Olaparib may be effective without hormone therapy for some men with biochemically recurrent prostate cancer

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The anti-cancer drug olaparib may be effective in treating biochemically recurrent prostate cancer without accompanying hormone therapy for

men who have mutations in genes such as BRCA2, according to results of a Phase II clinical trial of 51 patients conducted at the Johns Hopkins Kimmel Cancer Center and three other sites.

The study was done on men experiencing signs of cancer recurrence after surgical removal of the prostate, as measured by a high level of the protein prostate-specific antigen (PSA). Following treatment with olaparib, 13 participants, including all 11 who had BRCA2 mutations, had a decrease in PSA of at least 50%—a sign that their cancers were receding.

A report about the work was published Aug. 22 in *JAMA Oncology*. The other participating centers were the University of Nebraska Medical Center in Omaha, the Allegheny Health Network Cancer Institute in Pittsburgh and the Thomas Jefferson University Hospital in Philadelphia.

While most men with localized prostate cancer are cured with surgery or primary radiotherapy, up to 40% will develop a recurrence as measured by a rising PSA, explains lead study author Cathy Handy Marshall, M.D., M.P.H., an assistant professor of oncology at Johns Hopkins.

The study was co-led by former Kimmel Cancer Center prostate cancer expert Emmanuel Antonarakis, M.D., who is now associate director of translational research at the University of Minnesota Masonic Cancer Center. He maintains an adjunct professorship at Johns Hopkins.

A common treatment approach for recurrent prostate cancer is androgen deprivation therapy—medication to stop testosterone production. However, many men don't like taking the drug because the lack of testosterone can lead to side effects such as hot flashes, fatigue or weight gain, Marshall says.

"We have done a number of trials looking for therapies for prostate cancer that are not hormone-suppressing to avoid those side effects," she says.

Olaparib, a precision oncology drug which blocks the ability of the protein PARP to repair damaged DNA, is approved by the U.S. Food and Drug Administration for treatment of metastatic prostate cancer in combination with hormonal therapy, but it was unknown if the drug would work without the accompanying hormonal suppression, Marshall says.

Investigators enrolled 51 patients in the trial from May 2017 through November 2022. Each participant had biochemically recurrent prostate cancer following radical prostatectomy (surgery to remove the prostate, seminal vesicles and nearby lymph nodes).

Among participants, 27 (53%) were considered biomarker positive, meaning that they had mutations in some genes that were more likely to make their cancers sensitive to olaparib. Patients had a mean age of about 64 years and median baseline PSA of 2.8 nanograms per milliliter.

Most participants had a Gleason Grade Group 3 and above, meaning they had a high-grade cancer. Some 86% of participants had received radiotherapy after surgery. In patients who had positive biomarkers, alterations in BRCA2 were the most common (11 patients), followed by alterations in the ATM and CHEK2 genes (six patients each).

Participants were treated with 300 milligrams of olaparib by mouth twice daily (without hormonal suppression) until their baseline PSA level doubled, their cancer worsened as determined by imaging or other signs or symptoms, or they had unacceptable side effects/toxicity from the medication. The amount of time participants were on therapy varied—it was more than two years in some cases, Marshall says.

About half (13 of 27 patients) in the biomarker-positive group had a decrease in PSA of 50% or more, including all 11 patients with BRCA2 mutations. The median duration of response was 25 months. The other two PSA responses were seen in participants with a CHEK2 mutation and an ATM mutation.

No PSA responses were seen among the 24 men in the biomarker-negative group, leading the study authors to conclude that the therapy should not be considered for those patients in the future.

The median PSA progression-free survival (the length of time before PSA worsened) was 19.3 months overall and 22.1 months in the biomarker-positive subset, compared with 12.8 months in the biomarker-negative subset. The median metastasis-free survival (time from treatment to detection of metastasis) was 32.9 months overall and 41.9 months in the biomarker-positive subset, compared with 16.9 months in the biomarker-negative subset.

Also, the median time to next anti-cancer therapy was 15.4 months overall and 22.7 months in the biomarker-positive subset, compared with only 2.4 months in the biomarker-negative subset.

The most common adverse events with olaparib were fatigue, nausea and leukopenia (fewer than normal infection-fighting white blood cells).

"This study is a breakthrough because it is the first trial to show that a non-hormonal drug can induce durable complete remissions in recurrent prostate cancer patients with BRCA2 mutations—one of the most aggressive subtypes of this disease," Antonarakis says.

"It is a true paradigm shift, because now we can offer a non-hormonal precision therapy to these patients that is safe and effective while avoiding the side effects caused by hormonal deprivation."

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