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Treatment of Canine Osteosarcoma
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Each year about 10,000 dogs in the United States, mostly of the large and giant breeds, are diagnosed with osteosarcoma (OSA), a painful bone tumor. This disease also occurs in humans, though not in such high numbers. Osteosarcoma in dogs affects primarily the long bones of the leg, but can affect bones of the spine, skull, or ribs.

"Over the last ten years there have been major advances in treatment of this disease in both species," said Dr. M. Joy Weinstein, assistant professor of surgery at Penn's School of Veterinary Medicine, "but protocols are still needed. Therapy for osteosarcoma of long bones includes amputation with or without chemotherapy, or limb-sparing surgery and chemotherapy. Limb-sparing surgery involves removal of the primary tumor while preserving the limb through use of a bone graft or a prosthesis. Two chemotherapy drugs that appear to be most effective in this disease are Adriamycin and cisplatin. Unfortunately, at this point in time, we cannot cure the disease, but we can give the dog a good quality of life for a number of months or years."

Dr. Weinstein, who returned to Penn after surgical specialty training at Tufts University School of Veterinary Medicine, is conducting a study assessing perioperative and postoperative treatment of OSA by administering adriamycin and cisplatin concurrently. "These drugs usually are used alone or alternated to reduce the growth of metastases. By administering them together we hope to achieve an additive effect."

Osteosarcoma in dogs frequently manifests itself as a lump; the dog is in pain and often refuses to use the leg. Radiographs reveal a bone tumor at the end of the long bone of the leg, either front or rear. "When the patient comes to the veterinarian, the tumor has already spread through microscopic lesions to other parts of the body, primarily the lungs," said Dr. Weinstein. "If we amputate the leg and give postsurgery chemotherapy, the median survival time is about 18 weeks, though some dogs (10 percent) live more than a year. If the animal is treated with chemotherapy, either cisplatin or adriamycin, the median survival time increases to about 40-45 weeks, with nearly 50% of the dogs living more than a year."

Amputation of the affected limb is Dr. Weinstein's preferred surgical treatment. "It relieves the pain, allows the dog to get around quite well on three legs," she explained. "Most dogs walk one day after surgery and need exercise restrictions for only about two weeks." An alternative to amputation is limb sparing surgery. She recommends this treatment for dogs that would not get around well on three legs or those cases where an owner cannot accept amputation as an option for the dog. Here the tumor and the affected section of bone are removed, and a bone graft is used to replace the missing bone. The graft can be donor bone which has been frozen and stored, but infections are common with this method. Dr. Mark Cofone and Dr. David Diefenderfer have used autogenous bone in small joints as the graft. Small amounts of the soft bone from the marrow cavity of the dog's own shoulder (proximal humerus), pelvis (ilium) or knee (proximal tibia) are used to replace the diseased bone. Plates and screws hold the bones in their proper orientation. It is complicated surgery and the time period until the bone graft has healed may be several months. Limb-sparing surgery is most successful for tumors of the distal radius (lower foreleg) because the carpal joint (wrist) can be fused without problems.

Previously described chemotherapy treatment protocols for OSA incorporate cisplatin and/or adriamycin, usually given at three week intervals. The drugs are administered intravenously. They are both potent drugs that act on cell division. Adriamycin prevents DNA from replicating, thus slowing the growth of metastasized tumors. Cisplatin also affects DNA, binding to it, crosslinking the strands. Both drugs affect other rapidly growing cells in the body, such as bone marrow cells and intestinal cells. Side effects are often minimal, but can include decreased appetite, gastrointestinal upset, bone marrow suppression, kidney problems, or heart problems.

Dr. Weinstein proposes to use the two drugs concurrently, administering therapeutic doses of cisplatin and slightly lower doses of adriamycin to further slow down metastatic tumor growth. Preliminary studies have shown encouraging results, four dogs treated are doing well six to ten months after treatment. She proposes to use the drugs perioperatively, beginning two weeks after surgery, and concomitantly, administering therapeutic doses of cisplatin and slightly lower doses of adriamycin to further slow down metastatic tumor growth. In one group of patients for a total of three cycles, three weeks apart. In another group of patients, the first dose of drugs will be administered perioperatively, within 24 hours after surgery, followed by two additional treatments three weeks apart. "Studies in humans and rodents have shown that there is rapid growth of metastatic lesions in these species following surgical excision of primary tumor," she said. "Studies in laboratory animal models show that administration of perioperative chemotherapy prevents a rapid growth phase in metastatic lesions following removal of the primary tumor."

Dr. Weinstein explained that perioperative chemotherapy is not routinely administered to humans with the disease due to fear of postoperative surgical wound complications, such as infections and delayed wound healing. "Our previous results administering pre-, perioperative and postoperative adriamycin to dogs with osteosarcoma do not support high wound complication rates. We hope to document improved survival rates for patients treated with perioperative chemotherapy; this would advance canine osteosarcoma treatment and might also encourage similar studies in human patients with the disease."

Osteosarcoma in people is a disease of teenagers and young adults. In dogs it affects primarily middle-aged animals, though it does occur in dogs under two years of age and in elderly dogs. Canine osteosarcoma may serve as a model for human osteosarcoma and Dr. Weinstein is collaborating with researchers at the Medical School on several projects. "We are looking at MRI images of the amputated canine limb to establish how the tumor margins can be defined by histological examination," she explained. "It is very difficult for the surgeon, when doing limb-sparing surgery on people or dogs, to know exactly where the tumor ends," she said. "We hope to determine just how accurate the MRI scan is in defining the tumor margins."

The studies also encompass a look at the role of growth factors and their receptors in canine osteosarcoma. The role of P-glycoprotein in the resistance of canine osteosarcoma to chemotherapy will be investigated. The researchers hope to expand the project so that they can evaluate different clinical protocols in dogs with osteosarcoma and assess prognostic indicators and chemosensitivity assays to predict differences in the response to treatment.

Dr. Weinstein is currently searching for funding for the chemotherapy study from private sources or foundations to support the costs of the drugs. Without support, the cost of chemotherapy drugs cost about $2,000 per patient. If support can be found, these costs to the clients will decrease considerably. Dr. Weinstein is also looking for candidates who will reametastatic tumors with chemotherapy and refer them to the Veterinary Hospital of the University of Pennsylvania.

Dr. Weinstein graduated from the University of Pennsylvania School of Veterinary Medicine in 1983; she completed a surgery residency at Tufts University School of Veterinary Medicine and Angell Memorial Animal Hospital, and became an instructor in surgery at Tufts. She completed a research fellowship at Massachusetts General Hospital where she worked in the laboratory of Dr. Henry Mankin, a pioneering researcher in bone cancer in people.

Merck Supports Laboratory Animal Medicine Training

Merck Sharp & Dohme Research Laboratories Division of Merck & Co., Inc. has provided a postdoctoral fellowship grant in Laboratory Animal Medicine at the University of Pennsylvania. Dr. Laurence Handt, a 1987 veterinary graduate of Michigan State University, has been selected as the first recipient of the grant and is now in the first year of the program. The laboratory animal medicine program has been in existence since 1987 at the University of Pennsylvania. It is a three-year program combining a residency in laboratory animal medicine with a master's degree in a related scientific discipline. Individuals enrolled in this program also complete a one-month rotation in the Department of Laboratory Animal Resources at Merck's West Point, PA facility. This program is designed to develop competence in biomedical research and laboratory animal medicine, and prepare candidates for the American College of Laboratory Animal Medicine board certification. This joint effort of Merck and the University of Pennsylvania is an example of the growing trend of the business sector providing financial assistance to foster advanced training in scientific disciplines.

Shown here (left to right) are Dr. Harry Rozmara, director of the University of Pennsylvania Office of Veterinary Laboratory Animal Resources and director of the Laboratory Animal Medicine Training Program; Dr. Jeffrey Linn, associate director and clinical coordinator, Dr. Laurence Handt, Dr. Gwendolyn McCormick, veterinarian with Merck's Department of Laboratory Animal Resources at West Point, PA and Dr. Hilton Klein, director of Laboratory Animal Resources, MSDRL Division of Merck.