Adding topotecan to standard treatment for ovarian cancer does not improve progression-free survival

October 11 2010

Adding topotecan to carboplatin plus paclitaxel, the standard treatment for ovarian cancer, does not improve progression-free survival in patients and leads to greater toxicity, according to a study published online October 11 in the *Journal of the National Cancer Institute.*

Cisplatin plus paclitaxel, and carboplatin plus paclitaxel, are the most widely accepted first-line regimens for advanced epithelial ovarian cancer. Still, most women relapse and die from their disease. One possible solution is to add a third agent, such as topotecan, which has activity in the treatment of recurrent disease. However, combining topotecan with carboplatin plus paclitaxel as a triplet therapy is problematic because of bone marrow toxicity. So, to integrate topotecan into the standard regimen researchers tested cisplatin plus topotecan followed by carboplatin plus paclitaxel.

The phase III randomized study included 819 women aged 28-78 with newly-diagnosed stage IIB or more advanced ovarian cancer. The study was led by Paul Hoskins, M.D., of the British Columbia Cancer Agency in Vancouver and colleagues from three other groups: the NCIC Clinical Trials Group at Queen's University in Kingston, Canada, the European Organization for Research and Treatment of Cancer – Gynecologic Cancer Group, European Union, and the Grupo Español de Investigación en Cáncer de Ovario in Spain.

The women in the study were from Canada and Europe, and were randomly assigned to one of two study groups: the first arm received cisplatin and topotecan, followed by carboplatin and paclitaxel; the second arm received only carboplatin and paclitaxel.

The researchers found that after a median follow-up of 43 months, 650 patients had disease progression and 406 had died. The progression-free survival of patients in the first arm was 14.6 months compared to 16.2 months for those in the second arm. Furthermore, although survival data were not mature, there is no evidence to date that patients receiving topotecan had improved survival (with a median overall survival of 42.3 months for patients in the first arm, compared to 42.1 months for those in the second).

Patients in the first arm also had more toxicity than those in the second. The common side effects included gastrointestinal symptoms, myelosuppression, neurological toxicity and myalgia. Patients in the first arm had more myelotoxicity, nausea and vomiting, while patients in the second had more neurosensory effects and allergic reactions.

The authors concluded that carboplatin plus paclitaxel remains the best standard of care for epithelial ovarian cancer stage IIB or greater. They write, "The most sensible explanation for this lack of additional benefit is that the topotecan does not have sufficient cytotoxic impact on cells that are truly refractory to platins or taxanes."

Furthermore, they explain that a drug such as topotecan needs to be effective in the refractory setting—when the cancer grows during treatment—and not just in the resistant setting—when it recurs shortly after the end of treatment. They write, "Further cytotoxic drugs need to be able to convincingly kill truly refractory cells before being added to the preexisting standard drug or drugs for efficacy testing."

In an accompanying editorial, William P. McGuire, M.D., of the Weinberg Cancer Institute at Franklin Square Hospital Center, Baltimore, writes that the trial provides further confirmation of the inactivity of topotecan to treat standard ovarian cancer. He writes, "In the end, neither the dose of topotecan, sequence of drug administration, nor platinum compound used in combination made any difference."

McGuire also points to the emergence of targeted therapies to treat ovarian cancer instead of cytotoxic agents. He writes, "Clearly, the lack of any benefit from adding topotecan, gemcitabine, or pegylated liposomal doxorubicin to the platinum/taxane in the intergroup trial has signaled the need to try new approaches."

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