

Evolving strategies for ovarian cancer: gynecologic oncology in ASCO's 46th annual meeting

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The theme for the 2010 American Society of Clinical Oncology (ASCO) annual meeting is "Advancing Quality through Innovation." This meeting provided an exemplary forum for the dissemination and discussion of the latest innovations in research, quality, practice, and technology in cancer. In this year, the new trials in progress were presented in poster session without outcome data to encourage recruitment of new investigators or sites, to stimulate discussion of successor or confirmatory trials, and to discuss the background of the science behind the trial.

In the field of gynecologic cancer, 134 abstracts were presented in the 2010 ASCO (1 in Plenary Session, 5 in Oral Abstract Session, 10 in Trials in Progress Poster Session, 25 in Poster Discussion Session, 90 in General Poster Session, and 3 in Clinical Science Symposium). The number of abstracts presented this year was increased compared to the last year meeting which had 96 abstracts in the field of gynecologic oncology. The key topics among them will be presented again in Best of ASCO[®] International. (*Best of ASCO[®] is a conference where the 50 Best presentations made at ASCO will be presented by Members of the Scientific Committee. They will be presented and commented by different speakers.*) Herein, I'd like to introduce these abstracts to the readers briefly.

Among these, the most notable study was GOG 218 evaluating whether there is therapeutic impact from concurrent±maintenance bevacizumab (BEV) with standard chemotherapy (CP) in patients with stage III-IV epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian cancer (FC).¹ All women underwent abdominal surgery for staging and maximal tumor debulking before being randomly assigned to one of three treatment arms: 1) CP plus placebo during the induction phase (cycles 1 to 6), followed by placebo maintenance (cycles 7 to 22); 2) CP plus concurrent bevacizumab

during induction, followed by placebo maintenance; and 3) CP plus concurrent bevacizumab during induction, followed by bevacizumab maintenance. Bevacizumab was not administered during the first 21-day induction cycle so as to limit post-surgical bleeding complications. The entire treatment schedule took 15 months to complete. Although overall survival was originally selected as the primary endpoint, this was changed to progression-free survival (PFS) to accord with international consensus as a more appropriate endpoint for frontline phase III trials in this patient population, as well as pressure by patients to unblind their treatment assignment in the event of disease progression. The investigators monitored disease progression based on radiographic evidence, CA-125 measurements, and global clinical deterioration. Overall survival, safety, and quality of life comprised the secondary endpoints. 1,873 patients were enrolled from US, Canada, South Korea, and Japan between Sep 2005 and Jun 2009. Stage III optimally debulked (34%), stage III sub-optimally debulked (40%), and stage IV (26%) patients were similarly distributed in each treatment group. After a median follow-up of 17.4 months (range, 0 to 50.7 months), PFS was significantly prolonged by 3.8 months in R3 group compared with R1 (14.1 months compared with 10.3 months, respectively; hazard ratio [HR], 0.717; $p < 0.0001$). No significant difference in PFS was observed between R2 and R1 (11.2 months compared with 10.3 months, respectively; HR, 0.908; $p = 0.080$). At the time of analysis, overall survival did not show any differences between the three arms; the survival data are not yet mature. The addition of BEV to CP appeared well tolerated. Although hypertension occurred significantly more often in the BEV arms compared with the control arm ($p < 0.05$): Grade 3-4 hypertension was reported in 1.6% (R1), 5.4% (R2), and 10.0% (R3). The incidences of all other adverse events were similar across the arms. Gastrointestinal perforation events did not markedly increase with the use of BEV (2.6% to 2.8% in the BEV arms compared with 1.2% in the control arm). BEV as concurrent + maintenance regimen with standard CP is the first anti-angiogenic agent to demonstrate benefit (PFS) in advanced EOC, primary peritoneal cancer or FC (abstr LBA1). This study was presented in the Plenary Session, which in-

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cludes the abstracts of practice-changing findings.

Two abstracts in Oral Abstract Session will be reviewed in Best of ASCO®. One is about ovarian cancer screening study using the risk of ovarian cancer algorithm (ROCA).² 3238 postmenopausal women aged 50 to 74 with no significant family history of breast or ovarian cancer participated over an eight year period. It was prospective and multicenter screening study. Participants underwent a CA-125 blood test annually. Based on the ROCA result, women were triaged to the next annual CA-125 (low risk), repeat CA-125 in 3 months (intermediate risk), or transvaginal sonography (TVS) and referral to a gynecologic oncologist (high risk). Based on clinical findings and TVS, the gynecologic oncologist made the decision whether to proceed with surgery. The average annual rate of referral to 3 monthly CA125 was 6.8%, and the average annual rate of TVS and gynecologic oncologist referral was 0.9%. Eight women subsequently underwent surgery based on the TVS and referral, with 3 early-staged invasive ovarian cancers (two stage 1C and stage IIB), 2 borderline ovarian tumors and 3 benign ovarian tumors, providing a positive predictive value of 37.5% (95% confidence interval [CI], 8.5%, 75.5%). The combined specificity of ROCA followed by TVS for referral to surgery is 99.7% (95% CI, 99.5%, 99.9%). The ROCA followed by TVS demonstrated excellent specificity and PPV in a population of US women at average risk for ovarian cancer. This study provides early evidence that ROCA followed by TVS is a feasible strategy for screening women over 50 years of age (abstr 5003).

The other study is a phase III trial evaluating the efficacy of gemcitabine plus carboplatin (GC) or paclitaxel plus carboplatin (TC) induction followed by elective paclitaxel consolidation (Tcon:135 mg/m² every 28 days for 12 cycles).³ However, this trial was stopped in Aug 2009 because of low probability of a positive PFS on ad hoc analysis. For GC and TC, median PFS were 20.0 and 22.2 months (p=0.199); median overall survival (OS) were 43.8 and 57.3 months (p=0.013), respectively. But there was no statistical difference in OS after adjusting for significant covariates. For patients with complete response, median OS was 65.6 months with Tcon versus 51.4 months without Tcon (p=0.041). In conclusion, GC does not offer an advantage over standard of care TC for first-line chemotherapy in advanced ovarian cancer (abstr LBA5008).

Phase II study of new drug "AMG 386" was presented by Dr. Beth Karlan in Clinical Science Symposium.⁴ AMG 386 is an investigational peptide-Fc fusion protein that inhibits angiogenesis by neutralizing the interaction between the Tie2 receptor and angiopoietin 1 and 2. They evaluated the safety and efficacy of AMG 386 combined with weekly paclitaxel in recurrent ovarian cancer. 161 patients were randomized (paclitaxel at 80 mg/m² iv q w [3 on/1 off] plus AMG 386 at 10 mg/kg [arm A], 3 mg/kg [arm B] or placebo [arm C] iv q w). Median PFS (80% CI) were 7.2 (5.7, 7.5), 5.7 (5.2, 7.8), and 4.6 (2.0, 5.5) months, respectively. The hazard ratio for AMG

386 treated group was not significant over arm C. Notable adverse events included peripheral edema (Arm A/B/C, 71/51/29%; grade ≥3, 4/6/4%), hypokalemia (21/15/5%; grade ≥3, 12/11/4%), thromboembolic events (arterial, 2/2/0%, all grade ≥3; venous, 8/8/11%; grade ≥3, 6/6/9%) and hypertension (8/8/5%, no grade 3). There were no bowel perforations in AMG 386 treated patients. They concluded that AMG 386 combined with weekly paclitaxel was tolerable with a manageable safety profile distinct from VEGF inhibitors and showed promising evidence of antitumor activity with a dose-response effect (abstr 5000).

Final analysis of the Multicentre Italian Trials in Ovarian Cancer (MITO)-2 trial was presented in Poster Discussion Session.⁵ MITO-2 was to compare carboplatin (C) plus pegylated liposomal doxorubicin (PLD) versus carboplatin plus paclitaxel (CP) as first-line chemotherapy in patients with advanced ovarian cancer (IC-IV). This trial was introduced as an Oral Abstract in ASCO 2009 annual meeting. At that time, the conclusion was C-PLD produced a similar activity with a different toxicity profile, compared to CP. Hematologic toxicity and skin toxicity were common in C-PLD, but hair loss and neurotoxicity were common in CP group. Required events are awaited for final PFS analysis (abstr 5508 in ASCO 2009). From Jan 2003 to Nov 2007, 820 patients were randomized, 410 to each arm. Stage III (60%) and IV (21%) were prevalent. With a median follow-up of 40.2 months, median PFS was 19.0 and 16.8 months with C-PLD and CP, respectively (HR, 0.95; 95% CI, 0.81 to 1.13; p=0.58). Lack of significant difference was confirmed (HR, 0.96; 95% CI, 0.81 to 1.14) at multi-variable analysis. With 313 deaths recorded, median overall survival was 61.6 and 53.2 months with C-PLD and CP, respectively (HR, 0.89; 95% CI, 0.72 to 1.12; p=0.32). In the MITO-2 trial, C-PLD was not found to be superior to CP for advanced ovarian cancer. However, they suggested that C-PLD with different toxicity profile could be considered an alternative to CP (abstr LBA5033).

Space limitations prevent a fuller description of the numerous excellent abstracts. The reader is referred to the May-June 2010 Supplement to Journal of Clinical Oncology for more details. The readers can navigate the 2010 ASCO Online through Virtual Meeting. The 2011 ASCO annual meeting is scheduled for June 3-7 in Chicago.

REFERENCES

1. Burger RA, Brady MF, Bookman MA, Walker JL, Homesley HD, Fowler J, et al. Phase III trial of bevacizumab (BEV) in the primary treatment of advanced epithelial ovarian cancer (EOC), primary peritoneal cancer (PPC), or fallopian tube cancer (FTC): A Gynecologic Oncology Group study. *J Clin Oncol* 2010; 28: 7s (suppl; abstr LBA1).
2. Lu KH, Skates S, Bevers TV, Newland W, Moore RG, Leeds L, et al. A prospective U.S. ovarian cancer screening study using the risk of ovarian cancer algorithm (ROCA). *J Clin Oncol* 2010; 28: 7s (suppl; abstr 5003).
3. Teneriello MG, Gordon AN, Lim P, Janicek M. Phase III trial of

- induction gemcitabine (G) or paclitaxel (T) plus carboplatin (C) followed by elective T consolidation in advanced ovarian cancer (OC): Final safety and efficacy report. J Clin Oncol 2010; 28: 7s (suppl; abstr LBA5008).
4. Karlan BY, Oza AM, Hansen VL, Richardson GE, Provencher DM, Ghatage P, et al. Randomized, double-blind, placebo-controlled phase II study of AMG 386 combined with weekly paclitaxel in patients (pts) with recurrent ovarian carcinoma. J Clin Oncol 2010; 28: 7s (suppl; abstr 5000).
5. Pignata S, Scambia G, Savarese A, Sorio R, Breda E, Ferrandina G, et al. Carboplatin (C) plus paclitaxel (P) versus carboplatin plus pegylated liposomal doxorubicin (PLD) in patients with advanced ovarian cancer (AOC): Final analysis of the MITO-2 randomized multicenter trial. J Clin Oncol 2010; 28: 7s (suppl; abstr LBA5033).
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