New Ovarian Cancer Treatment Strategies

Researchers looking at ovarian cancer cells that resist chemotherapy hope to develop new therapeutic strategies.

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Despite breakthrough treatments for high-grade serous ovarian cancer, about 80 percent of patients relapse within two years, often resistant to treatment. The good news is that Dana-Farber scientists are pursuing multiple avenues of research that very well may improve outcomes.

“A number of patients develop progressive disease at a later point, potentially indicating that a subset of the cells were not sensitive to the initial chemotherapy and survived to later develop into a recurrent cancer,” says Elizabeth Stover, MD, PhD, a Dana-Farber oncologist.

Stover is among a handful of scientists working to understand how and why ovarian cancer cells resist chemotherapy. They hope to develop new therapeutic strategies to combat that drug resistance.

Stover’s 2019 paper in Molecular Cancer Research built on previous research out of Joan Brugge’s Lab at Harvard Medical School and suggests that targeting genes involved in apoptosis — a natural cell death process that often goes awry in cancer, allowing tumor cells to proliferate — could prevent recurrence.

“It was fairly striking that several of the anti-apoptotic genes, when overexpressed, provided some of the strongest protection against chemotherapy,” says Stover, whose research was funded by the National Cancer Institute. “And on the flip side, when those genes were knocked out, the cells were more sensitive to chemotherapy.”

Genome-wide sequencing approaches allowed Stover to study factors affecting chemotherapy resistance, and identify targetable proteins in an apoptotic pathway from tens of thousands of genes. Through collaboration with the Broad Institute of MIT and Harvard, she used CRISPR-Cas-9 to knock out chemo-resistant anti-apoptotic genes, and treated the cell lines with inhibitor drugs against the anti-apoptotic genes already approved for patients with other forms of cancer. Stover calls a drug that inhibits the BCL-XL protein “a potential treatment on the horizon” for chemo-resistance in high-grade serous ovarian cancer. The fact that these new drugs have already been developed for other cancers presents an accelerated path toward clinical trials.

Stover is hopeful that scientists like Joyce Liu, MD, MPH, associate chief and director of clinical research at Dana-Farber's Division of Gynecologic Oncology in the Susan F Smith Center for Women's Cancers, will soon develop a clinical trial incorporating inhibitors of BCL-XL.

"Our team is working on developing clinical trial concepts now," she says.

Preceding Stover's work, other DFCI scientists including Anthony Letai, MD, PhD, blazed the trail for strategies to inhibit specific anti-apoptotic proteins, such as BCL-XL and MCL1.

Inhibiting them could contribute to killing ovarian cancer cells and mitigate resistance, especially when combined with chemotherapy drugs like carboplatin and Paclitaxel, and another class of drugs, called PARP inhibitors, used in ovarian cancer, says Stover.

Kelley McQueeney, PhD, a scientist in Letai's lab, is now testing various combinations of anti-apoptotic and standard-of-care DNA-damaging drugs on patient tumor samples and tumors grown from samples, called organoids, to improve ovarian cancer outcomes.

"With a technology known as dynamic BH3 profiling, I manipulate the normal apoptotic machinery of the cell to get information much faster than the more commonly used viability assays," says McQueeney, who's testing the organoids in collaboration with Sarah Hill, MD, PhD.

As the research continues, Stover says: "I'm hopeful that if we perform additional in vivo studies in the coming year we'll find combinations that are effective in this disease."

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