Trabectedin May Prolong Ovarian Cancer Survival

BY JANE SALADOF MacNEIL
Senior Editor

STOCKHOLM — Trabectedin, a synthetic version of a compound derived from sea squirts, significantly delayed progression of recurrent ovarian cancer in a large, randomized phase III trial presented at the European Society for Medical Oncology Congress.

When combined with pegylated liposomal doxorubicin (Doxil/Caelyx), the novel drug brought progression-free survival to 7.3 months vs. 5.8 months for a control group treated with pegylated liposomal doxorubicin alone (hazard ratio, 0.79; $P = .0190$), reported the principal investigator, Dr. Bradley J. Monk of the University of California Irvine Medical Center.

Overall survival results, a secondary end point, were not yet mature, but also suggested the possibility of an advantage with trabectedin (Yondelis). With more than half of 672 women in the trial still alive, overall survival had reached 20.5 months in those given the combination and 19.4 months in the arm that received single-agent care (HR, 0.85; $P = .1506$).

More patients responded to treatment in the combination arm as well (28% vs. 19%).

Trabectedin is currently approved for treatment of advanced soft-tissue sarcoma in Europe and South Korea. Initially isolated from the marine animal *Ecteinascidia turbinate*, it binds selectively with the minor groove of DNA, and drives cells to apoptosis by interfering with DNA repair and transcription factors.

Two drug companies, PharmaMar, S.A. in Spain and Johnson & Johnson Pharmaceutical Research and Development in the United States, cosponsored the Ova-301 trial. PharmaMar has announced plans to seek European approval for trabectedin in ovarian cancer, and Johnson & Johnson is expected to seek an indication in the United States, according to Dr. Monk, who disclosed receiving honoraria from Johnson & Johnson.

Noting that numerous other agents are under study for ovarian cancer, he extolled trabectedin as the first to succeed in a phase III study. "The list is short in late-stage development, and many of those late trials are negative," he said in an interview. "To have a study which is actually positive for its primary end point, and to bring a new drug to cancer patients, is a big deal. And that is why we are so excited."

Investigators at 124 hospitals in 21 countries completed patient enrollment in the trial on May 29, 2007. Participants had to have measurable epithelial ovarian, epithelial fallopian tube, or primary peritoneal cancer that had progressed after six full cycles of therapy or 6 months after front-line therapy. Only patients with one previous platinum-based front-line therapy were included; women given anthracyclines were excluded as were those who progressed during platinum-based front-line therapy. Maintenance or consolidation therapy was allowed.

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Trabectedin is a synthetic version of a compound derived from the sea squirt, *Ecteinascidia turbinata*.

The study randomized 335 women to 50 mg/m^2 of pegylated liposomal doxorubicin by 90-minute infusion every 4 weeks and 337 women to the combination regimen: a 90-minute infusion of 30 mg/m^2 of pegylated liposomal doxorubicin followed by 1.1 mg/m^2 of trabectedin over 3 hours every 3 weeks. Of these, 330 and 333, respectively, were treated. Premedication with dexamethasone was required in the combination arm of the trial.

The population had a median age of 57 years; more than two-thirds had papillary/serous histology, of which 65% was platinum sensitive based on a platinum-free interval of more than 6 months from first-line therapy.

Dr. Monk reported that trabectedin appeared to be more active in women with platinum-sensitive disease, compared with patients who were platinum resistant. More platinum-sensitive patients responded to the combination than to the single agent (35.3% vs. 22.6%; $P = .0042$), he said. Response rates in platinum-resistant patients were lower and similar (13.4% and 12.2%, respectively).

Progression-free survival in those who did not have a recurrence for at least 6 months after their initial treatment for ovarian cancer reached 9.2 months with the combination vs. 7.5 months with the standard single-agent regimen (HR 0.73; $P = .0170$). This same measure was just 4 months and 3.7 months, respectively, in platinum-resistant patients.

Progression-free survival was based on review by an independent radiologist who used RECIST (Response EvaluationCriteria in Solid Tumors).

An analysis of grade 3/4 toxicity in treated patients showed less hand and foot syndrome and mucositis/stomatitis but more vomiting, nausea, and febrile neutropenia (8% vs. less than 3%) in the combination arm. More patients had severe neutropenia (52% vs. 30%) and elevated liver enzymes, but Dr. Monk said the latter were transient and mostly resolved without the need for dose reductions. Cardiac disorders were described as uncommon in both arms.

All told, 11% of patients discontinued treatment because of treatment-related adverse events. In all patients, the median number of completed cycles was five.

Discussant Dr. Cristiana Sessa of the National Cancer Institute in Milan, Italy, said preclinical data show trabectedin has a different mechanism of action from previous drugs and antitumor activity in xenografts. It has not shown significant activity in resistant ovarian disease, she said, but may have "a therapeutic index better than standard therapies in partially platinum-sensitive disease."

Its role in ovarian cancer will be determined by other studies, she suggested. These include trials comparing pegylated liposomal doxorubicin and trabectedin with paclitaxel and carboplatin, and comparing single-agent pegylated liposomal doxorubicin with single-agent trabectedin. ■

Exenatide/Metformin Combo Benefits Women With PCOS

BY MIRIAM E. TUCKER
Senior Writer

ROME — Treatment of polycystic ovary syndrome with exenatide plus metformin was more effective than either medication alone in improving menstrual cycle frequency and in ameliorating hormonal and metabolic derangements, according to a study of 60 patients.

The study findings were presented at the annual meeting of the European Association for the Study of Diabetes by Dr. Ted Okerson of Amylin Pharmaceuticals Inc. on behalf of the scheduled presenter, Dr. Rajat Bhushan of the Metabolic Center of Louisiana Research Foundation, Baton Rouge, who was unable to attend the meeting because of a hurricane. Dr. Karen Elkind-Hirsch of the same institution was the principal author of the study, published in the Journal of Clinical Endocrinology and Metabolism (2008;93:2670-8).

Metformin has been shown to reduce insulin resistance and androgen levels while increasing ovulation in women with polycystic ovary syndrome (PCOS). However, metformin does not alter insulin secretion. Exenatide (Byetta), used to treat type 2 diabetes, has been shown to restore first- and second-phase insulin secretion, which is attenuated in women with PCOS, as well as to promote weight loss, thereby potentially further improving insulin sensitivity, Dr. Okerson said.

An open-label, prospective 24-week pilot study of 60 obese oligo-ovulatory women with PCOS was funded by a grant from Amylin Pharmaceuticals and Eli Lilly & Co. In the study, 40 white and 20 African American women with PCOS were randomized to receive either 1,000 mg metformin twice daily, exenatide 10 mcg twice daily, or a combination of the two, for 24 weeks. All were aged 18-40, with a body mass index above 27 kg/m^2 and six or fewer menses per year. Forty-two patients (14 in each group) completed the study, with equal racial distribution across groups.

Menstrual cycle frequency, the primary study end point, was significantly increased in all treatment groups at 24 weeks and to a significantly greater degree with the combination, compared with metformin alone. The proportion of normal cycles in the group increased from a mean of 22% at baseline to 57% with exenatide alone, from 21% to 49% with metformin alone, and from 29% to 83% with both drugs. Ovulatory rates also improved with all three regimens, but significantly more so with the combination. Ovulation occurred in 12 of the combination patients (86%), compared with 7 who received exenatide alone (50%) and 4 with metformin alone (29%).

Body weight changes were significant in both groups receiving exenatide, but not in those receiving metformin alone. At 24 weeks, mean weight loss was 6 kg in the combination group and 3.2 kg with exenatide alone, vs. just 1.6 kg with metformin alone. Similar reductions were seen in body mass index. Abdominal girth diminished slightly in both exenatide groups but increased slightly between weeks 12 and 24 among the metformin-alone patients, Dr. Okerson reported.

Total testosterone was significantly decreased from baseline in all treatment groups, by 10.2 ng/dL with exenatide alone, 3.6 ng/dL with metformin alone, and 18.4 ng/dL with the combination. The free androgen index was significantly more reduced with the combination, compared with metformin alone but not compared with exenatide alone. Levels of sex hormone–binding globulin were increased, but not significantly, with all treatments, while levels of dehydroepiandrosterone sulfate and thyroid-stimulating hormone were not significantly altered in any group.

Insulin sensitivity improved significantly with all treatments, and was significantly higher in the combination group than in the metformin group at 24 weeks. After therapy, the calculated mean insulin secretion sensitivity index was 516 with combination therapy, 395 with exenatide alone, and 232 with metformin alone. Total cholesterol and triglycerides decreased significantly with combination therapy vs. metformin monotherapy, which did not consistently improve those levels, while HDL and LDL cholesterol levels did not change significantly with treatment. Adiponectin levels increased significantly with all treatments, while other inflammatory markers did not change.

The most common adverse events were mild or moderate gastrointestinal problems, including nausea, which occurred in 15% with exenatide alone, 20% with metformin alone, and 45% with the combination. ■