Highlights in Gynecologic Cancer

Commentary by Robert L. Coleman, MD

Simple Hysterectomy Noninferior to Radical Hysterectomy in Low-Risk, Early-Stage Cervical Cancer

Simple hysterectomy is noninferior to radical hysterectomy in reducing the 3-year pelvic recurrence rate among women with low-risk, early-stage cervical cancer, according to the results of the phase 3 SHAPE study. The use of simple vs radical hysterectomy also led to fewer surgical complications and a better quality of life.

The study, by Dr Marie Plante and colleagues, enrolled 700 women (median age, 44 years) with low-risk, early-stage cervical cancer, defined as stage IA2 or IB1 disease, a maximum diameter of 20 mm, and stromal invasion of less than 10 mm by loop electrosurgical excision or cone biopsy or less than 50% by magnetic resonance imaging. After stratification by cooperative group, intended use of sentinel node mapping, stage, histologic type, and tumor grade, patients were randomly assigned in a 1:1 ratio to radical or simple hysterectomy. The primary endpoint was the 3-year pelvic recurrence rate.

After a median follow-up of 4.5 years, 11 patients in the simple hysterectomy group and 10 patients in the radical hysterectomy group experienced pelvic recurrences. The 3-year pelvic recurrence rate in the intention-to-treat (ITT) group was 2.52% for simple hysterectomy and 2.17% for radical hysterectomy. The 3-year extrapelvic relapse-free survival rate was 98.1% vs 99.7% (P=.10), the 3-year relapse-free survival rate was 96.3% vs 97.8% (P=.30), and the 3-year overall survival (OS) rate was 99.1% vs 99.4% (P=.87) in the simple and radical hysterectomy groups, respectively.

The incidence of urinary incontinence related to surgery was significantly higher in the radical hysterectomy group than in the simple hysterectomy group, at 11.0% vs 4.7%, respectively (P=.003). Rates of urinary retention (9.9% vs 0.6%; P<.001) and quality of life measures also significantly favored simple over radical hysterectomy.

Dr Plante concluded that, following adequate and rigorous preoperative assessment, "simple hysterectomy can now be considered the new standard of care for patients with low-risk, early-stage cervical cancer."

Plante M, Kwon JS, Ferguson S, et al. An international randomized phase III trial comparing radical hysterectomy and pelvic node dissection (RH) vs simple hysterectomy and pelvic node dissection (SH) in patients with low-risk early-stage cervical cancer (LRESCC): a Gynecologic Cancer Intergroup study led by the Canadian Cancer Trials Group (CCTG CX.5-SHAPE) [ASCO abstract LBA5511]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: The SHAPE trial contributes to the ongoing narrative of surgery de-escalation, exploring the possibility of performing less radical surgery for patients with early-stage cervical cancer, who have traditionally undergone radical hysterectomy. By comparing simple hysterectomy with radical hysterectomy in a select group of low-risk patients, the trial aims to establish that the less radical procedure is not associated with inferiority. The trial successfully demonstrates that a simple hysterectomy is not inferior to a radical hysterectomy, making it a viable alternative with accessibility for more surgeons. Additionally, the less radical approach is associated with better quality of life, particularly as related to sexual health and complications related to the pelvic floor. The trial's global scope and noninferiority design are expected to bring about significant changes to the landscape of cervical cancer management.

Addition of Durvalumab and Olaparib to Standard Treatment Improves PFS in *BRCA* Wild-Type Advanced Ovarian Cancer

The addition of durvalumab (Imfinzi, AstraZeneca) and olaparib (Lynparza, AstraZeneca) to standard treatment improves progression-free survival (PFS) in patients with newly diagnosed, *BRCA* wild-type advanced ovarian cancer, according to interim results of the phase 3 DUO-O trial.

For the trial, Dr Philipp Harter and colleagues enrolled 1130 patients with newly diagnosed stage III or IV, high-grade, epithelial ovarian cancer that did not have tumor *BRCA* mutations. All patients had received 1 cycle of paclitaxel/carboplatin chemotherapy with or without bevacizumab and either had completed upfront debulking surgery or were planning to receive it. Patients were randomized in a 1:1:1 ratio to 1 of 3 arms. Arm 1 (n=378) consisted of chemotherapy plus bevacizumab, followed by maintenance bevacizumab. Arm 2 (n=374) consisted of the same treatments as arm 1, plus durvalumab in the initial and maintenance phases. Arm 3 (n=378) consisted of the same treatments as arm 2, plus olaparib in the maintenance phase.

After a median follow-up of approximately 2 years, results were available for the 143 patients in arm 1 and the 140 patients in arm 3 who were homologous recombination deficiency (HRD)-positive. The median PFS was significantly longer in arm 3 than in arm 1, at 37.3 vs

23.0 months, respectively (hazard ratio [HR], 0.49, 95% CI, 0.34-0.69; *P*<.001). The median PFS was also significantly longer in arm 3 (n=211) than in arm 1 (n=216) for the patients who were HRD-negative, at 20.9 vs 17.4 months, respectively (HR, 0.68; 95% CI, 0.54-0.86). The median PFS in the ITT population was also significantly longer in arm 3 (n=378) than in arm 1 (n=378), at 24.2 vs 19.3 months, respectively (HR, 0.63; 95% CI, 0.52-0.76; *P*<.001). There was a trend toward longer median PFS in arm 2 than in arm 1 in the ITT population, at 20.6 vs 19.3 months, respectively (HR, 0.87; 95% CI, 0.73-1.04; *P*=.13), but the difference was not statistically significant. Serious adverse events (AEs) were reported in 34%, 43%, and 39% of patients in arms 1, 2, and 3, respectively.

Dr Harter concluded that DUO-O demonstrated a "statistically significant and clinically meaningful improvement" in PFS with first-line carboplatin/paclitaxel plus bevacizumab plus durvalumab, followed by maintenance with bevacizumab, durvalumab, and olaparib, compared with control in patients with non–tumor *BRCA*-mutated advanced ovarian cancer.

Harter P, Trillsch F, Okamoto A, et al. Durvalumab with paclitaxel/carboplatin (PC) and bevacizumab (bev), followed by maintenance durvalumab, bev, and olaparib in patients (pts) with newly diagnosed advanced ovarian cancer (AOC) without a tumor BRCA1/2 mutation (non-tBRCAm): results from the randomized, placebo (pbo)-controlled phase III DUO-O trial [ASCO abstract LBA5506]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: The role of PARP inhibitors in ovarian cancer is evolving, and a recent study explored their effectiveness in patients without *BRCA*-mutated tumors. The trial combined the angiogenesis inhibitor bevacizumab, the immune checkpoint inhibitor durvalumab, and the PARP inhibitor olaparib in an effort to improve outcomes for less sensitive tumors. The primary endpoint analysis showed improved outcomes in a cohort of HRD-positive patients and promising results in the HRD-negative subgroup. Although further analysis is needed, this trial addresses a new hypothesis and contributes to our understanding of PARP inhibitor use in ovarian cancer treatment.

Mirvetuximab Soravtansine Improves OS in Patients With Platinum-Resistant Ovarian Cancer

The antibody-drug conjugate (ADC) mirvetuximab soravtansine (Elahere, ImmunoGen) improves OS in patients with platinum-resistant ovarian cancer with high expression of folate receptor α (FRα), according to the results of the phase 3 MIRASOL trial.

The open-label trial, by Dr Kathleen Moore and colleagues, enrolled 453 patients with platinum-resistant ovarian cancer who had high FRα expression and had received 1 to 3 prior lines of therapy. Patients were randomly assigned in a 1:1 ratio to receive mirvetuximab soravtansine at 6 mg/kg of adjusted ideal body weight every 3 weeks or the investigator's choice of chemotherapy, which could be paclitaxel, pegylated liposomal doxorubicin, or topotecan. The primary endpoint was PFS by investigator.

After a median follow-up of 13.1 months, the median PFS by investigator was significantly longer in the mirvetuximab group than in the chemotherapy group, at 5.62 vs 3.98 months, respectively (HR, 0.65; 95% CI, 0.52-0.81; *P*<.001). The overall response rate (ORR) by investigator was more than twice as high with mirvetuximab as with chemotherapy, at 42% vs 16%, respectively (odds ratio, 3.81; 95% CI, 2.44-5.94; *P*<.001). In addition, the median OS was significantly longer with mirvetuximab than with chemotherapy, at 16.46 vs 12.75 months, respectively (HR, 0.67; 95% CI, 0.50-0.89; *P*=.0046). In the bevacizumab-treated subset, median PFS continued to be significantly longer with mirvetuximab than chemotherapy, and there was a trend toward longer median OS with mirvetuximab. In the bevacizumab-naive subset, both median PFS and median OS were significantly longer with mirvetuximab than chemotherapy.

The AE profile of mirvetuximab was consistent with prior reports and included mostly ocular AEs and gastrointestinal AEs. Compared with chemotherapy, mirvetuximab was associated with lower rates of grade 3 or higher treatment-emergent AEs (TEAEs; 42% vs 54%), serious AEs (24% vs 33%), and discontinuations due to TEAEs (9% vs 16%).

Dr Moore concluded that "these data are practice-changing, and position mirvetuximab as the new standard of care" for patients with FRα-positive platinum-resistant ovarian cancer.

Moore KN, Angelergues A, Konecny GE, et al. Phase III MIRASOL (GOG 3045/ENGOT-ov55) study: initial report of mirvetuximab soravtansine vs. investigator's choice of chemotherapy in platinum-resistant, advanced high-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers with high folate receptor-alpha expression [ASCO abstract LBA5507]. *J Clin Oncol.* 2023;41(17)(suppl).

Commentary: The MIRASOL trial validated the effectiveness of mirvetuximab soravtansine, an ADC targeting FRα, vs standard of care for platinum-resistant ovarian cancer. The ORR was 42%, which was 3 times higher than expected for chemotherapy. The primary endpoint of PFS also was significantly improved. Particularly evident in the first assessment, mirvetuximab demonstrated its ability to prevent disease progression, which is common in the platinum-resistant ovarian cancer setting. Notably, the HRs for both PFS and OS were almost identical, suggesting that the

benefits observed in the study persisted across subsequent lines of therapy. These promising results are anticipated to pave the way for mirvetuximab's full regulatory approval.

Trastuzumab Deruxtecan Shows Activity in Multiple HER2+ Tumors, Including Gynecologic Cancers

The ADC trastuzumab deruxtecan, also known as T-DXd (Enhertu, Daiichi-Sankyo/AstraZeneca), is approved for use in human epidermal growth factor receptor 2–positive (HER2+) breast and gastric cancer. Now, the DESTINY-PanTumor02 study has demonstrated that T-DXd also shows activity in additional HER2+ solid tumors, including gynecologic cancers. This is the first tumor-agnostic global study of T-DXd in a broad range of HER2+ solid tumors.

The phase 2, open-label trial enrolled 267 patients with HER2+ locally advanced or metastatic cancer (primarily biliary tract, bladder, cervical, endometrial, ovarian, or pancreatic cancer) that progressed after 1 or more systemic treatment or where no other treatment options were available. HER2 positivity was defined as immunohistochemistry (IHC) 3+ or IHC 2+ by local or central testing. Patients received T-DXd at 5.4 mg/kg every 3 weeks. The primary endpoint was investigator-assessed ORR.

At a median follow-up of 9.7 months, Dr Funda Meric-Bernstam reported an ORR of 37.1% and a median duration of response (DOR) of 11.8 months. Among a subset of 75 patients with IHC 3+ expression, the ORR was 61.3% and the median DOR was 22.1 months. The ORR also was high among patients with gynecologic cancer, at 50.0% for cervical cancer, 57.5% for endometrial cancer, and 45.0% for ovarian cancer. The ORR was even higher among those with IHC 3+, at 75.0%, 84.6%, and 63.6%, respectively. Grade 3 or higher drug-related TEAEs occurred in 38.6% of patients. TEAEs led to dose discontinuation in 8.2% of patients, dose interruptions in 18.4%, and dose reductions in 18.7%. Drug-related interstitial lung disease or pneumonitis occurred in 20 patients (7.5%), including 6 patients with grade 1, 12 patients with grade 2, 1 patient with grade 3, and 1 patient with grade 5.

This trial is ongoing, with future results analyzing OS and PFS. "DESTINY-PanTumor02 shows T-DXd is a potential new treatment option for patients with HER2-expressing solid tumors," said Dr Meric-Bernstam.

Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-expressing solid tumors: DESTINY-PanTumor02 (DP-02) interim results [ASCO abstract LBA3000]. *J Clin Oncol*. 2023;41(17)(suppl).

Commentary: This highly anticipated trial is investigating an ADC that targets HER2 using the antibody trastuzumab. Trastuzumab has shown promising activity in breast cancer and endometrial cancer, but its use as a homing antibody for tumor expression of HER2, delivering the topoisomerase inhibitor deruxtecan, is also generating excitement. Despite small cohorts, the trial demonstrates high ORRs in gynecologic tumors, including cervical (50.0%), endometrial (57.5%), and ovarian (45.0%) cancers. This is important because previous studies had limited the use of trastuzumab in ovarian cancer owing to its low efficacy and the rarity of *HER2* amplification. The trial's findings reestablish HER2 as a potential target in ovarian cancer and pave the way for regulatory approval and confirmatory trials, similar to recent developments with mirvetuximab.

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