Study finds that less is more for common cancer drug

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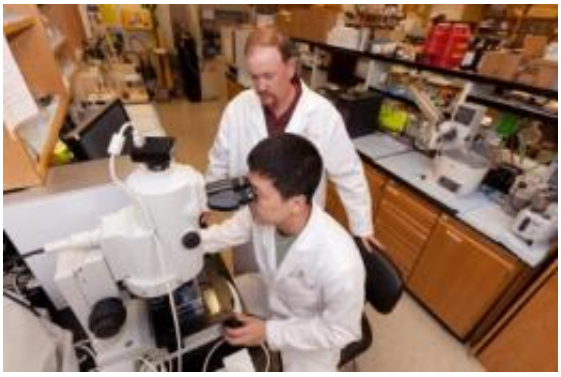

University of Georgia researcher Robert Arnold has found that smaller, less toxic amounts of chemotherapy medicine given frequently to mice with human prostate cancer noticeably slowed tumor growth. Credit: Image courtesy of Andrew Davis Tucker, University of Georgia

University of Georgia scientists have found that smaller, less toxic amounts of chemotherapy medicine given frequently to mice with human prostate cancer noticeably slowed tumor growth. The mice suffered fewer side effects compared with traditional cancer treatment relying on heavy doses that can cause hair and bone loss.

While chemotherapy given repeatedly in small portions, called metronomic dosing, is not new, the study's authors say that the dosing appears to alter the cellular activity of the drug topotecan. This finding offers promising new ways to use topotecan -- which is widely used and

approved by the Food and Drug Administration for cervical and other cancers—to combat slowly growing prostate tumors. The findings appear this month in the journal *Cancer Biology and Therapy*.

"At these lower doses, there isn't enough topotecan to follow a classic cell death pathway," said study co-author Robert D. Arnold, a Georgia Cancer Coalition Distinguished Scholar and assistant professor in the UGA College of Pharmacy. "Our research suggests that metronomic dosing altered topotecan's behavior."

Scientists have known that topotecan given to patients in large, traditional doses kills cancer cells by deactivating proteins known as enzymes that are necessary for cell growth, Arnold explained. By contrast, metronomic dosing of topotecan prevents new blood vessels -- which are necessary for growth -- from forming in the tumor. Arnold and his colleagues discovered that topotecan did not change the amount of blood vessels formed, but significantly decreased tumor size and altered genes critical for controlling cell growth.

Brian S. Cummings, a co-author and associate professor at the pharmacy college, compared topotecan's process of killing tumor cells to the everyday task of running an errand.

"Let's assume you're going to go to the grocery store and you could walk, ride your bike or take the car," he said. "Those are different mechanisms of action. You will still get to the same place."

He added that researchers try to determine which pathway, or transportation choice, cells take after different amounts of exposure to topotecan. Their results suggest that when topotecan is given frequently in low doses, the drug could be changing the type of genes turned on in the tumor. These changes may be related to the structure or architecture of a gene -- not a change in gene sequence. Such changes could be

considered epigenetic, but more research is needed, Arnold said.

The study suggests that metronomic dosing of topotecan can reduce prostate cancer growth at drug concentrations far below those that can be toxic to healthy cells in the body.

Given the limited treatment options for late-stage prostate cancer and clinical use of topotecan, new clinical trials could occur in the near future, Arnold said. The same research team is now studying the dosing effects of topotecan in breast cancer models.

Provided by University of Georgia