Nicole Ehrhart VMD, MS

Animal Cancer Center
Colorado State University

Isolated Limb Perfusion Using Samarium for Canine Osteosaracoma: Proof of Concept November 1, 2005

Background and Significance:

Canine OSA is a well-established model for human OSA with similar biologic behavior and clinical response to therapy. Even with the addition of aggressive multimodality therapy, survival of human and canine OSA patients has plateaued for more than a decade. Despite modern therapy protocols which include neoadjuvant chemotherapy, good local surgical control and post-operative chemotherapy, 20-40% of human patients with non-metastatic OSA of the extremities die of disease. In dogs, greater than 90% of patients eventually die of OSA. In addition, loss of limb and/or function is still a relatively common occurance for OSA patients, despite the increase in limb salvage procedures performed. Decisions about local control and amputation can be agonizing for patients and families.

Although radiotherapy is not part of the current standard of care for OSA control, recent evidence in human patients suggest that radiation improves progression-free interval and quality of life in patients with extremity OSA that have refused surgical therapy or in whom resection is not possible. In addition, existing evidence in dogs suggests that the use of radiation in combination with chemotherapy increased percent necrosis to clinically favorable levels over radiotherapy or chemotherapy alone. We believe the beneficial role of radiation for treatment of OSA has likely been underestimated. New readation modalities are available that can minimize radiation effects to normal adjacent tissues, yet provide improved tumor kill over standard OSA treatment. One such candidate therapeutic is the bone-seeking radioisotope, samarium 153 ethylenediamine-tetramethylene phosphonate. In high doses, samarium (Sm)has been shown to locally deliver 20 to 200 Gy of radiation to normal bone and osteosarcoma tumors, respectively. The efficacy of samarium in OSA patients has been previously reported. Studies on spontaneously - occurring OSA in dogs indicate that tumor doses equivalent to 20 Gy may be deposited in canine osteosarcomas using low- to moderate doses of intravenously administered samarium, and the ratio between tumor dose and dose to surrounding tissues is favorable. The treatment gives pain relief in canine patients and, in some cases, tumor growth delay but was not curative. The authors conclude that samarium in combination with surgery may provide better local and systemic control. Together, these data suggest that high-dose samarium has a role in the risk-adapted, multimodality treatment of OSA and may provide a local control and /or survival advantage in human and canine patients with OSA, especially when combined with traditional chemotherapeutics. However, the limiting issue with high dose samarium therapy is significant bone marrow suppression requiring peripheral stem cell support.

Isolated limb perfusion (ILP) is a regional cancer treatment that enables the administration of high doses of chemotherapeutic agents in a limb with minimum systemic exposure. During ILP, the circulation of the limb is isolated from the patient's systemic circulation and connected to a heart-lung machine. The extracorporal circulation allows delivery of high dose chemotherapy in concentrations 10-20 times higher than can be tolerated systemically. ILP has been used to deliver various anti-neoplastic agents for over 50 years; first for melanoma and, more recently, for extremity sarcoma. Until recently, ILP had never been performed using radioisotopes. We completed a pilot study that proves the feasibility of ILP using Sm in the normal dog. We

propose to use isolated limb perfusion to deliver samarium to slpontaneously-occuring canine appendicular OSA, thus minimizing systemic exposure and toxicity while enhancing delivery of Sm to the tumor.

Neoadjuvant chemotherapy is used in osteosarcoma to achieve a high percent tumor necrosis prior to surgery. A strong histologic response (greater than or equal to 90% necrosis) has been clinically associated with a longer survival time. High percentage tumor necrosis *in situ* is theorized to be associated with increased survival due to the fact that a high percent of primary tumor necrosis is likely an indirect measure of micrometastases to standard anticancer regimens. In addition to this, *in situ* tumor necrosis has also been theorized to have an immunomodulating effect favoring host cellular immune response to the tumor. The use of ILP-Sm has particular promise as it can be delivered directly to the tumor-bearing limb where it irreversibly binds to bone. Once bound, the remaining Sm is flushed from the circuit minimizing systemic and radiation exposure when host circulation is re-established. The use of targeted radionuclides in this local delivery manner may enhance early tumor response such that neoadjuvant chemotherapeutic dose-intensity can be decreased. Ultimately, this will result in more rapid induction of tumor necrosis, less systemic toxicity, higher rate of limb preservation surgery, fewer cycles of neoaduvant chemotherapy required and preservation of patient stem cell reserve.