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Late-stage ovarian cancer shows promise in two-drug phase I trial

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The combination of decitabine and carboplatin appears to improve the outcome of women who have late-stage ovarian cancer. In an upcoming issue of the journal *Cancer* (online today), Indiana University researchers report four of 10 patients who participated in a phase I clinical trial had no disease progression after six months of treatment. One patient experienced complete resolution of tumor tissue for a period of time.

Advanced ovarian cancer is often diagnosed too late for treatment to be effective. Patients are often told they have virtually no chance of recovery and only months to live.

Women participating in the study were between 51 and 71, and had previously exhausted all approved treatments for ovarian cancer. They enrolled in an Indiana University Melvin and Bren Simon Cancer Center clinical trial designed to increase their sensitivity to the commonly prescribed ovarian cancer drug, platinum-based carboplatin.

Women with ovarian cancer usually survive less than one year after they become resistant to carboplatin and their cancer recurs, said co-principal investigator Daniela Matei, M.D., an associate professor of medicine at the Indiana University School of Medicine. Matei led the clinical portion of the trial.

"Carboplatin is the most efficient drug therapy for ovarian cancer," Matei said. "Unfortunately, patients with recurrent disease become resistant to the drug after one or two rounds."

Decitabine was first used to treat the study patients intravenously daily for five days followed on the eighth day with carboplatin. After a month, the regimen begins again.

Six months after the trial began, four of the patients had no disease progression. At eight-and-a-half months, seven patients were alive (and at press time, still alive). Cancerous tissue in one of the patients shrank completely.

Adverse reactions to the treatment regiments were mild, including nausea, fatigue, and neutropenia (reduced white blood cell count).

Encouraged by the results of the phase I trial, which determined the safety of two different dosing regimens, a phase II trial is now under way with 17 patients already enrolled. Phase II trials are primarily focused on assessing the effectiveness of a drug or treatment protocol.

The study's other co-principal investigator, Kenneth Nephew, geneticist in the IU Medical Sciences Program-Bloomington, led the report's biochemical and DNA analysis.

In a bid to resensitize patients to carboplatin, Nephew and Matei and co-investigator Jeanne M. Schilder, M.D., associate professor of obstetrics and gynecology in the Division of Gynecologic Oncology at the IU School of Medicine, turned to the DNA demethylating agent, decitabine.

Why trial patients were responsive to the combination of decitabine and carboplatin is not yet known, but based on the literature and an analysis of biopsy tissue and blood samples, Nephew and Matei suspect decitabine reactivates tumor suppression genes that are turned off in ovarian cancer cells.

One of the hallmarks of ovarian cancer is the aberrant methylation of

cytosine, one of DNA's four nitrogenous bases. Methylation prevents DNA readers from expressing genes. Some of the silenced genes won't be terribly important, but some, like tumor suppression genes, are. Decitabine is a known methylation inhibitor that can help return tumor suppression genes to an active state, and also improve cells' susceptibility to anti-cancer drugs like carboplatin.

"Our hypothesis is that decitabine isn't just targeting active ovarian cancer cells, but also cancer stem cells that seem to survive the first treatments," Nephew said. "By keeping tumor suppression genes from being methylated, carboplatin and other platinum-based treatments for ovarian cancer have a better chance of success in the late stages."

The researchers also reported that decitabine appears to have caused six of the 10 patients to become hypersensitive to carboplatin (a mild allergic reaction, treatable with steroids). While Nephew and Matei say that the effect may not be observed in a larger patient population, the scientists say they are intrigued by the phenomenon.

Provided by Indiana University School of Medicine