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CYCLOPHOSPHAMIDE: NEW THOUGHTS ON AN OLD DRUG

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MECHANISM OF ACTION

Cyclophosphamide (Cytoxan®) belongs to the group of chemotherapy drugs known as classical alkylating agents. Other members of the drug group include nitrogen mustard, mephalan, chlorambucil, ifosfamide and the nitrosoureas. This group of drugs has a similar mechanism of action, alkylation. Alkylation involves loss of a chlorine molecule and replacement with -CH3. This produces intra- and interstrand DNA crosslinks inactivating DNA. The crosslinks are responsible for the cytotoxicity of the cyclophosphamide. Cyclophosphamide is a prodrug and is metabolized by the liver to form 4 hydroxycyclophosphamide. This compound exists in equilibrium with aldosphosphamide and produces phosphamid mustard and acrolein. Phosphoramid mustard is the active metabolite of cyclophosphamide and acrolein is the cause of cyclophosphamide cystitis.

Cyclophosphamide has been in use in veterinary medicine for several decades. It is used to treat lymphoid tumors such as lymphoma, multiple myeloma, and mammary gland carcinoma. In the 1980’s, its use was first recommended as an immunosuppressive agent in immune mediated hemolytic anemia, lupus and polyarteritis.

Cyclophosphamide is available in both parenteral and oral tablets. Tablets are 25 mg or 50 mg. The drug is encased in a protective outer coating to protect those dispensing and administering the drug from its toxic effects. Tablets should not be split as splitting defeats the purpose of the protective coating. Some recommended doses for oral or intravenous administration of cyclophosphamide are: 200-250 mg/m², 10 mg/kg, 50 mg/m² for 4 consecutive days.

EFFECTS AT THE CELLULAR LEVEL

Cyclophosphamide is a potent immunosuppressive agent and has effects on both B and T lymphocytes, but in vitro studies show little effect on immunoglobulin concentrations and lymphocyte blastogenesis.

TOXICITY OF CYCLOPHOSPHAMIDE

- Hematopoietic toxicity is the dose limiting toxicity of the drug. Cyclophosphamide is considered stem cell and platelet sparing since cumulative toxicity is not seen with this drug and thrombocytopenia is rare. Typically, neutropenia occurs 5-7 days after administration of a single dose of cyclophosphamide and neutropenia resolves quickly.
- Nausea and vomiting are common side effects of any chemotherapy agent. They can occur with cyclophosphamide, but other toxicities are of greater clinical importance.
- Alopecia occurs in dogs treated with cyclophosphamide; although most dogs receiving cyclophosphamide for the treatment of cancer receive multiple chemotherapy agents all of which can cause alopecia. Cats experience little alopecia from chemotherapy, but commonly lose their whiskers.
- Carcinogenesis. Transitional cell carcinoma has been reported in dogs following administration of cyclophosphamide.

- Bladder toxicity

Hemorrhagic cystitis is a unique toxicity associated with cyclophosphamide and its isomer, ifosfamide. The metabolite acrolein is excreted in the urine and causes urothelial edema necrosis, hemorrhage and fibrosis. Both dogs and cats have been reported to develop cyclophosphamide cystitis.

New thought #1

Cyclophosphamide has been recommended as an immunosuppressive agent in immune mediated hemolytic anemia, but has not previously been compared in a randomized prospective clinical trial to glucocorticoids alone. A recently published study has done this and found dogs receiving prednisone 1-2 mg/kg BID without cyclophosphamide (50 mg/m² x 4days for 4 weeks) responded to treatment equally if not better than those receiving cyclophosphamide. Within 8 days, 2/10 in the prednisone group and 3/8 in the prednisone and cyclophosphamide group had died due to ongoing hemolysis. Administration of cyclophosphamide appeared to suppress the reticulocyte count. This study, combined with results of a retrospective study indicating a similar negative prognosis with administration of cyclophosphamide suggests routine use of cyclophosphamide cannot be recommended in IMHA. Administration of cyclophosphamide early in the treatment course of IMHA does not result in a more rapid resolution of hemolysis and in fact may have a negative impact on the outcome of the case.

New thought #2

A second recently published study on cyclophosphamide looked at the frequency of occurrence of cyclophosphamide cystitis in dogs receiving multiagent chemotherapy protocol for lymphoma. In both protocols, the dogs received cyclophosphamide at a dosage of 200 mg/m² IV. In one protocol, the dogs received 2.2 mg/kg IV of furosemide at the time of cyclophosphamide administration. The 2 groups were compared to identify risk factors for the development of sterile hemorrhagic cystitis. Nine percent of dogs not receiving furosemide developed sterile hemorrhagic cystitis and only 1% of those receiving furosemide did. The median number of treatments of cyclophosphamide prior to the development of sterile hemorrhagic cystitis was 2. Age, sex, breed, body weight, prior urinary tract disease, neutropenia and chemotherapy agent administered prior to the dose of cyclophosphamide dose causing sterile hemorrhagic cystitis did not correlate with the development of cystitis. This study makes a compelling recommendation for the routine use of furosemide with cyclophosphamide in dogs receiving a lymphoma chemotherapy protocol containing cyclophosphamide. It is a simple and inexpensive method of reducing the occurrence of cyclophosphamide cystitis.

REFERENCES