. Their prescription by a veterinarian for a given patient depends on many factors beside the type of cancer diagnosed. Not the least of these are the personality of the animal being treated and the work schedule and transportation problems of the owner. Financial considerations are also important, although many protocols are surprisingly affordable for a cat, especially in comparison to the expense of treating a large breed dog. Three of the oldest, most familiar, and least expensive drugs are prednisolone (a glucocorticoid), cyclophosphamide (an alkylating agent), and vincristine (a plant alkaloid). Newer drugs that are available in pill form are also seeing increasing usage in veterinary medicine, due to the convenience of
home .
treatment; these include methotrexate and azathioprine (antimetabolites) and chlorambucil (an alkylating agent). In time, other drugs will be developed for man and become available to veterinarians and their clients, enabling the pet owner and the veterinarian together to make the best decision for an animal with cancer. In many cases, euthanasia will be chosen. But for many others, medication, with or without accompanying surgery, will extend a comfortable, quality life for many months, or even years, before euthanasia is necessary. Open discussion between the patient's owner and the patient's doctor will help make the best decision for the afflicted pet.