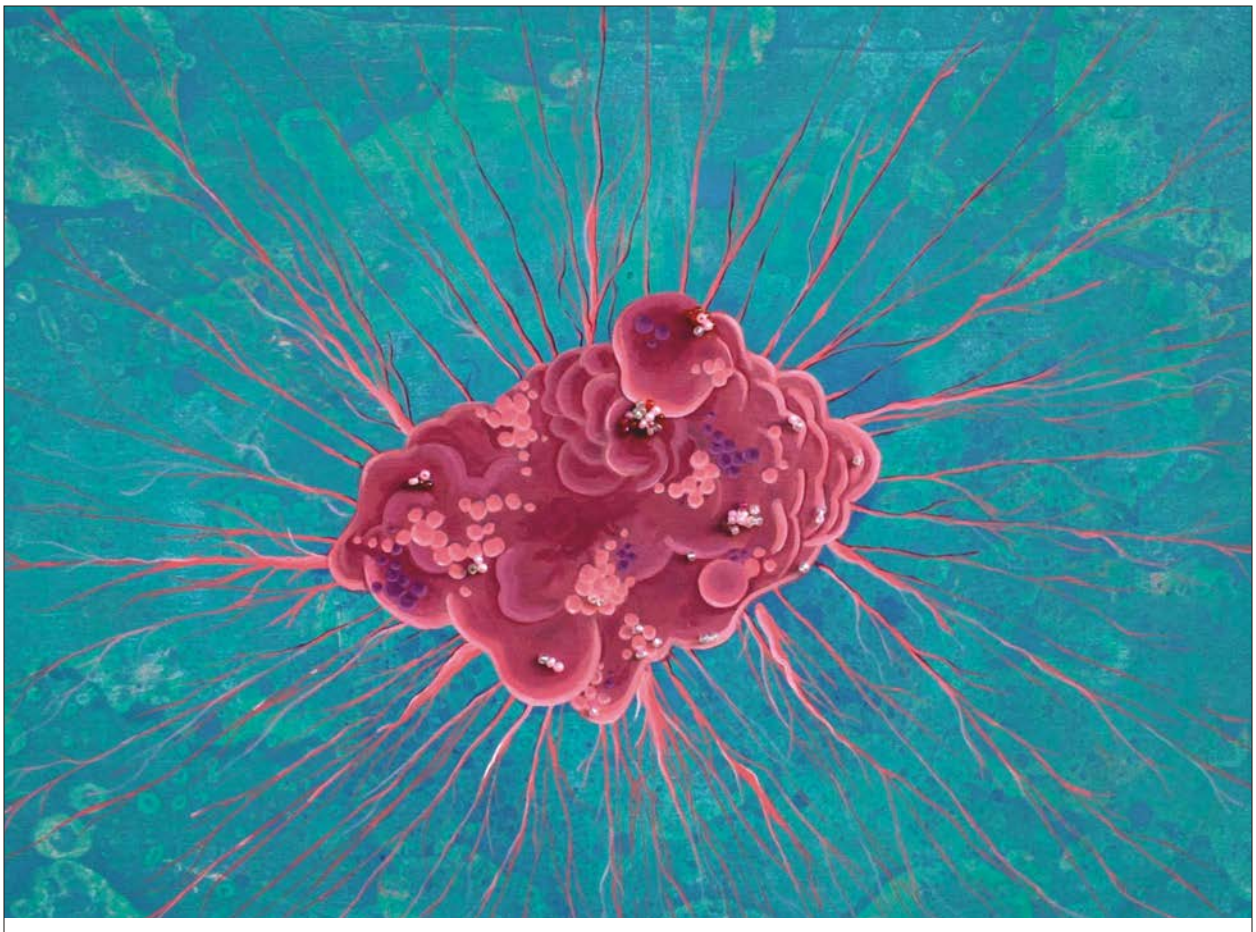

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Osteoporosis Drug Reduces Bone Loss, Tumor Size in Oral Cancer

A drug currently approved for osteoporosis treatment has been shown to reduce bone loss in a study of mice with oral cancer, suggesting it could serve as an important supplemental therapy in patients with head and neck cancers that erode bone.

In this Ohio State University study, the drug treatment also was associated with smaller tumors -- an unexpected result.

The drug, zoledronic acid, is known by the brand name Zometa. It is designed to inhibit bone resorption, the breaking down of bone caused by the release of a specific kind of cell.

Oral squamous cell carcinoma accounts for about 90 percent of all tumors in the mouth. The five-year survival rate for this form of cancer is 61 percent for all stages combined, according to the National Cancer Institute.

When these tumors form in the gums, their growth in the limited space of the mouth leads to bone loss in the jaw. In turn, bone erosion stimulates the cancer to grow. Scientists call this phenomenon, driven in part by the release of cancer stimulatory compounds from bone, a vicious cycle that occurs in this and other forms of cancer. So even though bone loss itself is not life-threatening, loss of bone means the tumor is continuing to grow.

"The goal is to stop the vicious cycle," said Thomas Rosol, professor of veterinary biosciences at Ohio State and senior author of the study. "Chemotherapy, radiation and surgery are all used to treat head and neck cancers. Zoledronic acid is a very safe drug and all it does is block bone resorption, so patients could receive all of the standard treatments, and this drug could be added as an additional benefit. That's the overall concept."

Further animal and human studies would be required to determine the proper dose and assure the drug's safety and effectiveness, he said.

The research is published in a recent issue of the journal Cancer Research.

The researchers injected mice with oral squamous cell carcinoma cells from cats to create a disease model for the study. They assigned mice to one of four groups: animals with and without tumors that received a placebo treatment, and mice with and without tumors that received a zoledronic acid treatment.

Animals treated with the drug retained twice as much total bone as did mice with cancer that were untreated. The bone that was present after treatment was a combination of reduced loss of pre-existing bone and an increase in new bone formation, said Rosol, also an investigator in Ohio State's Comprehensive Cancer Center.

Powerful images of the animals' skulls revealed that the bone loss was so severe in some untreated animals with cancer that their tooth roots were exposed. In comparison, animals with cancer that received the drug retained enough bone to keep the tooth roots covered with bone. Overall, on average, mice with cancer that received the drug treatment retained enough bone to match the amount of total bone in mice without tumors.

"When there is bone loss, there is formation of new bone to try to compensate for the loss," Rosol said. "The new bone is not perfect, but importantly, drug treatment prevented loss of both pre-existing normal bone and the new bone that formed."

"With less bone resorption, there might be less stimulation of the tumor," Rosol said. "So if you slow down bone loss, it's not as suitable an environment for the cancer to progress. We were not trying to cure the cancer, but what we're showing is that even with no other therapy than zoledronic acid, the disease is better."

The retention of bone was attributed at least in part to the drug's ability to reduce the number of activated osteoclasts

by 52 percent at sites where the tumor and bone met. Osteoclasts are the cells that are responsible for bone resorption.

The cancer cells that were injected into the mice had been altered to contain a protein that creates light so the scientists could track development of the tumors. At day 28, the tumors treated with zoledronic acid were, on average, at least 14 percent smaller than were tumors that were left untreated.

"With less bone resorption, there might be less stimulation of the tumor," Rosol said. "So if you slow down bone loss, it's not as suitable an environment for the cancer to progress. We were not trying to cure the cancer, but what we're showing is that even with no other therapy than zoledronic acid, the disease is better."

Rosol also noted that in the course of this research, an Ohio State graduate student developed the first mouse model of oral squamous cell carcinoma that leads to bone loss. Chelsea Martin, lead author of the study and a doctoral student in veterinary biosciences at the time, determined which kinds of cancer cells to use and where to inject them to produce the same cancer development in mice that is experienced by human patients.

"This new model mimics the disease very well," Rosol said.

It turns out that oral squamous cell carcinoma is also a common disease in cats. Knowing this, Martin, now a postdoctoral researcher in molecular and cellular biochemistry at Ohio State, produced the animal disease model by injecting oral cancer cells from a cat into the gums above the front teeth of mice whose immune systems were suppressed.

Rosol and colleagues plan to continue the research by testing the effects of zoledronic acid when it is combined with anticancer drugs in animals with head and neck cancer.

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Additional co-authors of the paper include Jillian Werbeck, Nanda Thudi, Lisa Lanigan and Tobie Wolfe of veterinary biosciences, and Ramiro Toribio of veterinary clinical sciences, all at Ohio State.

C. K. Martin, J. L. Werbeck, N. K. Thudi, L. G. Lanigan, T. D. Wolfe, R. E. Toribio, T. J. Rosol. Zoledronic Acid Reduces Bone Loss and Tumor Growth in an Orthotopic Xenograft Model of Osteolytic Oral Squamous Cell Carcinoma. Cancer Research, 2010; 70 (21): 8607 DOI: 10.1158/0008-5472.CAN-10-0850