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ORAL CHEMOTHERAPY DRUGS – WHAT’S NOT TO LIKE?

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PROS AND CONS OF ORAL CHEMOTHERAPY

Several oral drugs are now used routinely for cancer treatment, and others are under investigation. Advantages of an oral chemotherapy regimen include client convenience, reduced frequency of administration, potential for outpatient treatment and improved quality of life as possible discomfort of injections can be avoided. A recent survey of human cancer patients reported that 89% preferred oral to intravenous treatments; however, they were not willing to sacrifice efficacy for their preference. In addition to client/patient preferences, pharmacokinetic considerations may also favor oral delivery of drugs. Oral delivery may provide exposure to lower concentrations of cytotoxic drugs. For cell cycle-specific agents (eg. topoisomerase-1 inhibitors), this may offer higher antitumor efficacy than intermittently giving IV boluses, which provides short-lived, high drug levels. For cell cycle-specific drugs, duration of exposure to a plasma level above a cytotoxic level is considered more important than peak drug concentration.

Risk of subtherapeutic drug concentrations is a major disadvantage of oral delivery of chemotherapy agents. Clients that are noncompliant and miss treatments may be an obvious cause of subtherapeutic dosing. Some anticancer drugs have similar pharmacokinetic properties after oral and IV administration and oral formulations are considered as effective as the IV formulations. However, many drugs have low or variable bioavailability when given orally. In general, anticancer drugs have a narrow therapeutic window and should be given at the highest tolerated dose. Therefore, IV administration might be preferred if bioavailability is poor. Finally, oral delivery of chemotherapy drugs places patients at risk for medication errors by improper dosing and places clients/families at risk for environmental exposure by improper handling of drugs.

FOOD – TO GIVE OR NOT TO GIVE?

Food can significantly affect the pharmacokinetic profile of orally administered drugs and this is often overlooked when clients are instructed to give drugs at home. Giving food with some drugs may delay absorption, usually due to delayed gastric emptying. Food may lead to decreased drug absorption due to drug instability in gastric fluids, physical or chemical binding with food, or increased first-pass clearance. For some drugs, food may actually increase absorption possibly by increased micellar solubilization or decreased first-pass effect. Also, certain fatty acids may cause transient changes in the permeability of epithelial membranes leading to increased absorption. Manufacturer recommendations should be followed to avoid possible food-drug interactions.

BEWARE OF COMPOUNDING

Veterinarians must occasionally use compounded drugs to meet a specific patient's medical needs. However, compounding is likely to change a drug's behavior in the body, even if used in the same species for which the drug is approved. Most of the changes alter the stability of the drug in its preparation or alter its absorption. Generally, the more a drug is manipulated beyond its original dosing form or route of administration, the more likely the changes will negatively impact the drug's performance in the animal's body. Do not assume any compounded drug preparation will result in drug delivery that is equivalent to an approved version. If necessary, dispersing a tablet in a flavoring solution is preferred to simply crushing tablets or adding the contents of a capsule to food or water so that the administered dose is uncertain. However, enteric-coated or spansule products should never be crushed. Crushing oral tablets for suspension in syrup may lead to unequal distribution of dissolved drug in the finished preparation, and mixing the drug so that it is equally distributed throughout the preparation may not be possible. The addition of flavoring agents to oral products may decrease drug stability because of changes in pH. For all of these reasons, compounding chemotherapy drugs should be avoided.

SAFETY CONSIDERATIONS

Sending home oral chemotherapy drugs increases the risk of medication errors. Vials should be clearly labeled with specific instructions regarding number of pills to give, frequency, storage conditions, and whether or not the medication should be given with food. Vials containing chemotherapy drugs should be stored in a secure location away from other meds to minimize exposure. Many drugs are potentially carcinogenic, mutagenic and/or teratogenic and prolonged exposure might be hazardous. Clients should wear powder-free latex, nitrile, polyurethane, or neoprene gloves. Hands should be washed after removing gloves.

CCNU (CeeNU; LOMUSTINE)

Metabolism and pharmacokinetics

CCNU is an oral alkylating agent in the nitrosourea subclass. CCNU has virtually complete absorption following oral administration. Oxidation by hepatic microsomal (P450) enzymes occurs on first-pass through the liver. Metabolites are excreted mainly in the kidneys. CCNU is highly lipid soluble and has a low molecular weight. These unique properties allow CCNU to rapidly distribute across biological membranes, including the blood brain barrier.

Clinical Activity

CCNU is used mainly in the treatment of lymphoma and mast cell tumors. There is activity against histiocytic sarcomas in dogs and in a pilot study, CCNU had questionable efficacy against a variety of brain tumors.

Toxicity

CCNU has the potential to cause severe myelosuppression; up to 40% of dogs may have neutrophil counts $<1,000$ cell/ μL 7 days after treatment. We have also observed delayed and cumulative thrombocytopenia following consecutive treatments; the risk is minimized if a 4-week dosing interval is used. Hepatotoxicity is a major problem in dogs. In one large study of 179 dogs, 6% developed liver failure. It is likely the majority of dogs would develop hepatotoxicity if continually treated with CCNU. Renal toxicity is another potential adverse effect and is likely cumulative. Glucosuria may be an early indicator of renal tubular damage. Neutropenia 7-28 days after treatment is the major toxicity of CCNU in cats. Hepatotoxicity has not been observed in cats but we have seen renal failure and unexplained pleural effusions in some cats.

Clinical Recommendations

CCNU is supplied as 10, 40, and 100-mg capsules. The manufacturer recommends CCNU is given on an empty stomach with a glass of water. For dogs, CCNU at a dosage of 70-90 mg/ m^2 PO every 4 weeks can be used (q 6 wks for dogs with brain tumors). We routinely use prophylactic antibiotics after at least the first dose of CCNU. A CBC should be obtained on day 7 after treatment. If the neutrophil count is $<500/\mu\text{L}$, subsequent dosages are reduced. Platelet counts should be obtained immediately prior to each treatment. If the platelet count decreases below 150,000, CCNU may need to be discontinued. Since CCNU is hepatotoxic, chemistry panels should be monitored every 2 months. I discontinue CCNU if ALT increases to 3X the upper limit of normal. Cats can receive CCNU at 50-60 mg/ m^2 every 4-6 weeks. 5-mg reformulated capsules are helpful to more accurately dose cats.

CHLORAMBUCIL (Leukeran)

Metabolism and pharmacokinetics

Chlorambucil is a bifunctional alkylating agent that acts by crosslinking DNA. Orally administered chlorambucil is nearly completely absorbed from the GI tract and reaches peak plasma levels in 1-hour. The drug is oxidized to the active moiety, phenylacetic acid. Phenylacetic acid undergoes decomposition by hydrolysis. Less than 1% of the administered dose is excreted in urine. Food should not be given concurrently since it may increase gastric residence time, leading to increased hydrolysis and decreased absorption of the active drug.

Clinical Activity

Chlorambucil is mainly used to treat canine and feline chronic lymphocytic leukemia and low-grade lymphoma. Chlorambucil is often used to replace cyclophosphamide when sterile hemorrhagic occurs in a patient and may have some role to treat immune-mediated feline dermatoses.

Toxicity

Toxicity due to chlorambucil is uncommon. Bone marrow suppression (mainly thrombocytopenia but also neutropenia) is possible but is most often mild,

gradual, and reversible. Adverse GI effects (especially anorexia) are possible and occur more often in cats. Neurotoxicity in the form of myoclonus or seizures has rarely been observed in cats and may be linked to high-dosages.

Clinical Recommendations

Chlorambucil is available in 2-mg tablets. Tablets are enteric-coated and attempting to cut or split them is highly inaccurate and unsafe. Long-term exposure to alkylating agents can be mutagenic, carcinogenic, and teratogenic. For this reason, client education and safe handling are essential. The manufacturer recommends chlorambucil be taken 30-60 minutes before meals (see above). Multiple dosing schedules are available. In dogs and cats, I generally use 6-8 mg/m² PO on alternating days. Very small cats (<3 kg) may need to be dosed on a Monday, Wednesday, Friday schedule or every third day if that schedule cause anorexia. A CBC should be monitored monthly.

CYCLOPHOSPHAMIDE (Cytoxan)

Metabolism and pharmacokinetics

Cyclophosphamide is a bifunctional alkylating agent that acts by crosslinking DNA. Cyclophosphamide is a prodrug requiring hepatic activation to 4-hydroxycyclophosphamide (4-HC). 4-HC spontaneously breaks down to the active moiety, phosphoramidate mustard, and the inactive by-product, acrolein, that can cause bladder damage. In people, oral bioavailability may be 90%.

Clinical Activity

Cyclophosphamide is commonly used in combination chemotherapy regimens for lymphoma. It is often combined with doxorubicin to treat aggressive carcinomas or with doxorubicin and vincristine to treat aggressive sarcomas. Cyclophosphamide may have a role in the treatment of autoimmune diseases.

Toxicity

Cyclophosphamide has the potential for severe bone marrow toxicity 7 days after treatment. GI upset is uncommon. Alopecia and poor hair growth is common in dogs receiving long-term treatment. Cats may lose their guard hairs and whiskers. Hemorrhagic cystitis is related to the concentration and duration of contact of acrolein, an inactive metabolite, with the bladder epithelium. Incidence may be as high as 10% if measures are not used to protect the bladder.

Clinical Recommendations

Cyclophosphamide is available as 25 and 50-mg tablets. Tablets contain a core of active ingredients sealed within a compressed coating. Distribution of the active ingredient may not be uniform if tablets are split or crushed. Client education and safe handling are essential. The manufacturer recommends cyclophosphamide be taken with food or on an empty stomach. Giving cyclophosphamide to dogs with bacterial cystitis should be avoided. The tablet(s) should be given in the morning. A single dose of furosemide reduces

the incidence of cyclophosphamide-induced cystitis to 1%. Cyclophosphamide is given at a dosage of 200-250 mg/m² PO. Generally the drug is combined with vincristine or alternated with other drugs in lymphoma protocols. Fractionated dosing (50 mg/m² on alternate days or daily x 4 days) are also reported. When fractions of the tablet size are needed, options include giving an IV dose or rounding down to the nearest 25-mg.