Anticancer drug restores hearing in some patients with neurofibromatosis

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In a small clinical study with an anticancer drug that halts blood vessel growth, a handful of people with neurofibromatosis type 2 (NF2) and hearing loss had restoration of hearing.

Results of the collaborative study by researchers at Johns Hopkins Medicine, the National Institutes of Health and Massachusetts General Hospital were described online March 14, 2016 in the *Journal of Clinical Oncology*.

An estimated one in 25,000 people is born with NF2, a hereditary tumor syndrome in which virtually everyone progresses to deafness because of vestibular schwannomas—tumors growing on the nerves responsible for hearing. The tumors arise from the Schwann cells that support and insulate nerves. These tumors also cause balance problems and brain stem compression.

"Our study shows that the hearing loss suffered by at least a subset of these patients isn't permanent and that there is hope of reversing it," says Jaishri Blakeley, M.D., director of the Johns Hopkins Comprehensive Neurofibromatosis Center and associate professor of neurology, neurosurgery and oncology at the Johns Hopkins University School of Medicine. "We made life-changing hearing restoration our priority measure of success with this trial rather than relying on outcomes that may not affect a patient's life, such as change in tumor size."

Vestibular schwannomas churn out unexpectedly high levels of a protein

called VEGF that promotes blood vessel growth, which feeds tumors. Bevacizumab reduces VEGF levels in certain cancers and in so-called wet macular degeneration, a blinding eye condition. Because of the drug's well-documented effects, Blakeley and her colleagues thought the drug might shrink the tumors and improve hearing in patients with NF2.

For the study, they treated 14 patients—four males and 10 females—ages 14 to 79 with NF2 and progressive hearing loss. Each got 7.5 milligrams per kilogram body weight of bevacizumab intravenously every three weeks for 48 weeks, followed by 24 weeks of observation—a dose lower than what is given to cancer patients.

Three patients experienced clinically important adverse events most likely due to the treatment: high blood pressure in two of them, and excessive bruising and bleeding in a third.

All patients underwent hearing evaluations at the start of the trial, and at weeks 13, 25, 49, 60 and at the end of study. The test asked patients to repeat back 100 one-syllable words played through headphones in a quiet room. Word recognition scores varied from 0 percent if no words were correctly identified to 100 percent if all words were correctly identified.

At the start of the study, the average word recognition score from all the patients was 60 percent, and only four patients possessed hearing considered "serviceable" by the American Academy of Otolaryngology-Head and Neck Surgery. Five patients (36 percent) achieved sustained hearing improvement with the treatment, and 12 patients transitioned from nonserviceable to serviceable hearing in the affected ear.

None of the patients experienced further hearing loss during the study, even though all patients had progressive hearing loss at the start of the study as a requirement for enrolling. All patients stopped bevacizumab treatment after 12 months to assess how long the hearing improvement

lasted. Five of nine ears with improved hearing maintained this improvement for six months after the drug was stopped.

"The trial results, although limited by the small number of patients, suggest that patients may not need to get doses of drug as frequently as may be required for cancer and also may be able to take breaks in treatment. This may help reduce the frequency of negative side effects and control long-term health care costs," says Blakeley.

To measure changes in the size of their tumors, patients underwent MRI scans of the brain before, during and after treatment. Six patients (43 percent) showed a reduction in the size of their vestibular schwannoma tumors by more than 20 percent. Reduced tumor size did not correlate with hearing improvement in the study.

"We showed that the size of the tumor didn't affect the function of the nerve," says Blakeley. "Just because the image looked better, that didn't translate reliably into hearing improvement."

The researchers are exploring certain biomarkers indicating a drug response that could be used in future trials to better select patients that respond to the treatment. Further clinical trials are needed to confirm these results.

Each intravenous infusion of bevacizumab costs up to $5,000 per dose. The drug also causes adverse effects, such as slower wound healing, high blood pressure and bleeding.

Bevacizumab is mostly used to treat colorectal and lung cancers, as well as certain eye diseases, like age-related macular degeneration and diabetic retinopathy.

Citing the high costs and potentially harmful side effects of

bevacizumab, the investigators caution that the treatment is not ready for general use in all patients with hearing loss because of neurofibromatosis. However, this study laid the groundwork for identifying the best NF2 candidates for treatment with the drug and the optimal dosing.

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