MedicalXpress

Drug now used to treat erectile dysfuncton may enhance delivery of herceptin to certain brain tumors

May 7 2010

New research by scientists at Cedars-Sinai's Maxine Dunitz Neurosurgical Institute suggests that a drug currently approved to treat erectile dysfunction may significantly enhance the delivery of the anti-cancer drug Herceptin to certain hard-to-treat brain tumors. The research, published in the journal *PLoS ONE*, could help doctors improve treatments for lung and breast cancers that have metastasized to the brain.

While cancers that originate in the brain are relatively rare—approximately 22,000 patients are diagnosed with a primary brain tumor every year—nearly 10 times that many people develop brain tumors from cancers that began elsewhere in the body. Lung cancer remains the leading cause of cancer death in the U.S., and about 20 percent of lung cancers metastasize to the brain. Breast cancer and melanoma may also spread to the brain, and once this happens, the cancer becomes extremely difficult to treat and the prognosis turns poor.

Even if a cancer is susceptible to drugs, these drugs must penetrate the "blood-brain barrier" if they're to treat cancer that's metastasized to the brain. "Mother Nature created this barrier to protect our brains from dangerous substances, but here we need to get through the barrier to deliver the drugs, and that's a problem," says study author Julia Y. Ljubimova, M.D., Ph.D., a research scientist at the Cedars-Sinai Maxine Dunitz Neurosurgical Institute in Los Angeles.

Keith Black, M.D., chairman of Cedars-Sinai's Department of Neurosurgery and director of the Maxine Dunitz Neurosurgical Institute, is the lead research scientist on this project and senior author of the paper. He has studied the blood-brain barrier for about two decades, and his work in this field received the Jacob Javits award from the National Advisory Neurological Disorders and Stroke Council of the National Institutes of Health in June 2000. Since then, research conducted by his team found that the erectile dysfunction drugs sildenafil (Viagra) and vardenafil (Levitra), which inhibit the enzyme phosphodiesterase 5 (PDE5), could increase the permeability of the blood-brain tumor barrier and boost the effectiveness of the chemotherapy drug doxorubicin.

"No matter how effective against cancer a chemotherapeutic agent may be, it can have little impact on brain tumors if it cannot cross the blood-brain tumor barrier," he said. "As we find new drugs that are able to target these tumor cells, it is imperative that we develop better ways to enable the medications to reach their targets."

In the current study, the researchers examined whether PDE5 inhibitors might also increase the blood-brain tumor barrier's permeability to Herceptin, a monoclonal antibody used to treat lung and breast tumors that are positive for HER2/neu. Herceptin is a large molecule that does not easily cross the blood-brain tumor barrier, a limitation that severely reduces its effectiveness at treating brain metastases.

The researchers first measured vardenafil's effects on the permeability of the blood-brain tumor barrier. Using a mouse model, the scientists showed that vardenafil led to a two-fold increase in the amount of Herceptin that reached brain metastases of lung and breast cancers. Next, they examined whether this increase in blood-brain barrier permeability improved Herceptin's effectiveness at treating these brain metastases by giving mice vardenafil in tandem with Herceptin. The results showed that the combination of vardenafil plus Herceptin boosted

mean survival by 20 percent, compared to Herceptin alone (72+/-18 days versus 59+/-9 days).

Mice whose tumors were not HER2-positive did not experience the same increase in survival that those with HER2-positive tumors did when given vardenafil, indicating that the survival benefit was indeed due to an increase in the amount of Herceptin reaching the tumors, says Ljubimova.

"Now that we've demonstrated that big molecules can cross the blood-brain tumor barrier, we're going to continue this strategy with other big molecule drugs, such as nanomedicine drugs" says Ljubimova. "This opens a new world for brain tumor treatments."

More information: Hu J, Ljubimova JY, Inoue S, Konda B, Patil R, et al. (2010) Phosphodiesterase Type 5 Inhibitors Increase Herceptin Transport and Treatment Efficacy in Mouse Metastatic Brain Tumor Models. PLoS ONE 5(4): e10108. doi:10.1371/journal.pone.0010108

Provided by Cedars-Sinai Medical Center