Arsenic agent shuts down two hard-to-treat cancers in animal experiments

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Researchers at the Georgetown Lombardi Comprehensive Cancer Center, a part of Georgetown University Medical Center, have found that an arsenic-based agent already FDA-approved for a type of leukemia may be helpful in another hard-to-treat cancer, Ewing's Sarcoma (ES). The research, based on animal studies, also suggests the drug might be beneficial in treating medulloblastoma, a highly malignant pediatric brain cancer.

In the December 22 issue of the Journal of Clinical Investigation, the investigators describe how years of research has uncovered a common pathway in these tumors, known as hedgehog/GLI1. They further detail how they used an existing drug, arsenic trioxide (Trisenox®), to shut down that pathway in mice models of ES and medulloblastoma.

This pathway is also common in other cancers, such as colon, pancreatic, and basal cell skin cancer, among others, says the study's lead investigator, associate professor Aykut Üren, M.D., of Georgetown Lombardi.

"The significance of our finding is that this FDA approved agent can be tested immediately in other cancer types. It is a perfect translational research project," he says. "This laboratory research has immediate clinical implications."

Üren adds that researchers are moving quickly to find an effective inhibitor of the hedgehodg/GL1 pathway because it is so powerful in cancer development. Hedgehog controls cell division in embryonic development, but when it is turned on, and out of control in adult cells, cancer results. Because of that, there are a number of clinical trials underway testing new compounds that inhibit this pathway at the surface membrane of cancer cells, he says.

The compound they tested, however, inhibits the pathway in the nucleus, so it may be effective in cancers that have pathway activation downstream of the membrane molecules, Üren says. "Many of the current clinical trials involve agents that act at the membrane. Ewing sarcoma and colon cancer will not benefit from that approach. Furthermore, medulloblastoma patients treated with hedgehog inhibitors are developing resistance at the membrane level. Therefore, clinical trials can evaluate alternative therapies for patients whose treatment fails with current hedgehog inhibitors," he says.

Arsenic trioxide has been approved for use of acute promyelocyctic leukemia (APL) as a second-line therapy for patients who do not respond to standard therapy.

Arsenic trioxide is generated from processing arsenic compounds, and while a high level of arsenic is known to be carcinogenic, low doses can be therapeutic in selected patients, Üren says. In fact, he says starting in the 17th century, arsenic was the primary therapy for treating leukemia, specifically chronic myelogenous leukemia (CML). He also cites a Dutch population study that concluded low levels of arsenic concentrations in drinking water not only didn't increase cancer incidence in people who drank it, but resulted in a decrease in nonmelanoma skin cancers.

"Like any chemotherapy, high doses of arsenic can be toxic, while lower doses can treat cancer," he says.

In 2009, Üren and his research team, which includes first author Elspeth Beauchamp, Ph.D., showed that the hedgehog/GLI1 pathway is activated in ES. They are now the first to inhibit this pathway by arsenic trioxide in ES, and among the first to show its activity in medulloblastoma.

More information: View this article at: www.jci.org/articles/view/4287 …

Provided by Georgetown University Medical Center

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