Sequencing of Treatments for Patients With Ovarian Cancer

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The challenge for advanced practitioners (APs) in oncology who treat women with ovarian cancer is that 80% of advanced ovarian cancers will recur during or after first-line treatment (Hanker et al., 2012). Thus, at JADPRO Live 2018, Laura Doherty, FNP-BC, AOCNP®, and Katina Robison, MD, both of the Warren Alpert Medical School of Brown University, Providence, Rhode Island, brought attendees up to date on the newest approaches to sequencing treatments in the management of patients with ovarian cancer.

Ovarian cancer—which comprises ovarian, fallopian tube, and primary peritoneal cancers—is a heterogeneous disease that includes different biologic behaviors at both the clinical and molecular levels. More than 90% of ovarian cancers are epithelial, with about 10% of ovarian cancers developing from germ cells or granulosa-theca cells.

Current treatment and maintenance modalities include bevacizumab (Avastin), rucaparib (Rubraca), niraparib (Zejula), olaparib (Lynparza), topotecan, altretamine (Hexalen), cisplatin, carboplatin, paclitaxel, doxorubicin, and gemcitabine (Figure 1). While some are useful as treatment, many of these have proved ineffective as maintenance therapy. For example, two studies demonstrated that additional taxane maintenance after response to taxane treatment did not alter overall survival (Copeland et al., 2017; Markman et al., 2003).

The most common time for initial recurrence is within the first 2 years of treatment (Copeland et al., 2017). "We see the next recurrences getting shorter, meaning that most women are on some type of treatment for the remainder of their lives," noted Dr. Robison. At most, 30% of women with any stage of ovarian cancer diagnosis are cured of this disease. "That is not good enough," she added.

UNDERSTANDING RECURRENCE

Approximately 25% of women diagnosed with ovarian cancer have a hereditary tendency for the disease, most strikingly an inherited genetic mutation in one of two genes: *BRCA1* or *BRCA2*. In addition, Lynch syndrome is most often associated with mutations in the *MLH1* or *MSH2* gene and accounts for between 10% and 15% of hereditary ovarian cancers (Singh & Resnick, 2017). Altogether, at least 16 genes are known to

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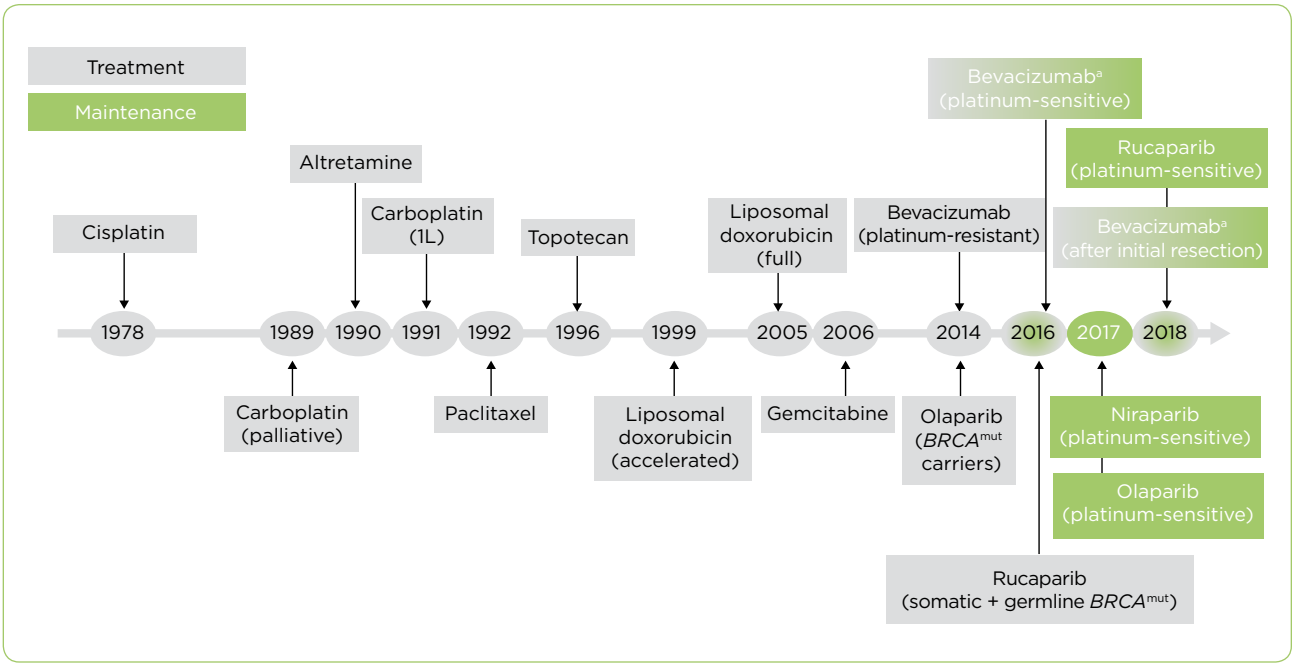

Figure 1. Landmark FDA approvals in ovarian cancer therapy. L = line; mut = mutation. Information from Kelland (2007); US Food and Drug Administration (2018).
[a]In combination with carboplatin and paclitaxel, followed by bevacizumab alone.

be involved in the mechanism of hereditary ovarian tumorigenesis, and several other mutations remain unknown and cannot be detected by specific tests (Toss et al., 2015). The impact of genetic mutations in this disease points to genetic testing for all patients, Dr. Robison emphasized.

According to clinical behavior and molecular genetic abnormalities, ovarian cancer can be classified into two different types (Kurman, 2013). Type I tumors include low-grade serous carcinomas, borderline serous tumors, low-grade endometrioids, and mucinous and clear cell carcinomas. These types of tumors are relatively genetically stable, and the most frequent mutations involve *KRAS, BRAF, ERBB2, PTEN, PIK3CA*, b-catenin gene (*CTNNB1*), *ARID1A*, and *PPP2R1A*. Type II ovarian cancers include high-grade serous carcinomas, carcinosarcomas, and undifferentiated cancers. Type II tumors, which comprise almost 70% of all epithelial tumors, are aggressive and present in advanced stages (Toss et al., 2015).

THE BIOLOGY BEHIND GENE MUTATIONS

"Whenever you have a problem with gene mutations, either something is missing or something is deleted," Dr. Robison indicated. "Then our own cells typically have something in them that makes repairs. When things go wrong, repairs do not occur, and now damaged cells continue to survive and proliferate."

One of the key aspects regarding gene mutations is heterozygosity. This is usually defined as the possession of two different alleles of a particular gene or genes by an individual. Loss of heterozygosity (LOH) is a cross-chromosomal event that results in the loss of the entire gene and the surrounding chromosomal region. As Dr. Robison explained, "Most of us have two sets of genes, and we inherit them. It's like having a spare key for your house; you have a backup in case something goes wrong."

Associated with heterozygosity are the terms LOH-low and LOH-high. "When you see the term LOH-low, that means you have both sets," she said. "When you see the term LOH-high, you've lost that spare key; you don't have both sets and you don't have a backup."

INITIAL AND SUBSEQUENT THERAPY

The mainstay of initial drug treatment for ovarian cancer remains paclitaxel and carboplatin, which

were approved by the US Food and Drug Administration (FDA) nearly 30 years ago. In 2018, the FDA approved bevacizumab added to adjuvant chemotherapy with carboplatin and paclitaxel, followed by a course of bevacizumab alone as maintenance therapy.

Patients with recurrent ovarian cancer have experienced a period of "remission" following initial surgery and first-line systemic therapy, but they subsequently develop cancer recurrence. Both the effectiveness and type of therapy for recurrence depend on the first-line systemic therapy received, the length of time since finishing treatment, and the extent of recurrent cancer. For recurrence more than 6 months after first-line chemotherapy, the identical first-line regimen may be used again. Patients who recur within 6 months from first-line chemotherapy seem less likely to benefit from the same anticancer drugs.

MAINTENANCE THERAPY

Women who achieve a response to initial adjuvant chemotherapy may be candidates for maintenance therapy, the aim being to induce a lasting remission or prolong the disease-free interval before recurrence. These approaches result in clinical remission for the vast majority of patients (DiSilvestro & Secord, 2018).

When selecting a drug for maintenance, APs in oncology should consider the effectiveness, adverse effects, and convenience of the regimen. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) recommend maintenance therapy as an option for patients with a response to platinum-based chemotherapy (NCCN, 2018). With maintenance therapy, oral medications are preferable. "The treatment you select should be something with which women can go out and live their lives normally and can ensure their quality of life," emphasized Dr. Robison.

Bevacizumab is a potential choice for front-line maintenance, although olaparib was approved for front-line maintenance for patients with *BRCA* mutations. The 2018 NCCN Guidelines also suggest the tyrosine kinase inhibitor pazopanib (Votrient) as an add-on to postremission therapy (category 2B ranking) for patients with stages II to IV disease who achieved a complete clinical remission after first-line therapy (DiSilvestro & Secord, 2018). Thus, women who have not received bevacizumab as upfront treatment may be prescribed pazopanib. The vascular endothelial growth factor inhibitor cediranib may also offer a benefit in terms of progression-free survival (DiSilvestro & Secord, 2018).

It is important to consider the timing of dosing when starting maintenance. Bevacizumab is typically started with 3-week interval dosing. Therefore, for the patient who achieved remission with cytotoxic chemotherapy and bevacizumab, the cytotoxic agents are stopped and bevacizumab infusion is continued every 3 weeks. Platelet counts of 75,000/mm^3 and an absolute neutrophil count of 1,000/mm^3 are parameters for starting bevacizumab maintenance therapy (Garcia & Singh, 2013).

Upswing in FDA-Approved Maintenance Therapies

In the past 2 years, four drugs have been approved by the FDA for maintenance therapy. "What's different? What's changing?" posed Dr. Robison. "We're understanding the genetics of ovarian cancer and can now determine what it is in both the patient and in the tumor that makes ovarian cancers tick."

For older agents, the clinical benefit from maintenance therapy never became apparent, although 12 months of a taxane did provide some clinical benefit. In GOG 212, an improvement in progression-free survival was achieved, however, grades 3 and 4 adverse events were also increased (Ozols, 2016).

An important advance in maintenance therapy came with the emergence of the poly(ADP-ribose) polymerase (PARP) inhibitors. These agents, olaparib, rucaparib, and niraparib, have demonstrated in various clinical studies the ability to improve progression-free survival (Table 1).

Olaparib is indicated for the upfront maintenance treatment of patients with *BRCA*-mutated advanced ovarian cancer (SOLO-1), the maintenance treatment of patients with recurrent ovarian cancer (SOLO-2), and the treatment of patients with *BRCA*-mutated advanced ovarian cancer who have been treated with three or

Table 1. Summary of FDA-Approved Maintenance Therapies

Agent	Current label	Registrational trial	Label dosing and scheduling
Bevacizumab	In combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by monotherapy for recurrent ovarian cancer with response to platinum-based chemotherapy	OCEANS (phase III) GOG-0213 (phase III)	IV infusion 15 mg/kg q3wk
	In combination with carboplatin and paclitaxel, followed by monotherapy for stage III/IV ovarian cancer following initial surgical resection	GOG-0218 (phase III)	
Olaparib	Recurrence maintenance 2+ lines	Study 19 (phase II) SOLO-2 (phase III)	300 mg (two 150-mg tablets); po bid
Niraparib	Recurrence maintenance 2+ lines	NOVA (phase III)	300 mg (three 100-mg capsules); po daily
Rucaparib	Recurrence maintenance 2+ lines	ARIEL 3 (phase III)	600 mg (two 300-mg tablets); po bid

Note. Information from AstraZeneca Pharmaceuticals (2018); Clovis Oncology (2018); Genentech, Inc. (2018); Roche (2016); Tesaro, Inc. (2018).

more prior lines of chemotherapy (Study 42). The SOLO-1 trial was a randomized, double-blind, placebo-controlled, multicenter trial that compared the efficacy of olaparib with placebo in patients with *BRCA*-mutated newly diagnosed advanced ovarian cancer (Moore et al., 2018). The primary efficacy outcome was progression-free survival, which has not yet been reached in the olaparib arm and was 13.8 months in the placebo arm (hazard ratio, 0.30; 95% confidence interval = 0.23–0.41; $p < .0001$; Moore et al., 2018). The SOLO-2 trial was a double-blind placebo-controlled trial of 295 platinum-sensitive, relapsed ovarian cancer patients with a *BRCA*1/2 mutation. Progression-free survival was 19.1 months with olaparib and 5.4 months with placebo (Pujade-Lauraine et al., 2017).

Rucaparib is indicated for treatment in patients with ovarian cancer and a germline or somatic *BRCA* mutation and who have received at least two prior lines of chemotherapy. It was approved based on data from ARIEL3, a randomized, placebo-controlled, double-blind study of 561 patients (Coleman et al., 2017). The median progression-free survival was 8.3 months for patients receiving rucaparib and 5.5 months for patients receiving placebo; this increased to 16 months in patients with *BRCA* mutations.

Niraparib is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had a complete or partial response to platinum-based chemotherapy. Its approval was based on data from the NOVA trial, a double-blind, placebo-controlled study of 553 patients who were treated within 8 weeks of the last therapy (Mirza et al., 2016).

CHOOSING THE APPROPRIATE PARPi

"Multiple factors can affect which PARP inhibitor is selected, from clinical trial results to other drugs the patient is taking, to dosing schedules, to insurance coverage," Ms. Doherty noted. She presented information summarizing clinical trial results, FDA approvals and dosing, homologous recombination deficiency results (where applicable), drug-drug interactions, and which enzymes the various PARP inhibitors use to metabolize the drugs, as this can have a corresponding effect on certain cell transporters (Ween, Armstrong, Oehler, & Ricciardelli, 2015).

The challenge for clinicians, Ms. Doherty said, is choosing a PARP inhibitor that has associated toxicities that do not exacerbate the toxicities that patients had on their prior treatment (i.e., anemia, thrombocytopenia).

ADVERSE EVENTS ASSOCIATED WITH PARP INHIBITORS

As with other ovarian cancer therapies, adverse events are observed with PARP inhibitors. Olaparib is associated with anemia, decreased appetite, nausea and vomiting, diarrhea, fatigue, and a decrease in hemoglobin (AstraZeneca Pharmaceuticals, 2018). Rucaparib is associated with anemia, thrombocytopenia, decreased appetite, nausea and vomiting, diarrhea, constipation, fatigue, rash, and a decrease in hemoglobin (Clovis Oncology, 2018). Niraparib has its own associated adverse effects, which include anemia, thrombocytopenia, neutropenia, decreased appetite, nausea and vomiting, diarrhea, constipation, fatigue, rash, hypertension, and a decrease in hemoglobin (Ledermann et al., 2016; Tesaro, Inc., 2018). All three can lead to myelodysplastic syndrome and acute myeloid leukemia. "It is vital, therefore, for advanced practitioners to monitor patients [who are on these agents] for both of these conditions," Ms. Doherty said.

The following guidelines should be followed when treating women with PARP inhibitors:

- Do not start PARP inhibitors until patients have recovered from hematologic toxicity from prior therapy
- For prolonged hematologic toxicity, interrupt treatment and monitor complete blood cell (CBC) counts weekly until recovery
- If CBC counts do not recover in 4 weeks, refer the patient to a hematologist for further investigation, including bone marrow analysis and blood sampling for cytogenetics
- If myelodysplastic syndromes/acute myeloid leukemia is confirmed, discontinue the PARP inhibitor.

Strategies for Managing PARP Inhibitor–Related Side Effects

Ms. Doherty discussed the management of side effects related to PARP inhibitors (Table 2). For gastrointestinal side effects, simple measures can help, such as taking the drug with food or immediately before going to bed. For nausea and vomiting, prophylactic antiemetics taken 30 to 60 minutes prior to the drug can help, especially in the initial weeks of therapy (O'Cearbhaill, 2018). "We send patients home with at least two different kinds of antiemetics, and they're counseled to call us if they are nauseous and vomiting," she said.

In patients prone to constipation, low-dose olanzapine (Zyprexa; 2.5–5.0 mg) can be used as an alternative to ondansetron but may cause sedation, she cautioned. Fosaprepitant (Emend) should be avoided in patients taking olaparib, since inhibition of CYP3A may increase plasma concentrations of the PARP inhibitor. Lorazepam may be helpful for anticipatory nausea. With rucaparib, the gastrointestinal side effects are often most pronounced in the first weeks of therapy and can be mitigated by starting rucaparib at a lower dose—300 mg instead of 600 mg—twice daily for the first 3 to 4 weeks.

When patients report bouts of fatigue, APs should rule out other contributing factors, such as disease-related fatigue, depression, insomnia, anemia, and sedation from concomitant medications. Patients should self-monitor fatigue levels and be encouraged to remain active. Pharmacologic interventions, such as the treatment of underlying pain, depression, or insomnia, may improve energy levels, and methylphenidate can be considered. For symptomatic anemia, red blood cell transfusions may be required. "It is also recommended to manage any underlying vitamin and/or iron deficiencies," Ms. Doherty added.

Anemia and leukopenia are common adverse events with all three PARP inhibitors (olaparib, rucaparib, and niraparib). Before initiating these drugs for maintenance, patients may need time to recover from any hematologic toxicity caused by previous chemotherapy. "In addition, with niraparib, there is also a risk of profound thrombocytopenia, notably in the first 4 to 6 weeks of therapy," Ms. Doherty warned. "This would necessitate initiating weekly CBC counts."

Bleeding precautions should be carefully reviewed with patients receiving niraparib. They should know how to recognize thrombocytopenia and be instructed to withhold niraparib and seek medical attention if signs appear.

Rucaparib is often associated with a rise in transaminase levels; this usually occurs within the first 4 months of therapy and is not indicative of liver dysfunction. The transaminase increases are not usually associated with hyperbilirubinemia and generally resolve over time.

Table 2. Strategies for Managing Adverse Events of PARP Inhibitors

Adverse event	Characteristics	Treatments
Diarrhea[a]	• Increase in number of stools per day over baseline • Increase in ostomy output	• Hydration and electrolyte replacement (oral or IV fluids) • Dietary modifications • Antidiarrheal, antibiotic, and/or anticholinergic medication • Complicated diarrhea may require hospital admission; consider somatostatin analog
Nausea and vomiting[b]	• Vomiting results from stimulation of a multistep reflex pathway • Nausea can be acute or delayed	• Oral antiemetic prophylaxis
Cancer-related fatigue[c]	• Distressing and persistent sense of tiredness or exhaustion • Not proportional to recent activity • Interferes with usual functioning	• Management of concurrent symptoms and treatable contributing factors • Nonpharmacologic interventions (e.g., physical activity, massage therapy, psychosocial interventions, and energy conservation) • Pharmacologic management

Note. [a]Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Palliative Care V.1.2018. © National Comprehensive Cancer Network, Inc. 2018. All rights reserved. Accessed June 27, 2018. To view the most recent and complete version of the guideline, go online to NCCN.org.
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All PARP inhibitors, particularly olaparib, have been associated with nasopharyngitis. Use of a humidifier at night, decongestants, and throat lozenges can be recommended to patients. In addition, both olaparib and rucaparib have been associated with a rash, especially photosensitivity, and patients should be counseled to reduce sun exposure and wear sunblock, she advised.

Advanced practitioners should also consider the potential interactions of PARP inhibitors with concomitant medications. Since olaparib is metabolized by CYP3A, patients should be given a list of common CYP3A inhibitors and be told to avoid strong or moderate inhibitors or inducers of this enzyme. If coadministration of a PARP inhibitor with a strong CYP3A inhibitor cannot be avoided, then olaparib should be dose reduced from 300 mg to 100 mg twice daily. Similarly, patients should be advised to avoid grapefruit and Seville oranges, since they may inhibit intestinal CYP3A4, and therefore interfere with the metabolism of olaparib. It also should be noted that absorption of olaparib may be slowed when taken with a high-fat meal, but this does not appear to decrease its efficacy.

Rucaparib is predominantly metabolized via CYP2D6 and minor pathways, including CYP1A2 and CYP3A4, and may increase systemic levels of substrates of these enzymes, which could result in toxicity.

PARP INHIBITOR COMBINATIONS

Multiple trials are evaluating PARP inhibitors with immune checkpoint inhibitors. Trials are also underway studying the class with bevacizumab alone, bevacizumab plus immunotherapy, and even triplet therapy with PARP inhibitors, immunotherapy, and bevacizumab. For example, a phase II study is evaluating the combination of niraparib and bevacizumab in the maintenance setting for patients with advanced ovarian cancer. Additionally, results from the phase II MEDIOLA trial, which were presented at the 2018 Society of Gynecologic Oncology Annual Meeting, showed

that combination therapy with olaparib and durvalumab induced objective responses in more than 70% of patients with relapsed, platinum-sensitive, *BRCA*-mutated ovarian cancer (Drew et al., 2018).

In the recurrent, platinum-sensitive setting, a combination of olaparib and the antivascular agent cediranib is being investigated as an alternative to platinum-based chemotherapy (ClinicalTrials.gov identifier NCT02446600). Ongoing trials may soon help validate the concept of using PARP inhibitors as part of primary therapy (ClinicalTrials.gov identifier NCT02470585) or in the front-line maintenance setting (ClinicalTrials.gov identifier NCT02655016).

Disclosure

Ms. Doherty and Dr. Robison have no conflicts of interest to disclose.

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