Study drug is first to help patients with recurrent low-grade ovarian cancer

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Low-grade serous ovarian cancer is less common and aggressive than the high-grade variety, yet exceptionally difficult to treat when frontline therapy fails.

"After surgery, with or without pre-surgical chemotherapy, when low-grade serous ovarian cancer persists or returns, chemotherapy and hormonal therapy are relatively ineffective," said David Gershenson, M.D., professor in The University of Texas MD Anderson Cancer Center Department of Gynecological Oncology and Reproductive Medicine.

Response rates for treatment are measured in single digits. Gershenson and colleagues have spent the greater part of 20 years characterizing the disease, which makes up 10 percent of ovarian cancer cases, and searching for new ways to treat it. Cancer recurs or persists in 80 to 85 percent of patients.

A phase II clinical trial by the National Cancer Institute's Gynecological Oncology Group provides the first evidence of a drug that shows a relatively high response rate for these patients.

Selumetinib halts growth or shrinks tumors

In the first-targeted therapy clinical trial for low-grade serous ovarian cancer, eight of 52 (15 percent) patients had a complete or objective

partial response (tumor shrinkage) and 34 (65 percent) had no disease progression during the two-year course of the study. Study results appear in the February edition of *The* Lancet Oncology.

"These are remarkably encouraging results for what can ultimately be a devastating disease," said Gershenson, the paper's senior author.

These patients have a median overall survival of 80 months, about twice as long as those with high-grade disease, who are typically in their 60s when diagnosed and comprise 90 percent of ovarian cancer patients. The average age of women with low-grade cancer falls in the early 40s, Gershenson said, and it's not uncommon to see women in their 20s, 30s and 40s and the occasional teenager with the disease.

High-grade serous ovarian cancer is susceptible to chemotherapy upon relapse or recurrence.

Median overall survival not reached

Cancer-causing genetic mutations in BRAF and KRAS genes occur more frequently in low-grade ovarian cancer, so the researchers chose a drug that targets the molecular network that includes those genes.

Selumetinib inhibits MEK1/2, a critical molecule in what's known as the MAPK pathway, which includes BRAF and KRAS.

All 52 patients had received at least one previous therapy, with 30 having had three or more. Clinical trial results with selumetinib include:

- Median progression-free survival of 11 months and 34 patients (65 percent) went at least six months without their disease worsening.

- Two-year overall survival of 55 percent.
- Median overall survival had not been reached, because more than half of patients (61 percent) remained alive at the time of data cutoff for the study.
- No treatment-related deaths.

Side effects ranged from cardio and gastrointestinal toxicity to pain, fatigue, anemia and dermatological effects. Of the 52 patients, 22 had their doses reduced and 13 ultimately left the study due to side effects.

Researchers obtained tumor samples sufficient for DNA analysis from 34 patients. While 14 patients had KRAS mutations and two had BRAF mutations, there was no connection between having those mutations and whether the patients responded to selumetinib.

Gershenson said researchers will further explore the question of matching drug to mutation during a larger phase 2/3 clinical trial that he will lead with investigators from the NCI Gynecological Oncology Group and the United Kingdom. The study will enroll 250 patients and is likely to begin later this summer.

Phase 2 trials generally do not include a control or comparison group, but the team noted treatment results for 58 women not in the trial who were treated at MD Anderson with current options. Between them, these patients received 108 different chemotherapy regimens, which produced one complete and three partial responses for an overall response rate of 3.7 percent.

A step toward personalized therapy for ovarian cancer

In an accompanying commentary, Sven Mahner, M.D., and Jacobus

Pfisterer, M.D., Ph.D., German oncologists who did not participate in the research, note that the study is a step toward individualized treatment for ovarian cancer that reflects important molecular differences between low-grade and high-grade disease.

The response rate and disease stabilization rate are "particularly promising in a setting of heavily pretreated recurrent disease."

"A strength of the study is mandatory reference pathology of recurrent disease to ensure exclusion of patients with progression to high-grade disease, who are likely to benefit from chemotherapy, and recurrent borderline ovarian tumors that have excellent prognosis with salvage surgery alone," Mahner and Pfisterer wrote.

Provided by University of Texas M. D. Anderson Cancer Center