

OVARIAN CANCER IN FOCUS

Current Developments in the Management of Ovarian Cancer

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Update on Strategies for Platinum-Resistant Ovarian Cancer



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H&O How common are primary and secondary resistance to platinum therapy in ovarian cancer?

BP Primary resistance to platinum occurs in approximately 20% of patients with ovarian cancer. By contrast, secondary resistance eventually develops in nearly all patients with a recurrence of ovarian cancer.

H&O What causes resistance to platinum therapy?

BP Several mechanisms lead to platinum resistance: tumor heterogeneity, alteration in drug efflux, alteration in intracellular proteins that bind and sequester platinum, and altered expression of pro-survival or anti-survival proteins. Because the main target of platinum is DNA, sensitivity to platinum is modulated by the ability of cells to recognize and repair drug-induced DNA damage. We believe that one important mechanism of resistance to platinum therapy is caused by mutations that affect the ability of cells to repair their DNA. For example, patients with *BRCA* mutations become resistant to both poly(ADP-ribose) polymerase (PARP) inhibitors and platinum therapy; this resistance may be a consequence of reversion mutations or epigenetic reasons such as methylation.

H&O Is there a way to predict the patients in whom resistance will develop?

BP We currently are not able to identify the patients in

whom platinum resistance will develop, but this is an area of active investigation. However, we are able to identify reversion mutations associated with rucaparib (Rubraca, Clovis Oncology) resistance in post-progression tumor samples, as has been reported in ARIEL2. We hope to gain some insights as we study the interesting agents such as prexasertib (ACR-368) that are being developed to treat patients with platinum resistance.

H&O What is the prognosis for patients with platinum-resistant ovarian cancer?

BP Their prognosis is poor. The prognosis is especially poor for patients with primary platinum resistance, whose survival is approximately 9 to 12 months after diagnosis. Typical survival is longer for patients with secondary resistance, at approximately 22 months after the development of resistance.

H&O What options are available for managing patients with resistance to platinum therapy?

BP The standard therapy for patients with platinum-resistant disease used to be the sequential use of nonplatinum agents as monotherapy. The drugs that are most often used are pegylated liposomal doxorubicin, paclitaxel, gemcitabine, and topotecan; with all 4 of these drugs, response rates (10%-15%), progression-free survival (3-4 months), and overall survival (approximately 12 months) are similar. The choice of the treatment is based on prior therapies, the toxic effects and residual side effects of prior

therapies, underlying comorbidities, and availability. The new standard for patients with platinum-resistant disease in whom bevacizumab is not contraindicated is bevacizumab plus one of the following: pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan. The AURELIA study, which was published in 2014, showed that the response rate with combination therapy containing bevacizumab was significantly higher than the rate with previous monotherapy options, at 27.3%. Bevacizumab and weekly paclitaxel had the highest response rate of the regimens in AURELIA, at approximately 50%.

Fortunately, we have a new option for these patients that received accelerated approval on November 14, 2022: the novel antibody-drug conjugate mirvetuximab soravtansine (Elahere, ImmunoGen). In results from the phase 3 SORAYA trial, which Dr Ursula Matulonis presented at the Society of Gynecologic Oncology 2022 annual meeting, the confirmed investigator-assessed objective response rate after treatment with mirvetuximab soravtansine was 32.4% among 106 patients with platinum-resistant, high-grade serous epithelial ovarian, primary peritoneal, or fallopian tube cancer. This is the first antibody-drug conjugate to be approved for the treatment of ovarian cancer.

For patients with a prior response to platinum but the later development of secondary resistance, re-treating with platinum is still an option. In a 2003 study by Leitao and colleagues, re-treatment was effective only if no more than 3 intervening therapies had been used. Although previously reported, this use of platinum in the platinum-resistant setting is a newer approach to treatment. Furthermore, in the era of targeted therapy and PARP inhibitors, the duration of the platinum-free interval may not be a valuable criterion.

Finally, a reasonable option for patients with a poor performance status is supportive oncology care. We need to discuss quality of life with our patients and bring up the option of early access to palliative care when appropriate.

H&O What new treatments are being investigated for patients with platinum-resistant ovarian cancer?

BP We are investigating many newer therapies in this space, which represents a true unmet need. Options in combination with a taxane include batiraxcept (also called AVB-S6-500), tumor treating fields, afuresertib, and relacorilant. Batiraxcept is a novel Fc fusion protein that binds the GAS6 ligand and inhibits AXL signaling; a phase 3 trial called AXLerate-OC is investigating this agent in combination with weekly paclitaxel in patients with platinum-resistant recurrent ovarian cancer (NCT04729608). A single-arm phase 2 study called

INNOVATE-3 is looking at the use of tumor treating fields from Novocure in combination with paclitaxel in patients with recurrent, platinum-resistant ovarian cancer (NCT03940196). Tumor treating fields, in which electromagnetic waves are used to disrupt the mitotic spindle, have already received US Food and Drug Administration approval for use in glioblastoma. An ongoing study called PROTECTA-II is evaluating the pan-AKT inhibitor afuresertib in combination with paclitaxel (NCT04374630), and the ROSELLA trial is evaluating the selective glucocorticoid receptor modulator relacorilant in the platinum-resistant setting (NCT05257408).

There is still a dire need to find additional effective therapies for patients with platinum-resistant ovarian cancer, especially in the *CCNE1*-amplified population.

Additional antibody-drug conjugates that are in development for platinum-resistant ovarian cancer include upifitamab rilsodotin, STRO-002, and MORAb-202. Upifitamab rilsodotin, which targets the sodium-dependent phosphate transport protein NaPi2b, is being studied in a phase 1/2 trial in patients with platinum-resistant ovarian cancer or metastatic non-small cell lung cancer (NCT03319628). STRO-002, which targets folate receptor alpha (FR α), is being studied in combination with bevacizumab in a phase 1 trial of patients with epithelial ovarian cancer (NCT05200364). Finally, MORAb-202, which also targets FR α , is being evaluated in a phase 2 trial in patients with platinum-resistant high-grade serous ovarian, primary peritoneal, or fallopian tube cancer (NCT05613088).

Other interesting agents target replication stress. One example is the Wee1 inhibitor adavosertib. In a phase 2 trial published in *Lancet* in 2021 by Lheureux and colleagues, median progression-free survival was longer in women with recurrent platinum-resistant or platinum-refractory high-grade serous ovarian cancer who were randomly assigned to receive adavosertib plus gemcitabine than in those who received placebo plus gemcitabine, at 4.6 vs 3.0 months, respectively. More recently, a phase

2 trial called IGNITE has been looking at the use of single-agent adavosertib in patients with recurrent, platinum-resistant high-grade serous ovarian, fallopian tube, or primary peritoneal cancer. In results that Dr George Au-Yeung presented at the 2022 American Society of Clinical Oncology annual meeting, the overall response rate was 53% and the clinical benefit rate was 61% among 32 patients with tumors in which the cyclin E1 (*CCNE1*) gene was overexpressed and nonamplified. These were very impressive findings.

Although checkpoint immunotherapy strategies have not shown great promise in ovarian cancer, cellular therapy is an exciting novel approach. I look forward to seeing future studies of cellular therapies using engineered T-cell receptors.

H&O Is surgery ever an option, such as for palliation?

BP We typically do not offer surgery to patients with platinum-resistant disease, whose survival is limited and who usually have ascites and multifocal disease. The only patients to whom we would offer palliative surgery are those with isolated disease and those with disease that is causing a problem—such as a bowel obstruction—that can be addressed with surgery.

H&O What questions remain to be answered regarding effective treatment for patients with platinum-resistant ovarian cancer?

BP There is still a dire need to find additional effective therapies for patients with platinum-resistant ovarian cancer, especially in the *CCNE1*-amplified population. We also need to learn much more about the mechanisms of resistance, not just to platinum but to other therapies as

well, in this population. Finally, these patients often have poor performance status due to multiple lines of therapy, so it is especially important to identify agents that are easy to administer and have few adverse effects, so that these patients' quality of life can be preserved.

Disclosure

Dr Pothuri has consulted for, served on the advisory board of, or received personal fees from Arquer Diagnostics, AstraZeneca, Atossa Therapeutics, Clovis Oncology, Deciphera Pharmaceuticals, Eisai, Elevar Therapeutics, GlaxoSmithKline, I-Mab, Lilly, Merck, Mersana Therapeutics, Seagen, Sutro Biopharma, Tesaro, Toray, and Vanium Group. She has served as a local principal investigator for or has an institutional financial interest in AstraZeneca, Celgene, Clovis Oncology, Eisai, GlaxoSmithKline, ImmunoGen, Immunon, Incyte, Karyopharm Therapeutics, Merck, Mersana Therapeutics, Roche/Genentech, Seagen, Sutro Biopharma, Takeda, Tesaro, Toray, and VBL Therapeutics.

Suggested Readings

Au-Yeung G, Bressel M, Prall O, et al. IGNITE: a phase II signal-seeking trial of adavosertib targeting recurrent high-grade, serous ovarian cancer with cyclin E1 overexpression with and without gene amplification [ASCO abstract 5515]. *J Clin Oncol*. 2022;40(16)(suppl).

Leitao MM Jr, Hummer A, Dizon DS, et al. Platinum retreatment of platinum-resistant ovarian cancer after nonplatinum therapy. *Gynecol Oncol*. 2003;91(1):123-129.

Lheureux S, Cristea MC, Bruce JP, et al. Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomized, placebo-controlled, phase 2 trial. *Lancet*. 2021;397(10271):281-292.

Matulonis UA, Lorusso D, Oaknin A, et al. Efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression: results from the SORAYA study [SGO abstract 242]. *Gynecol Oncol*. 2022;166(1)(suppl).

Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308.