PARP inhibitor becomes new treatment option for some men with advanced prostate cancer

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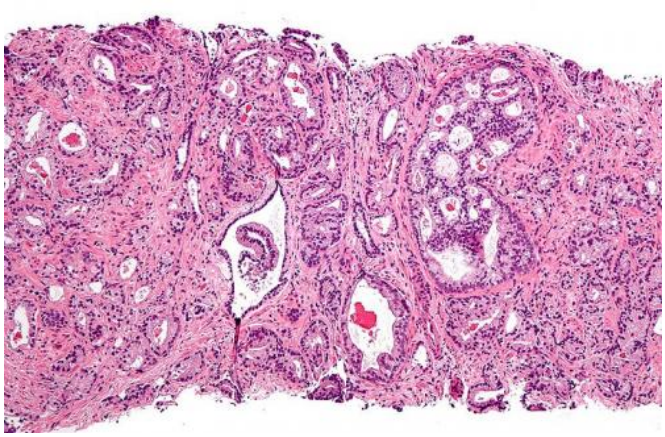

Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia

Results from an international clinical trial found that men with advanced prostate cancer who have mutated BRCA1/BRCA2 genes can be treated successfully with a targeted therapy known as rucaparib, resulting in recent FDA approval.

Prostate cancer is the most common cancer and the second leading cause of cancer death among men in the United States. Metastatic, castrate-resistant prostate cancer (mCRPC) is an incurable form of prostate cancer that keeps growing even when the amount of testosterone in the body is reduced to very low levels. Researchers are looking for new treatment options to use for mCRPC.

Rucaparib (trademarked as Rubraca) is one of a new class of anticancer drugs called poly (ADP-ribose) polymerase inhibitors, or PARP inhibitors, which work by targeting cancer cells that have a defect in how they repair damage to their DNA.

PARP inhibitors are already successfully used to treat ovarian cancers and some inherited forms of breast and pancreatic cancer.

"There is a critical need for personalized medicines to effectively treat advanced prostate cancer," said Akash Patnaik, MD, Ph.D., national authority on prostate cancer research at the University of Chicago Medicine and one of the study authors, who presented the findings from this study at the Genitourinary Cancers Symposium sponsored by the American Society of Clinical Oncology in San Francisco in February 2020. "Approximately 12% of advanced prostate cancer patients have tumors that harbor a BRCA1 or BRCA2 alteration. We have arrived at an exciting inflection point in the field, as we now have the first FDA approved targeted therapy that can effectively treat a genetically defined subset of mCRPC patients, with poor prognosis and worse clinical outcomes on conventional treatments."

The TRITON2 phase II study investigated whether or not rucaparib can safely and effectively treat men with mCRPC who are predisposed to prostate cancer because of their genetic profile. Men whose cancer had progressed after completing hormone therapy and chemotherapy were eligible to participate. The University of Chicago Medicine Comprehensive Cancer Center was the second lead site internationally to enroll patients to this practice-changing study.

Patnaik and colleagues from cancer centers in the U.S. and across the world enrolled 115 patients whose genetic screening revealed abnormalities in their BRCA genes. The patients then received 600 mg of rucaparib twice a day. The objective response rate was 41%. Over half of the patients (53.9%) had improvements in their prostate-specific antigen (PSA) levels.

The researchers noted that in addition to demonstrating a significant anti-cancer response in mCRPC patients that had progressed on two prior lines of therapy, the rucaparib treatment had a manageable safety profile consistent with that reported in other solid tumor types, with the most common side effect reported being anemia.

Based on the initial efficacy and safety results from TRITON2, the FDA granted accelerated approval for rucaparib in mCRPC patients with BRCA1/2 mutations on May 15, 2020. Results from TRITON2 have been previously presented to the medical community at the European Society for Medical Oncology (ESMO) Annual Congress (October 19-23, 2018, and September 27-October 1, 2019), the American Society of Clinical Oncology (ASCO) Annual Meeting (May 31-June 4, 2019), and the ASCO Genitourinary Cancers Symposium (February 13-15, 2020).

A publication summarizing the TRITON2 results was published today at the *Journal of Clinical Oncology*. "In a separate publication, we have demonstrated that additional non-BRCA1/2 mutations within the DNA repair pathway in mCRPC patients could confer sensitivity or resistance to PARP inhibitor rucaparib," Patnaik said. "We still have a lot more to learn about which patients with additional genetically defined alterations in the DNA repair pathway will benefit most from this therapy."

He continued, "Studies are underway within our laboratory and clinical trials to test combinations of PARP inhibitors with other conventional or experimental therapies to substantially increase the fraction of mCRPC patients that respond to PARP inhibitors. Based on these investigations, we are optimistic about the development of additional personalized treatment options for our mCRPC patients."

More information: Wassim Abida et al, Rucaparib in Men With Metastatic Castration-Resistant Prostate Cancer Harboring a BRCA1 or BRCA2 Gene Alteration, *Journal of Clinical Oncology* (2020). DOI: 10.1200/JCO.20.01035

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