Canfosfamide Disappoints in Ovarian Cancer Trials

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CHICAGO — The experimental drug canfosfamide failed to achieve survival end points in two phase III trials that enrolled patients with platinum-refractory or platinum-resistant ovarian cancer.

One study compared the combination of canfosfamide (TLK286, Telcyta) and carboplatin with pegylated liposomal doxorubicin (Doxil) as second-line treatment in 247 patients recruited at 66 sites. The data failed to meet primary and secondary end points demonstrating superiority in objective response rate and progression-free survival, according to a research team led by Dr. Peter G. Rose.

Progression-free survival was 3.5 months in both arms of the trial. A subgroup of 38 patients (19 in each arm) who were characterized by a drug-free period of 6 months or longer responded more favorably to the combination therapy, with an overall response rate of 31.6%. Drug-free period was defined as the date from last treatment with platinum-based chemotherapy to the date of initiation of first study treatment.

The second trial compared single-agent canfosfamide and topotecan (Hycamtin) or pegylated liposomal doxorubicin in 461 women with disease progression following second-line treatment with doxorubicin or topotecan.

Dr. Ignace Vergote reported median overall survival was actually worse in the canfosfamide group: 8.5 months versus 10.8 months with topotecan and 14.2 months with doxorubicin (median 13.5 months for the latter two). The difference was statistically significant, said Dr. Vergote, of University Leuven (Belgium).

Both studies were sponsored by Telik Inc., and were presented in posters at the annual meeting of the American Society of Clinical Oncology.

In the trial reported by Dr. Rose, 123 women were randomized to receive intravenous canfosfamide (750 mg/m^2) in combination with carboplatin once monthly, while 124 women received doxorubicin at 50 mg/m^2 once monthly.

Hematologic toxicity was more frequent in the combination arm but was well managed with growth factor support or dose reductions, according to the investigators. Grade 3-4 thrombocytopenia occurred in 33% of the women taking both canfosfamide and carboplatin. About 20% of both arms experienced grade 3-4 neutropenia.

Failure of the canfosfamide-carboplatin regime to meet established end points in second-line treatment of metastatic ovarian cancer "may in part be due to the challenges of radiologic imaging interpretation in ovarian cancer as well as to the complex biology involved in platinum resistance and resensitization," said Dr. Rose, a professor of reproductive biology and oncology at Case Western Reserve University, Cleveland.

According to the independent radiology review, approximately one-fourth of patients may have been prematurely discontinued from study involvement. This may have confounded the analysis of progress.

In a discussion, Dr. Carol Aghajanian of Memorial Sloan Kettering Cancer Center in New York said, "It's unfortunate that the response rate is not reported—the authors explaining that response rate varied too much between clinician assessments and radiology review assessments—and it's disappointing that the trial's final results could not be analyzed."

In the trial presented by Dr. Vergote, 232 patients received canfosfamide at 1,000 mg/m^2 intravenously every 3 weeks, while 229 patients received either topotecan at 1.5 mg/m^2 daily for 5 days once every 3 weeks, or doxorubicin at 50 mg/m^2 once monthly. In addition to worse overall survival, Dr. Vergote reported median progression-free survival was 2.3 months for canfosfamide and 4.3 months for topotecan or doxorubicin. The overall response rate was 11% for topotecan or doxorubicin and 4% for canfosfamide.

"This study showed us that, as a single agent, canfosfamide doesn't have a lot of cytostatic effects, but other studies suggest that we may get better results by using this drug in combination," he said.

The most common grade 3-4 adverse events for canfosfamide were nausea (32%), vomiting (9%), fatigue (6%), and anemia (6%). For the traditional drugs, the primary grade 3-4 adverse events were nausea (55%); anemia (15%); fatigue (7%); neutropenia (23%); thrombocytopenia (12%); and febrile neutropenia, stomatitis, or palmar-plantar erythrodysesthesia (6%). ■