New for Canine Lymphoma

Rabacfosadine (Tanovea-CA1) is a newly approved canine lymphoma. This drug was originally explored by Gilead Sciences as an antimetabolite and is an acyclic nucleotide that acts as an artificial pro-drug on the nucleotide base guanine. This means it is in the class of drugs called "antimetabolites" which have very complicated biochemistry. This drug was previously called GS-9219 and also VDC-1101 during its development. To be precise, rabacfosadine is a double pro-drug of acyclic nucleotide phosphonate 9-(2-phosphonylmethoxyethyl) guanine or PMEG. When this pro-drug is taken up preferentially by lymphoid cells, where it is phosphorylated in 2 positions to become PMEGpp. PMEGpp then inhibits the activity of nuclear DNA polymerases alpha, delta and epsilon. This ultimately results in cell death due to inability to complete DNA replication. This drug selectively depletes lymphoid tissues at doses that spare normal cells, and thus has been shown to have cytotoxic activity in lymphoma and multiple myeloma in dogs.

Every drug that acts as a cytotoxin has potential down sides, and in the case of rabacfosadine those dose-limiting toxicities are generally similar to those seen with other anti-cancer drugs, and include gastrointestinal and bone marrow toxicity. Dropping the white blood count appears to be at a nadir of 5-7 days, as for most chemotherapy drugs. Most dogs experienced mild (Grade II) neutropenias, but some Grade V toxicities have been noted. The nadir of neutropenia occurs at 5-7 days after administration. Gastrointestinal toxicities are also generally mild (Grade II) vomiting and diarrhea, but anorexia lasting for 1-2 weeks has been seen in some dogs. Other less frequent toxicities include side effects of the dermal, renal and pulmonary systems. Dermatologic lesions include otitis and pruritic and erythematous skin lesions. Excessive skin pigmentation has been observed. Gastrointestinal toxicity is noted in some dogs. Most of these are self-limiting and managed by appropriate supportive care (anti-emetics, anti-diarrheals). The skin lesions seem to benefit from administration of steroids. Unfortunately, dogs that develop pulmonary toxicity can have irreversible toxicity that can results in pulmonary fibrosis and ultimately euthanasia. Pulmonary fibrosis is a rare but highly fatal adverse effect. Approximately 3-4% of patients can experience pulmonary fibrosis, which appears to be truly and idiosyncratic reaction and can happen months after administration. For this reason, it is recommended that West Highland White Terriers not receive this drug due to their breed related predisposition to pulmonary toxicity.

This agent is administered as a 30-minute intravenous infusion in 5% dextrose, at a dosage of 1 mg/kg every 21 days for 5 treatment cycles.
The response rates to this drug are similar to the MOPP protocol in the rescue setting for lymphomas, and it seems to be better for T cell lymphomas. Protocols alternating doxorubicin with Tanovea for 3 doses each have outcomes similar to CHOP and is more convenient to give chemotherapy on an every 3 week rather than every week basis. In a study of 14 dogs with multiple myeloma, 82% of the dogs had evidence of response to therapy, including complete responses (3 dogs) and partial responses (6 dogs). Dogs that had a response had a progression-free interval (PFI) 172 days (range 95 days to greater than 1024 days.) Unfortunately, as a new drug Tanovea is very costly and we are working on establishing our pricing structure at this time.

New for Osteosarcoma

A new recombinant Listeria vaccine is able to induce tumor specific T cell responses in canine patients with osteosarcoma. Dogs to be treated are positive for expression of a specific growth factor receptor, Her2/neu, that is expressed in their osteosarcoma cells. The Her2/neu gene codes for a receptor tyrosine kinase molecule that is the receptor for a form of epidermal growth factor. It is estimated that 40% of canine osteosarcomas express this receptor, and it may be expressed specifically on cancer stem cells that exist at low levels within osteosarcoma tumors, contributing to their ability to become metastatic and to survive chemotherapy exposure.

The vaccine product is a fusion protein that incorporates a human Her2/neu gene in the setting of a highly attenuated recombinant Listeria monocytogenes bacterial organism. In the initial published studies, 18 dogs were treated after limb amputation for osteosarcoma, followed by 4 doses of carboplatin chemotherapy in the standard of care protocol. Vaccination with the bacterial recombinant product was performed by IV injection every 3 weeks for 3 treatments.

Patients were pre-treated with ondansetron to prevent nausea and vomiting, and diphenhydramine was given to prevent anaphylaxis. Dogs received a 3 day course of amoxicillin and a 7 day course of S-Adenosylmethionine (SAMe) to block liver toxicity. Toxicities were reported to be mild, and included low-grade fever the day of treatment with the vaccine, and mild nausea and vomiting within 4 hours of injection. Increased white blood cells, especially neutrophils and monocytes were noted. Dogs that survived more than 18 months had higher white blood cell count responses than those that lived less long. Slight increase in liver enzymes were noted after vaccination. No cardiac toxicity was noted, despite this being observed in other species, although 2 dogs developed transient arrhythmias that resolved within one week.

Dogs developed antigen-specific responses against the Her2/neu gene product in 15/18 dogs. This resulted in significant prolongation of survival time and 1, 2, and 3 year survival rates were also increased. For these 18 dogs, the median Disease Free Interval was 615 days and the median survival time was 956 days. Overall survival rates of 1, 2, and 3 years were 77.8%, 67%, and 56% respectively. This response rate is significantly greater than that seen with
chemotherapy alone, and this allowed additional studies to be undertaken to further develop this product. New expanded data will be presented at the meeting, and hopefully this product will be commercially available at the time of the 4 Corners Symposium.