Pet dog with tumor pioneered treatment
Gracie's tumor was treated with a trial process that may help humans.

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When Gracie, an 11-year-old Jack Russell terrier, was diagnosed with a malignant brain tumor after a seizure, owner Anita Ziebe of Napa was presented with three options.

They could do nothing, which would mean that her "bouncy little dog that followed me everywhere" would probably die within three months; she could have surgery, which might prolong her life for up to six months; or she could undergo a clinical trial using a novel delivery system of a cancer drug - prognosis unknown.

Ziebe, a registered nurse, picked the last, not knowing that Gracie would become a trailblazer in an upcoming trial at UCSF in which human patients will undergo the same experimental treatment.

"Brain tumors in dogs are very similar to brain tumors in people. Some features are virtually indistinguishable, both under the microscope and in neuroimaging," said Dr. Peter Dickinson, a veterinary neurologist who led the canine trial at the School of Veterinary Medicine at UC Davis, which is partnering with UCSF.

The type of tumors that develop in older dogs, as well as their rate of occurrence, parallel brain tumors in humans, making pet dogs more appealing to scientists than lab rodents, the mainstay of preclinical studies.

"Learning about brain tumors in people from mice has limitations, because these tumors develop artificially, following the injection of human brain tumor cells," Dickinson said. These lead to "very uniform tumors that do not reflect the complexity and heterogeneity of human brain tumors."
Gracie was the first of 18 pet dogs studied in the trial of a unique drug delivery technique designed by two UCSF neuro experts to prolong the lives of people with fatal brain tumors.

More than half the dogs responded to treatment with tumors that receded, sometimes dramatically so, or remained stable for prolonged periods. It is difficult to quantify success, because the end point is usually euthanasia, a decision made by the owners who use very different criteria in determining when the time is appropriate, Dickinson said.

But some dogs lived longer than a year - which might equal seven years in canine time - and three dogs died of old age, results that Dickinson and his colleagues at UCSF believed were promising.
Following a scan, Gracie had a biopsy to confirm her diagnosis of grade III astrocytoma, and started treatment in February 2006. Every six weeks she traveled to Davis to have MRIs and drug infusions delivered directly to the tumor, via burr holes in the skull.

"Gracie loved to play with squeaky toys. That never changed throughout the trial. She had a good appetite, didn't lose weight or seem sick. She showed no side effects or symptoms of the tumor," said Ziebe, whose love for her canine companion prompted her to start a hospital pet therapy program and become a certified dog trainer.

Gracie's tolerance of the treatment was fairly typical of the dogs, with no permanent side effects noted - a finding that has caused a quiet commotion among brain tumor specialists at UCSF.

Drugs to treat brain tumors in humans are typically taken orally or intravenously, but a major challenge is that they do not cross the blood-brain barrier in sufficient quantities to attack the tumor. Increasing dosage is not feasible because of systemic side effects, such as nausea, vomiting and neutropenia, a condition in which a type of white blood cell plummets, making the patient vulnerable to life-threatening infections.

**Bypassing a barrier**

Bypassing this systemic route is one solution. About a decade ago Drs. Krystof Bankiewicz and John Park of UCSF's department of neurological surgery embarked on a project using a drug that would be toxic to the tumor and a delivery system that would be exquisitely targeted to reach the tumor alone.

The upshot was CPT-11, an existing cancer drug called irinotecan that Park modified by encapsulating it into oil droplets that would remain inactive until they reached their destination. Bankiewicz developed a complex device in which a thin tube is inserted through a port attached to the skull. The drug is injected through the tube, which is removed after infusion. To maximize safety and efficacy, neurosurgeons track the drug's distribution throughout the tumor in real time, via MRI.
**Cause for hope**

A study on lab mice with brain tumors, published earlier this year in the journal Neuro-Oncology, shows there might be cause for optimism. Researchers led by Bankiewicz and colleague David James compared CPT-11 treated in the usual manner with its administration directly to the tumor. Those in the latter group were found to have fewer tumors and improved survival. "Apparent cure," as evidenced by imaging, was noted in some mice.

Brain tumor specialists at UCSF are now waiting for FDA approval to start recruiting human patients with the most challenging tumors: recurrent grade III gliomas, which include astrocytoma like Gracie's, and recurrent glioblastoma, a deadly grade IV brain tumor with a mean survival of 14 months. Principal investigator Dr. Nicholas Butowski expects to enroll up to 24 adults and anticipates that a trial for children will start once the adult study has demonstrated safety.

"The goal of the trial is not a cure, but extended survival and higher quality of life during that extended survival," Bankiewicz said. In many patients, quality of life is compromised not only by the tumor but also by "systemic administration of powerful chemotherapy drugs and radiation," he said.

Tumors that return after treatment may continue to be treated with this method, something that cannot usually be done with other therapies, he said. "This technology holds promise that we may be able to encapsulate in nano-particles drugs that when delivered locally might target migrating tumor cells and suppress recurrences."

**Helping humans**

Progress in the human trial is an exciting step for Ziebe, who lost her beloved Gracie nine months into the trial, but says her goal was to help people, too. In the end, the cause of death was not brain tumor.

"After Gracie's last MRI, I got a call from Dr. Dickinson," she said. "The good news was that she was beating the brain tumor. The bad news was that a new cancer had been found."

That new diagnosis was hemangiosarcoma, a virulent blood cancer that occurs in older dogs,
believed to be unrelated to her treatment. Gracie became withdrawn almost immediately, rejecting treats and company and curling up on her bed. Ziebe made the painful decision to euthanize Gracie a few days later.

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