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GERMAN SHEPHERD DOG Update

A NESTLÉ PURINA PUBLICATION DEDICATED TO GERMAN SHEPHERD DOG ENTHUSIASTS

VOLUME 18 | FALL 2020



NO. 1 BONE CANCER
Osteosarcoma Research Focuses on Extending Life

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GERMAN SHEPHERD DOGS MAY BENEFIT FROM OSTEOSARCOMA RESEARCH OF VACCINE THERAPY & IMMUNE RESPONSES

Based on radiographs and her veterinarian's diagnosis, Julia Priest of Galt, California, believed that her 10-year-old German Shepherd Dog "Jessy" had torn the cranial cruciate ligament in her left stifle joint. The independent, rambunctious female had come limping into the house after a playful romp in the backyard. Opting for palliative care over surgery as recommended by her veterinarian, Priest began to notice a gradual diminished effect from the medications prescribed for pain and inflammation.

A versatile performance dog, Herret's Fire Jessy von Sontausen CDX TD BH PT JHD had earned titles in obedience, tracking and herding. Now in pain, Jessy had

morphed into a couch potato not wanting to put weight on the hurt leg. Priest consulted a specialist about the leg. Radiographs indicated osteosarcoma.

"Sadly, the cancer was advanced, and nothing could be done for Jessy," Priest says. "The time-frame from the original diagnosis to euthanasia was approximately six months, though the cancer progressed rapidly over the last eight weeks of her life. Jessy lived to be 11 years and 34 days of age."

Osteosarcoma, or bone cancer, is a tough, challenging malignancy. No one knows exactly what causes osteosarcoma; however, large and giant breeds are considered to be at higher risk due to their size and weight. A [review article published in June 2019 in *Veterinary Sciences*](#) cited research indicating that osteosarcoma most commonly develops at or near the site of the growth plates, where cell turnover is highest. The extremely high risk of osteosarcoma developing in the limbs of large- and giant-breed dogs may be the result of replicative mutations during the normal processes of cell division required to create longer bones, with only modest contributions from heritable or environmental factors, according to sources referenced in the article.



"Jessy," an accomplished performance German Shepherd Dog, developed osteosarcoma at age 10. The devastating bone cancer occurs most commonly in large and giant breeds.

Standard treatment for the aggressive, most common primary bone cancer in dogs is surgical amputation of the affected leg followed by chemotherapy to help slow the development of metastasis. According to the Modiano Lab at the University of Minnesota, about [50 percent of dogs receiving the standard of care treatment live approximately one year](#). About 30 percent live two years, and 10 percent survive three years. Comparatively, dogs receiving neither surgery nor chemotherapy survive less than three months.

The gravity of canine osteosarcoma and its devastating effect on dogs and their families have prompted the American German Shepherd Dog Charitable Foundation Inc. (AGSDCF) to support [research at the University of Florida investigating a vaccine therapy](#) and to [fully fund an AKC Canine Health Foundation Clinician-Scientist Fellowship](#) allowing a medical oncology resident at the University of Minnesota to investigate the unique DNA methylation patterns that characterize the immune cells present in osteosarcoma tumors. The vaccine therapy study is also funded through the AKC Canine Health Foundation.

GD3-BASED VACCINE

Efforts to develop a life-extending vaccine for dogs with osteosarcoma that can be used as an adjuvant immunotherapy with standard of care treatment was the purpose of the two-year study at the University of Florida. Lead investigator Rowan J. Milner, BVSc,

CANINE CANCER RESEARCH INITIATIVE

Since 1995, the [AKC Canine Health Foundation](#) has provided funding of over \$12 million to support 207 studies of canine cancer. These investigations have helped scientists learn more about how cancer affects dogs. Discoveries across many types of canine cancer have contributed to earlier diagnoses and more effective treatments and often inform human cancer research via comparative oncology.



MMedVet, PhD, DACVIM (Oncology), DECVIM (Oncology), professor and director of Clinical and Translational Research, conducted a vaccine clinical trial to evaluate the effectiveness of a nanoscale liposomal disialyl-ganglioside (GD3)-based vaccine.

Found on the cellular surfaces of normal neural cells and melanocytes, GD3 is also highly expressed on osteosarcoma and melanoma cells and is believed to enhance malignancy in cancers and thus is being tested as a tumor antigen for immunotherapy. Forty dogs diagnosed with osteosarcoma were enrolled in a phase one vaccine trial conducted from January 2016 through April 2018.

“We vaccinated 34 dogs in phase one that received the vaccine, surgery and carboplatin chemotherapy and compared their survival to 30 dogs that received surgery and chemotherapy alone,” says Dr. Milner. “The dogs receiving vaccination had four treatments. The sequence began in week one with carboplatin chemotherapy, followed in week two by vaccination, which coincided with dogs having

Purina and the AKC Canine Health Foundation have worked together since 1997 to support canine health research to benefit all dogs.



a low white blood cell count, and a repeat of chemotherapy in week three. Altogether, dogs received chemotherapy over six three-week periods, and were vaccinated four times in the three-week rotation schedule. This is a unique study as most immunotherapies are given after chemotherapy is complete. We wanted to capture those dogs that typically get metastases during chemotherapy.”

An abstract of the research, [published in the September 2018 issue of *Cancer Immunology Research*](#), reported on the early results. “Dogs with osteosarcoma have increased myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Treg) cells compared to dogs without cancer that may be a factor in their maintaining a welcoming tumor microenvironment and resistance to immunotherapy,” Dr. Milner explains. “Approximately 30 percent of the vaccinated dogs lived significantly longer than the dogs receiving the standard of care treatment only.”

“We’ve continued the study and just completed phase two,”

Dr. Milner says. “In this part of the trial, we extended the vaccine protocol by adding two vaccines so dogs received a total of six vaccinations in combination with the carboplatin chemotherapy. In this phase, the last vaccine was given two weeks after the last chemotherapy treatment, thus we ended with a vaccine rather than chemotherapy as in phase one. Dogs that received six chemotherapy treatments and six vaccinations did even better than the dogs in phase one.”

Phase three of the study, scheduled to begin in the fall of 2020, involves giving dogs the vaccine prior to amputation and chemotherapy. “We hypothesize that stimulating the immune system before removing the cancer will enhance the effects of the vaccine,” says Dr. Milner.

“Our goal is to see if we can improve overall survival and delay the time to metastasis with chemotherapy and vaccine immunotherapy by improving the immune system’s response to osteosarcoma. We will continue to closely watch for changes in dogs’ immune function to deter-

A SNAPSHOT OF CANINE OSTEOSARCOMA

Most Common Bone Cancer

Osteosarcoma is the most common primary bone cancer in dogs, accounting for an estimated

85% OF CASES



Immediately See Your Veterinarian

Timeliness is critical should you notice these signs of osteosarcoma in your dog: lameness, swelling at the tumor site, and joint and bone pain. Behavioral changes may include irritability, aggression, loss of appetite, weight loss, whimpering, sleeplessness, and reluctance to exercise

Concerns About Fast Growth

Factors that increase risk are rapid growth in puppies, thus owners are advised to feed a large breed puppy food that promotes slower growth



MANY THOUSANDS OF NEW CASES A YEAR

Large and giant breeds are at greatest risk of developing osteosarcoma

10-50X MORE COMMON IN OLDER DOGS THAN PEOPLE

A rare, highly fatal cancer in humans, mostly affecting children, adolescents and young adults, osteosarcoma occurs at a much higher rate in dogs

Occurs in Senior Dogs

Usually becomes evident around 8 to 10 years of age, though osteosarcoma can affect dogs under 1 year

56-86%

Occur in Long Bones of the Legs

The majority of osteosarcoma tumors develop in dogs' long bones of the limbs

Treatment Extends Life

Standard of care treatment involving surgical amputation of the affected limb to remove the primary tumor followed by adjuvant chemotherapy extends life 9 to 12 months versus no treatment or palliative treatment



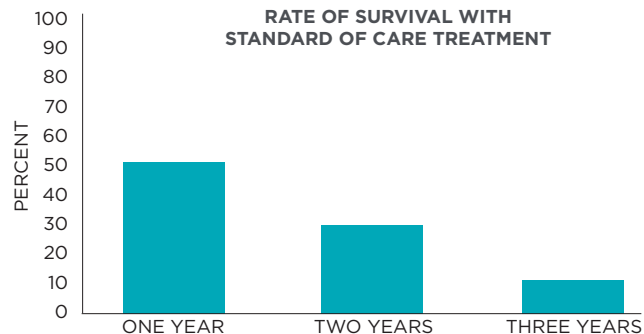
Gender Predisposition



No gender predisposition has been documented in dogs developing osteosarcoma and no risk is seen from neuter or spay surgery

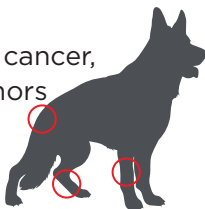
Boosting Survival with Treatment

About 50% of dogs survive one year with standard of care treatment, about 30% survive two years, and about 10% survive three years. Without treatment, a dog may live less than three months



Highly Metastatic

A very aggressive cancer, osteosarcoma tumors have likely spread beyond the primary site when diagnosed



Sources: [The National Canine Cancer Foundation](#) and [Modiano Lab at the University of Minnesota](#)

AMERICAN GERMAN SHEPHERD DOG CHARITABLE FOUNDATION HELPS FUND OSTEOSARCOMA RESEARCH

The American German Shepherd Dog Charitable Foundation Inc. (AGSDCF) is a significant source of funding for research that helps to advance the health and well-being of German Shepherd Dogs. The osteosarcoma research featured in this issue of the *German Shepherd Dog Update* is an example of the important research that AGSDCF helps to support.

The AGSDCF was founded in 1984 by devoted supporters of the German Shepherd Dog to provide an independent nonprofit organization that could accept tax-deductible donations for the benefit of funding research studies aimed at reducing disease incidence in the breed and improving treatment options for these conditions. Among the diseases supported are: cardiac defects, esophageal deficits, pancreatic insufficiency, toxic gut syndrome, bloat, degenerative myelopathy, hypothyroidism, and canine cancer. A founding member of the AKC Canine Health Foundation since 1997, the AGSDCF has provided funding for the Foundation's Clinician-Scientist Fellowship program. AGSDCF also supports the Veterinary Student Scholars Program of the Morris Animal Foundation.

German Shepherd Dog breeders and owners are encouraged to contribute to the AGSD Charitable Foundation. To learn more, please visit agsdcf.com.



mine the optimal vaccine protocol that will help dogs with osteosarcoma live longer lives.”

CHARACTERIZING IMMUNE CELLS

Caroline Wood, DVM, PhD, a recent medical oncology resident at the University of Minnesota whose AKC Canine Health Foundation Clinician-Scientist Fellowship is funded by AGSDCF, is focusing on the immune system of osteosarcoma by looking at the DNA methylation patterns of lymphocytes, the main immune cells in the body.

“DNA methylation is a biological process by which a molecule acts as a chemical tag on DNA, which can alter the expression of the gene without changing its

sequence,” Dr. Wood explains. “This leads to either increased or decreased transcription, and usually changed activity of the gene. The goal of this study is to further characterize the specific types of memory T-lymphocytes that help the immune system kill cancer cells present in osteosarcoma.”

Her mentor, Jaime Modiano, VMD, PhD, the Perlman Endowed Chair of Animal Oncology at the University of Minnesota, is a longtime cancer researcher. “The data tell us that the magnitude of immune infiltrates in dog osteosarcoma seems to be larger than in human osteosarcoma, and yet the presence of immune cells in the tumor environment is a favorable prognostic indicator in humans but not in dogs,” he says.

“This work will help us to better understand these differences and learn more about the patterns of methylation in each of these immune subsets,” says Dr. Modiano. “This is a completely new application to canine cancer studies, though similar approaches have been used in human tissues to quantify the immune response.”

Dr. Modiano reflects that over the past 30 years, the prognosis and treatment for osteosarcoma has changed little. “Trying to develop a single approach to treat, prevent and manage osteosarcoma that will be effective across the board is very challenging,” he says. “In every dog, the tumor is different. This makes it virtually impossible to know how or whether an individual dog will respond to treatment.”

In recent years, Dr. Modiano has focused on gene expression profiling to predict a dog's prognosis and response to treatment



and to understand the biological behavior of osteosarcoma tumors. Insights from his research may help advance understanding of how quickly the disease progresses locally, how quickly it spreads to other sites, and what factors may accelerate or delay disease progression.

“The goal is to one day be able to associate tumors with predictable behaviors that will improve our ability to determine outcomes of individual therapies or to deploy novel therapies or immunotherapies that will change tumor metabolism,” he says. “Learning how tumors communicate is producing exciting information that will help us determine an individual dog’s cancer risk to develop effective strategies to treat and prevent osteosarcoma.”

For the many thousands of new canine cases of osteosarcoma that occur every year — many dogs die only months after diagnosis — the good news is that progress is being made, thanks to support from AGSDCF and the AKC Canine Health Foundation.

Ultimately, insights from research such as Dr. Wood’s Clinician-Scientist Fellowship and the vaccine work at the University of Florida will contribute to understanding osteosarcoma and how to improve the outcomes for dogs with the cancer.

“As we learn more about what causes cancer in dogs, we will be able to develop more effective and less harmful treatment options,” Dr. Wood says. “In essence, we hope that one day cancer will become a manageable chronic condition rather than a terminal diagnosis.” ■

Purina appreciates the support of the American German Shepherd Dog Charitable Foundation (AGSDCF), particularly Ginny Altman, current vice president of the Foundation and past president of the German Shepherd Dog Club of America, in helping to identify topics for the *German Shepherd Dog Update*. The AGSDCF board of directors also helps to identify topics.

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