Medical Xpress

Drug with new approach on impeding DNA repair shows promise in first clinical trial

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In its first randomized clinical trial, a drug that targets a protein needed by cancer cells to maintain their dogged growth and division has shown considerable promise in combination with chemotherapy in patients with a common form of ovarian cancer, investigators at Dana-Farber Cancer Institute report.

As detailed in a paper published online today by *The Lancet Oncology*, patients with high-grade serous ovarian cancer (HGSOC) who were treated with the drug, berzosertib, and chemotherapy lived substantially longer before their disease began to worsen than did those treated with chemotherapy alone. The findings may set the stage for testing berzosertib—an inhibitor of the ATR protein—in a range of other cancers, investigators say.

"Our results in his phase 2 trial suggest that ATR inhibition in combination with chemotherapy has the potential to offer significant benefit to patients with chemotherapy-resistant HGSOC and, potentially, other tumor types where ATR plays a key role," says the study's lead author, Panagiotis Konstantinopoulos, MD, Ph.D., director of translational research, Gynecologic Oncology, at Dana-Farber.

Berzosertib is designed to take advantage of one of the most glaring vulnerabilities of some cancer cells. Like a tractor run non-stop, a tumor cell, driven by a constant imperative to proliferate, is apt to need frequent repairs. In a tumor cell, that involves fixing broken strands of DNA.

HGSOC, like other types of cancer, relies heavily on the ATR protein in

making those repairs. That reliance becomes even greater when these cancers are treated with chemotherapy, which disrupts cells' ability to copy their DNA.

"The unbridled growth of cancer cells places enormous stress on the process of DNA replication," Konstantinopoulos explains. "ATR helps them survive that stress: its job is to coordinate the halting of the cell cycle to check if the DNA is intact or needs repair. Drugs that inhibit ATR—that deprive tumor cells of such repair—have the potential to be particularly effective in some cancers."

In the study, investigators at 11 cancer centers around the country enrolled 70 patients with HGSOC that was resistant to platinum-based chemotherapy. Half the participants were randomly assigned to receive the standard chemotherapy agent gemcitabine alone and half received gemcitabine in combination with berzosertib.

The estimated median progression-free survival of patients receiving gemcitabine alone—the period in which their disease was in retreat or stable—was 14.7 weeks. For those receiving gemcitabine and berzosertib, it was 22.9 weeks. Among patients with the most platinum resistant tumors (i.e. those who had progressed within 3 months from prior platinum-based chemotherapy), the difference was even greater: 9 weeks for gemcitabine versus 27.7 weeks for gemcitabine and berzosertib.

Side effects were similar in the two groups. Those receiving the combination therapy, however, had a higher rate of thrombocytopenia, or low blood platelet levels.

Provided by Dana-Farber Cancer Institute

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