Chemo may be preferred option for some with advanced prostate cancer

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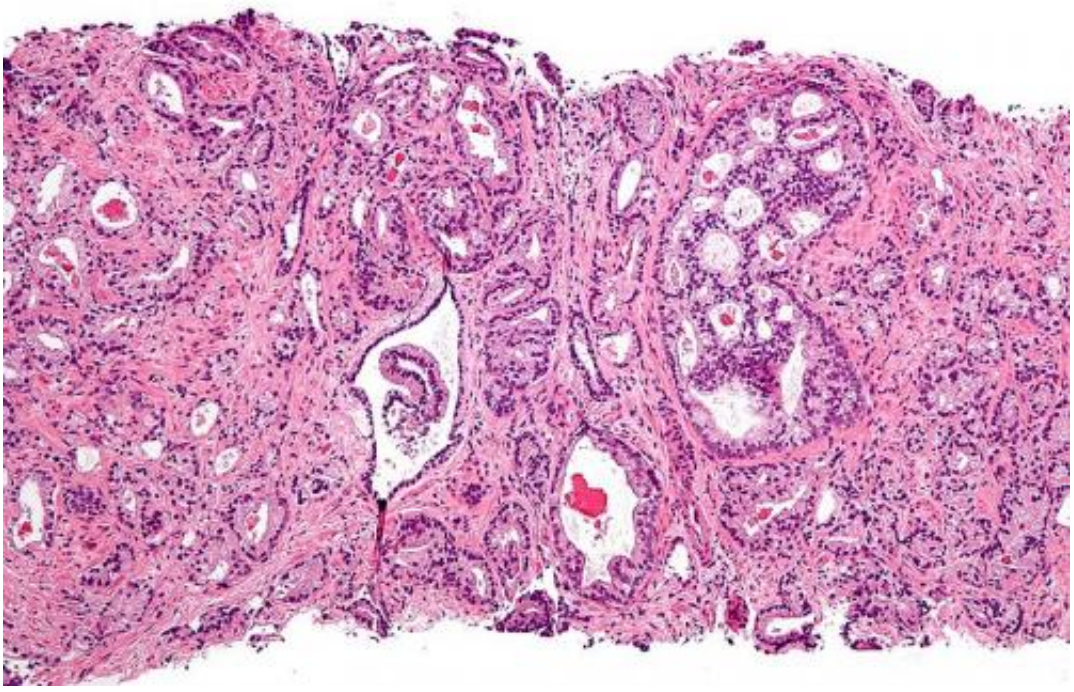

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

In a small clinical trial, scientists at Johns Hopkins' Kimmel Cancer Center and James Buchanan Brady Urological Institute found that men with advanced prostate cancer and detection of androgen receptor splice variant-7 (AR-V7) respond to chemotherapy just as well as men who lack the variant.

The findings, the researchers say, may be significant for patients who carry the AR-V7 variant, because they are more likely to develop resistance to one of two hormone drugs routinely used to treat their disease. Results of the trial are published online in the June 4 issue of *JAMA Oncology*.

"Our study shows that men who have the AR-V7 gene variant and usually don't respond to either abiraterone or enzalutamide, are not at a disadvantage when given chemotherapy drugs," says Emmanuel Antonarakis, M.D., an oncologist at the Kimmel Cancer Center. Seven of the 17 men in the trial who carried the AR-V7 variant and received chemotherapy experienced a 50 percent reduction in their prostate-specific antigen (PSA) level.

The National Cancer Institute estimates that more than 220,000 men will be diagnosed with prostate cancer in 2015 and more than 27,000 will die from it. Approximately 5 percent (11,000) of patients with prostate cancer have advanced disease.

The AR-V7 gene variant was discovered in 2008 by James Buchanan Brady Urological Institute researcher Jun Luo, Ph.D. In a previous study, Luo and Antonarakis found that men with the AR-V7 variant were resistant to hormonal drugs, such as enzalutamide or abiraterone, which are androgen receptor-directed therapies used for treating the type of advanced cancer called castration-resistant prostate cancer.

Abiraterone and enzalutamide, says Antonarakis, aim to block the production and function of male hormones. The AR-V7 variant codes for shortened proteins that, unlike full-length AR proteins, regulate prostate cancer growth, which is not dependent on male hormones, or androgens. Therefore, men who have the AR-V7 variant are more likely to be resistant to hormone drugs, rendering them ineffective.

In the new trial with 37 men being treated with either of two chemotherapy drugs, docetaxel or cabazitaxel, at The Johns Hopkins Hospital, 17 had detectable levels of the AR-V7 variant in their blood. In comparing men with and without the gene variant, there was no statistical difference in how much patients' PSA levels declined, how long it took for their cancers to progress or their overall survival. PSA levels are markers for prostate cancer.

In a previous clinical trial of 62 patients with castraction-resistant prostate cancer, the same researchers found that 18 AR-V7-positive patients who took either enzalutamide or abiraterone showed no reduction in their PSA levels, indicating that the drugs were not effective in these patients. However, the current study showed that seven of 17 (41 percent) AR-V7-positive patients receiving chemotherapy achieved a 50 percent reduction in PSA levels.

Taken together, Antonarakis says, the findings, if confirmed in larger trials, suggest that the presence of the AR-V7 variant could be used someday as a biomarker to improve treatment decision-making for patients with prostate cancer.

When some patients take either enzalutamide or abiraterone, the drug stops working, and their cancer grows and spreads, explains Antonarakis. The incidence of AR-V7 among these patients may be as high as 30 to 40 percent, he notes.

"It would be very useful to know if such patients are AR-V7-positive," Antonarakis says, "because if they were, a better step for them might be chemotherapy rather than the alternative androgen receptor-directed hormonal therapy."

"We think AR-V7 would have the greatest utility as a biomarker to guide further treatment in men with castration-resistant prostate cancer, and

not for earlier stages of the disease so far," Luo says. "But that's something we should test in further studies."

The researchers also detected what they say is an intriguing change among seven of the patients in the study who were AR-V7-positive at the start of their chemotherapy: During the course of that treatment, they converted to AR-V7-negative. "The clinical significance of this is unknown, but one hypothesis is that some of these patients could possibly become re-sensitized to enzalutamide or abiraterone."

There is no commercially available test yet for AR-V7, Antonarakis notes, which is detected in tumor cells circulating in a patient's blood. But Luo and Antonarakis say that they are working to develop and validate an AR-V7 test that could be used more widely.

"The ultimate goal is to address needs of patients who are failing standard therapy," says Luo. "By using the biomarker to improve patient-doctor decision-making, we could realize a therapeutic benefit without having to find a new drug."

The researchers also note that the two hormone therapies, abiraterone and enzalutamide, are considerably more expensive than chemotherapy. At more than $30,000 for a six-month treatment, the hormone-based therapies are more than double the chemotherapy costs.

More information: *JAMA Oncology*, oncology.jamanetwork.com/artic… px?articleid=2300763

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