Bisphosphonates: Key to Cancer Treatment?

Malignant histiocytosis (MH), or histiocytic sarcoma, is a tumor that arises from cells of the histiocytic lineage (e.g., monocytes, dendritic cells). MH may develop as either a localized tumor (where distant metastases are common) or disseminated disease with primary origins from the bone marrow, spleen, or lung. Prognosis for long-term survival is poor to grave. Chemotherapy with such drugs as prednisone, doxorubicin, lomustine (CCNU), and carboplatin can help with local of systemic recurrence of MHs in dogs. However, median survival time for the disseminated form is still 2–4 months from diagnosis. Bisphosphonates are frequently used to treat cancers with bone involvement and are known for their ability to deplete macrophages. This study examined whether bisphosphonates adjunctive to cytotoxic chemotherapy can potentiate effectiveness.

The results of in vitro combinations of 6 commonly used chemotherapeutic agents and 5 bisphosphonates showed that effectiveness of select chemotherapy agents may be improved by adding a bisphosphonate. In particular, combination of clodronate with vincristine caused synergistic cytotoxicity and significant increase in cell-cycle arrest. Zoledronate combined with doxorubicin also significantly increased cell death and uptake of doxorubicin by MH cells. The evidence presented may support using these drugs together, particularly in advanced cases of MH.

Commentary

The use of bisphosphonates to improve histiocytic cell death has recently triggered research interest. Pilot studies have shown that this class of drugs shows promise as adjunctive therapy in dogs with MH. Bisphosphonates are important in human medicine because of their safety profile and variety of indications, such as treatment of osteoporosis, potential decreased risk for colorectal cancer, and decreased resistance of osteosarcoma to chemotherapy. However, they are also associated with pathologic fractures and renal failure and can be cost prohibitive. Future studies are warranted.—Heather Troyer, DVM, DABVP, CVA

Source

Bisphosphonates significantly increase the activity of doxorubicin or vincristine against canine malignant histiocytosis cells. Hafeman SD, Varland D, Dow SW. VET COMP ONCOL 10:44-56, 2012.

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FOCUS Detecting Ketonemia in Diabetic Cats

Diabetic ketoacidosis (DKA) is a common emergency in newly diagnosed and treated diabetic cats. Signs are nonspecific; diagnosis is often based on presence of hyperglycemia, positive urine or plasma dipstick measuring acetoacetate, and high anion gap metabolic acidosis. Measuring ketones is important, as a high anion gap may be seen with other diseases (e.g., hyperlactatemia, deteriorating chronic renal failure). This study evaluated a handheld ketone meter (Precision Xtra, abbott.com) that measures β-hydroxybutyrate (β-OHB) using whole blood. To validate the ketone sensor, β-OHB samples from 43 newly diagnosed or insulin-treated diabetic cats were measured 3 times and compared with a laboratory reference method. Two representative samples with low, medium, and high β-OHB concentrations were involved. At low to moderate concentrations of β-OHB, there was good linear correlation with the reference and reproducibility was acceptable. A significant negative bias was found when β-OHB concentrations were >2.55 mmol/L. Many cats with high β-OHB and normal blood pH had an elevated chloride gap, suggestive of superimposed hypochloremic metabolic alkalosis. At β-OHB concentrations <2.55 mmol/L, DKA can be excluded. However, β-OHB measurement cannot replace traditional blood gas analysis and should be used as a complementary diagnostic measure.

Commentary

This paper documented point-of-care testing as a means of evaluating diabetic cats for ketonemia. Although the test is not specific enough to definitively diagnose DKA, it is sensitive for ruling out ketonemia in ill diabetic cats. This may not necessarily change the treatment course, but it may help better characterize concurrent illness and guide additional diagnostics. The high sensitivity of this test may also provide a good method when monitoring for ketonemia as it resolves in cats treated for DKA.—Jennifer Ginn, DVM, MS, DACVIM

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