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Researchers identify biological indicator of response to new ovarian cancer drug

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Researchers have found a way of identifying which ovarian cancer patients are likely to respond well to a new anti-cancer drug called rucaparib.

Results of clinical trials have shown that women with tumours that are sensitive to platinum-based chemotherapy and who carry inherited mutations in the BRCA1/2 genes respond well to rucaparib. But in new findings presented today (Thursday) at the 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics in Barcelona, Spain, researchers say that they have identified a biological indicator (biomarker) that can predict which women without BRCA1/2 mutations will respond to the drug as well.

Rucaparib is designed to inhibit a protein called poly (ADP-ribose) polymerase (PARP), which is involved in repairing damaged DNA. Inhibiting PARP can prevent cancer cells from repairing themselves and so they die. Women with BRCA1/2 mutations who have developed ovarian cancer respond well to rucaparib because the genetic mutation has already affected one method of repairing damaged DNA in cells, and the PARP inhibitor attacks the cancer cells' only other DNA repair mechanism.

However, Professor Elizabeth Swisher, from the University of Washington School of Medicine (Seattle, USA), will tell the Symposium that, in addition to identifying BRCA1/2 mutations, there are other indicators of defective DNA repair that could be used to predict

responsiveness to PARP inhibitors. She and her colleagues from research centres in the North America, Europe, and Australia have seen good responses to rucaparib in women with ovarian cancers exhibiting a form of cell damage called genomic loss of heterozygosity (LOH), in which an entire chromosomal region on one copy of the genome is lost.

In the ARIEL2 phase 2 clinical trial of rucaparib, which started in October 2013, preliminary data from 121 patients have shown responses to the drug in women with tumours that have high genomic LOH, as well as in patients with BRCA1/2 mutations. [2]

"This is the first time that we have predictors to identify women with ovarian cancer other than those with a known BRCA1 or BRCA2 mutation who are likely to respond to a PARP inhibitor. This will allow more focused application of PARP inhibitors to the women most likely to benefit from treatment with a PARP inhibitor. The more we can identify responders to specific therapies, the better women and their doctors can select the most effective treatments option," Prof Swisher will say.

Women with platinum-sensitive ovarian cancer can be treated with platinum-based chemotherapies, which can be repeated if the cancer should recur. However, the toxicity of the chemotherapy results in serious, adverse side-effects and, furthermore, it has to be given intravenously. Rucaparib is taken in pill form and is less toxic.

Women with advanced ovarian cancer that had recurred were eligible to join the ARIEL2 clinical trial. Patients underwent a biopsy done with a small needle, guided usually with a CT scan. Tissue was then sent to the testing laboratory, where it took between two to three weeks to test for LOH. Women had to be willing to undergo a biopsy to enter the study and to have a tumour that could be biopsied, but the results did not have to be back before they were enrolled and the results did not dictate

whether or not they could join the trial. However, the trial aimed to recruit more women who did not have BRCA1/2 mutations in order to identify biomarkers indicating who would respond to the drug amongst this group. Over 80% of the planned 180 patients on ARIEL2 will be non-BRCA1/2 mutation carriers.

The women were treated with 600mg of rucaparib twice a day until the disease progressed. So far, results have shown that not only do non-BRCA1/2 mutation carriers with high genomic LOH respond to rucaparib, but that testing for genomic LOH is an effective way of identifying those women who will respond to the drug.

Of the 121 women recruited to the trial by the end of October 2014, 25% had the BRCA1/2 mutations, 42% (the majority) did not have the mutations but had high genomic LOH, and 33% had neither. The overall response rate among the 61 patients who were evaluable by the end of October was 38%, with 77% of the women having a complete response (the tumour disappearing completely), a partial response (tumour shrinkage) or stable disease (the cancer remaining unchanged).

"We found that, as expected, rucaparib had the greatest clinical activity in the 23 women with the BRCA 1/2 mutations. There was an overall response rate of between 61-70%, and 83% of the patients are continuing on the treatment," Prof Swisher will say. "However, among the women without the BRCA 1/2 mutations, the 25 with a high genomic LOH had an overall response rate of between 32-40%, with 52% continuing on treatment, while the 13 women without the LOH biomarker had an overall response rate of just eight percent, with 38% continuing on treatment.

"In this early analysis it appears that our molecular predictors are working to identify women with better response rates from women unlikely to respond to rucaparib."

Overall, 61% of the patients remain on the treatment, which has been well tolerated, with no patients having to stop it due to unacceptable side-effects. Most of the adverse side-effects were mild and included nausea, fatigue, liver problems, loss of taste and appetite, anaemia, vomiting and constipation.

Already, genomic LOH as a biomarker for predicting response to rucaparib has been incorporated into a test for a second clinical trial, ARIEL3, which is currently recruiting approximately 540 women with either serous or endometrioid platinum-sensitive, advanced ovarian, fallopian or primary peritoneal cancer. The effects of rucaparib versus placebo will be evaluated in groups of patients who have been molecularly defined according to their biomarker test.

Dr Kapil Dhingra, managing member of KAPital Consulting, LLC, USA, who is a member of the EORTC-NCI-AACR Symposium scientific committee, commented: "This is an important study that confirms important therapeutic effect of rucaparib in patients with BRCA1/2-related ovarian cancer and, additionally, suggests a novel way to select patients who may benefit from rucaparib treatment. If confirmed in subsequent studies, this marker may significantly advance the application of a personalised medicine approach using PARP inhibition."

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