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New Advances in Combination Therapy For Ovarian Cancer

Atlanta – Ovarian cancer accounts for 4% of all cancers among women. The five-year relative survival rate for all stages of ovarian cancer – the most deadly cancer of the female reproductive system - is 50%. It has been previously demonstrated that a combination of cisplatin plus paclitaxel is superior to cisplatin plus cyclophosphamide as chemotherapy for previously untreated advanced stage ovarian cancer patients. Now, a Phase III, multi-centred trial presented here has found that the combination of carboplatin plus paclitaxel is significantly less toxic that the cisplatin/paclitaxel combination, while maintaining the same level of efficacy. The trial found that carboplatin/paclitaxel can be administered in a three-hour infusion instead of the 24 hour infusion period for cisplatin/paclitaxel. Patients receiving carboplatin/paclitaxel experienced fewer gastrointestinal and metabolic effects, and the decrease in toxicity was not associated with any decrease in efficacy. These results dispel concerns that carboplatin would have less efficacy than cisplatin when used with paclitaxel, investigators said.

Dr. Robert Ozols, Senior Vice-President, Medical Science at Fox Chase Cancer Center, in Philadelphia, Pennsylvania, told delegates here that GOG 158, a Phase III study by the Gynecologic Oncology Group, was designed as an equivalency trial of carboplatin/paclitaxel versus cisplatin/paclitaxel in optimal stage III ovarian cancer patients.

He noted that it had previously been demonstrated that cisplatin plus paclitaxel was superior to cisplatin plus cyclophosphamide in previously untreated advanced stage ovarian cancer patients. In addition, it had previously been demonstrated in a GOG Fox Chase Cancer Center Phase I study that paclitaxel 175 mg/m^2 in a three-hour infusion could be combined with carboplatin at an area under the curve (AUC) of 7.5, with acceptable toxicity and with both drugs administered at full therapeutic doses. In that pilot study, the overall response rate was 75%, with two-thirds of patients achieving a clinically-complete remission. Completed in 1996, the GOG 111 study showed that the median survival of women with advanced ovarian cancer was extended by more than 50% (37.5 months compared to 24.4 months) when they received cisplatin/paclitaxel instead of cisplatin/cyclophosphamide.

Dr. Ozols noted some investigators previously believed that carboplatin had less efficacy than cisplatin in ovarian cancer patients, particularly in patients with optimal stage III disease. Furthermore, based on in vitro cytotoxicity studies and some Phase II clinical trials in other tumours, it was felt that a shorter three-hour infusion of paclitaxel may not be as effective as a 24-hour infusion.

These concerns were put to the test in GOG 158, one of three randomized trials done throughout the world comparing carboplatin/paclitaxel (carbo/pac) versus cisplatin/paclitaxel (cis/pac). “However, GOG 158 was unique in that only patients with optimal stage III disease were eligible for participation,” Dr. Ozols said.

Methodology and Results

Untreated epithelial ovarian cancer patients with optimal (less than 1 centimetre) stage III disease were randomized to cisplatin 75 mg/m^2 plus paclitaxel 135 mg/m^2 in a 24 hour infusion or carboplatin of AUC 7.5 plus paclitaxel 175 mg/m^2 in a three-hour infusion. Six courses were administered every 21 days to outpatients.

A total of 425 patients were randomized to cisplatin/paclitaxel and 415 patients to

carboplatin/paclitaxel. There was no significant difference in age, performance status, cell type, tumour grade or residual disease between the two treatment arms.

Both treatments were well tolerated, Dr. Ozols commented. With cisplatin/paclitaxel 85% of patients completed six courses of treatment; with carboplatin/paclitaxel 87% of the patients completed six courses.

“Furthermore, the chemotherapy was administered almost at full dose,” he told delegates. The median cisplatin/paclitaxel dose was 74 mg/m^2 for cisplatin and 133 mg/m^2 for paclitaxel; the median carboplatin/paclitaxel dose was an AUC of 7.43 for carboplatin and 174 mg/m^2 for paclitaxel.

There was a statistically significant increase in Grade 4 leukopenia (12% in patients receiving cisplatin/paclitaxel compared to carboplatin/paclitaxel (6%).There was also more Grade 3 /4 gastrointestinal toxicity (23% vs. 10%), Grade 1-4 fever (29% vs. 16%) and Grade 1-4 metabolic toxicity (27% vs. 14%) in patients receiving cisplatin/paclitaxel. In the carboplatin/paclitaxel arm, there was more Grade 3/ 4 thrombocytopenia (39% vs. 5% cisplatin/paclitaxel) and patients reported more Grade 1/ 2 pain (26% vs. 15%).

A timed analysis after six cycles of therapy, found there was no significant difference in grade 2 and 3 neurotoxicity for patients receiving cisplatin/paclitaxel compared to carboplatin/paclitaxel. Long-term effects of neurotoxicity are not yet available, Dr. Ozols said.

The study found no difference in recurrence-free survival: 21.7 months with cisplatin/paclitaxel and 22 months with carboplatin/paclitaxel. The final analysis of survival is premature since it was to be conducted when 382 deaths were observed and currently there are 186 deaths - 96 deaths on the cisplatin/paclitaxel arm and 90 deaths on the carboplatin/paclitaxel arm, Dr. Ozols explained. Approximately 80% of the deaths were due to disease and only six patients – four on cisplatin/paclitaxel and two on carboplatin/paclitaxel – were felt to have treatment related deaths, he said.

Speaking about the major endpoint of this trial, Dr. Ozols noted that the relative risk of failure was 0.90 when comparing carboplatin/paclitaxel to cisplatin/paclitaxel.

“This means that there is a 10% decreased risk of failure in patients receiving carbo/pac,” Dr. Ozols explained. “And as can be seen from (90%) confidence intervals of 0.75 to 1.10, the results of this study essentially eliminate the possibility in this trial that carbo/pac was inferior to cis/pac with regards to progression-free survival.”

Second Look

The impact of second look surgery on recurrence-free survival in ovarian cancer has been controversial. In this trial, 395 patients were registered for second look surgery, while 403 were registered for no second look surgery at the time of randomization to either of the two arms.

“There’s absolutely no difference in progression-free survival in patients who underwent second look or those who did not,” Dr. Ozols said in discussing results.

The negative second look rate was 51.5% (84 of 163) for patients treated with carboplatin/paclitaxel and 45.2% (76 of 168) for patients treated with cisplatin/paclitaxel.

“Second look surgery does not influence recurrence-free survival in optimal stage III ovarian cancer,” he said.

Conclusion

In conclusion, Dr. Ozols said not only do results of this largest reported randomized trial in optimal stage III ovarian cancer make it clear that the carboplatin/paclitaxel regimen is not inferior to cisplatin/paclitaxel, but that the carboplatin/paclitaxel combination contains certain benefits.

“Carboplatin/paclitaxel is a preferred regimen, due to the ease of administration and a clinically significant decrease in toxicity,” Dr. Ozols stressed. The carboplatin/paclitaxel regimen “presents fewer troublesome side effects for patients.”

In addition, he said, “there is no advantage to a 24 hour infusion compared with a three-hour infusion of paclitaxel.”