Breast cancer drug may help men with prostate cancer

PHILADELPHIA, PENNSYLVANIA—A new type of cancer drug originally aimed at women with rare, inherited forms of breast and ovarian cancer may also help a broader swath of patients, according to a small clinical study. The drug halted tumor growth in a third of men with a typically deadly form of advanced prostate cancer. Nearly all of those who responded had related mutations in their tumors, indicating the drug was targeting a common cell process, researchers reported here this week at the annual meeting of the American Association for Cancer Research (AACR).

The drug blocks an enzyme called poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP), which helps cells repair a certain type of DNA damage. Oncologists are mostly testing PARP inhibitors in ovarian and breast cancer patients born with mutations in *BRCA1* or *BRCA2*, two of the most infamous cancer-related genes. These mutations raise a woman's risk for breast and ovarian cancer, as well as a man's risk of prostate cancer, because they disable proteins that repair DNA damage that can result in additional cancer-spurring mutations. But flaws in either gene also make tumor cells vulnerable to PARP inhibitors, because the drugs further impair tumor cells’ DNA repair machinery. This combination renders tumor cells unable to fix DNA damage and they die, an idea known as *synthetic lethality*.

In December, the first PARP inhibitor, AstraZeneca’s olaparib, received approval in the United States and Europe for ovarian cancer patients who had inherited a *BRCA1* or *BRCA2* mutation.

But some cancer patients who lack such mutations have also seen their tumors shrink in trials. A team led by Johann de Bono of the Institute of Cancer Research and the Royal Marsden NHS Foundation Trust, both in London, suspected that these patients had
inherited errors in other DNA repair genes or had acquired mutations in \textit{BRCA} or the other genes in a tumor as it formed or grew. Three years ago, a large sequencing project found that such DNA repair gene defects are common in advanced prostate tumors.

To test their hypothesis, de Bono’s group and collaborators, whose funding was independent from AstraZeneca, gave the drug to 50 men with metastatic castration-resistant prostate cancer, which means their tumors had stopped responding to drugs that block the hormones that drive prostate cancer growth. Of the 49 men who stayed in the trial, 33\%, or 16 patients, responded to the drug, according to one of three measures—a drop in levels of tumor cells in the patient’s blood, a decline in blood levels of the biomarker prostate-specific antigen, or imaging scans that found their tumors shrank. When the researchers sequenced the patients’ tumor DNA, they found their hunch was correct: Fourteen of the 16 who responded had mutations in one or more of a dozen DNA repair genes in their tumors, and only two nonresponders had these mutations, reported Joaquin Mateo, a clinical fellow in de Bono’s lab, at the AACR meeting. (While three responders had inherited \textit{BRCA2} mutations, four had apparently new mutations in this gene.) Most of these patients responded to the drug for at least 6 months (four for more than 1 year), while those without such mutations usually got worse within 3 months.

Although genetic tests of tumors are already used to determine whether certain drugs will work for several types of cancer, this is the first time researchers have found such a test for prostate cancer, de Bono’s group says. Olaparib could offer a new option for these men: The trial shows “this is a good swat at that disease,” said prostate cancer researcher William Nelson of Johns Hopkins University in Baltimore, Maryland, at an AACR press conference, adding that the prospect of genetic testing to identify prostate cancer patients who could benefit from olaparib “looks very promising.”

The results also suggest that women with ovarian and breast cancer who lack an inherited\textit{BRCA} mutation might still respond to PARP inhibitors, if they have DNA repair
mutations in their tumors, de Bono’s group says. Ursula Matulonis of the Dana-Farber Cancer Institute in Boston, who presented results at AACR from a trial of olaparib combined with another drug for breast and ovarian cancer patients, said at the press conference that her team plans to explore that possibility by DNA testing biopsies from the patients.

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