Poly (ADP-ribose) Polymerase Inhibitors in the Management of Ovarian Cancer: A Drug Class Review

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ABSTRACT

Objective: To review the pharmacology, safety, efficacy, and role of poly adenosine diphosphate [ADP]-ribose polymerase (PARP) inhibitors in the treatment and maintenance of relapsed, advanced ovarian cancer.

Summary: A total of 3 phase 2 trials and 2 phase 3 trials were reviewed that evaluated the safety and efficacy of oral niraparib, olaparib, and rucaparib in patients with ovarian cancer. Progression-free survival (PFS) was evaluated in the maintenance setting for niraparib and olaparib, resulting in a PFS of 21.0 months and 8.4 months, respectively. Olaparib and rucaparib were evaluated in the treatment setting, producing a PFS of 9.4 months and 12.8 months, respectively. PFS was higher in patients with *BRCA* mutation when compared to patients with *BRCA* wild-type in both the maintenance and treatment setting across all trials evaluated. Niraparib, olaparib, and rucaparib were found to be relatively well tolerated in clinical trials, with the most common adverse events being anemia, fatigue, and nausea.

Conclusion: PARP inhibitors appear to be a safe and effective new option in the treatment and maintenance of relapsed, advanced *BRCA1/2* mutant ovarian cancer. This drug class will likely have an expanding role in ovarian cancer as further trial results are published.

Keywords: PARP, inhibitors, review, ovarian, niraparib, olaparib, rucaparib

INTRODUCTION

Epithelial ovarian cancer is the leading cause of death due to a gynecological malignancy in the United States.[1] In 2017, an estimated 22,440 cases of ovarian cancer were expected to be diagnosed with approximately 14,000 deaths. Ovarian cancer carries a relatively poor prognosis because approximately 75% of all new cases present with stage 3 or 4 disease.[2] Epithelial ovarian cancer, fallopian tube carcinoma, and primary peritoneal carcinoma are considered to be distinct entities of different origins; however, they are managed in a similar manner. The diagnosis of ovarian cancer includes fallopian tube and primary peritoneal carcinoma. Although there are a number of different pathologic entities that comprise ovarian cancer, epithelial adenocarcinoma is the most common type. Epithelial adenocarcinoma is made up of 4 unique histopathological subtypes: serous (most common), endometrioid, clear-cell, and mucinous.[3]

Ovarian cancer typically occurs in postmenopausal women with a median age of 63 at diagnosis.[4] Most cases of ovarian cancer are idiopathic and occur sporadically.[5] Sporadic cases comprise approximately 85% to 90% of all ovarian cancer in the United States. Familial and hereditary factors have been identified in the development of some cases of ovarian cancer, with approximately 10% to 15% of ovarian cancer cases associated with inherited mutations of the *BRCA1* and *BRCA2* genes.[3] These tumor suppressor genes are responsible for encoding proteins that correct DNA double-strand breaks, which may occur secondary to environmental exposures or damage that occurs during the homologous recombination of DNA.[6] *BRCA1/2* mutations can cause a genomic loss of heterozygosity (LOH), which further leads to defective DNA repair and subsequent tumorigenesis.[7] LOH is a genetic event that occurs when there is the presence of one abnormal and one normal allele at a particular locus. When LOH involves loss of the normal allele, a cell is created that is more likely to demonstrate unregulated malignant cell growth if the affected gene is a tumor suppressor gene such as *BRCA1/2*.

A number of patient-specific factors have been identified that increase the risk of developing ovarian cancer. Late menopause, early menarche, and nulliparity have been found to increase the risk of developing ovarian cancer due to the increased number of ovulatory cycles.[8] Although an identifiable genetic predisposition, such as *BRCA1/2* mutation, is present in only a small subset of patients, a strong family history of ovarian or breast cancer is the most important risk factor in the development of ovarian cancer.[3] Women with a *BRCA1* or *BRCA2* mutation have a 39% to 46% or 12% to 20% risk of developing ovarian cancer, respectively. Conversely, patient-specific factors associated with a decreased risk of developing ovarian cancer include ovulatory cycle count reduction through pregnancy, prolonged use of oral contraceptives, tubal ligation, and prophylactic oophorectomy or salpingectomy.[8]

Patients with ovarian cancer often experience a constellation of symptoms known as the Ovarian Cancer Symptom Index, which include bloating, pelvic or abdominal pain, difficulty eating or feeling of fullness, and urinary frequency or urgency.[9] Women should seek medical attention by a gynecologist if they experience this constellation of symptoms for 12 or more days out of a month for at least 2 consecutive months.[8] Gastrointestinal symptoms such as dyspepsia, nausea, vomiting, and early satiety often manifest in the setting of advanced ovarian cancer.[9] Additionally, abdominal distention may occur with the presence of ascites and abdominal pain, and alterations in bowel or bladder function can occur with the presence of a pelvic mass.

An initial primary treatment modality for suspected ovarian

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Disclosure: The authors report no commercial or financial interests in regard to this article.

cancer is surgical staging and cytoreduction.[10] Surgical staging and debulking may consist of total abdominal hysterectomy and bilateral salpingo-oophorectomy. Following surgery, adjuvant systemic chemotherapy given for curative intent may be considered for some patients depending on the stage of disease. Adjuvant chemotherapy for ovarian cancer typically consists of platinum-based doublet regimens, such as carboplatin-paclitaxel or carboplatin-docetaxel.[11,12] In the setting of advanced disease, first-line treatment with platinum-based chemotherapy can boast a median PFS of 16 to 21 months, although approximately 70% of all patients with ovarian cancer will have a relapse in their disease.[2,12,13] Also, with each subsequent relapse, the duration of remission is likely to be shorter than the previous remission.[14] Upon recurrence of disease, the goal of treatment is no longer curative, but instead becomes palliative, aimed at improving disease-related symptoms, prolonging survival, and trying to improve quality of life.

The choice of treatment for relapsed ovarian cancer is often determined by the response to the first-line chemotherapy given. For patients with platinum-sensitive disease (defined as a disease-free interval of greater than 6 months following platinum-based therapy), retreatment with platinum-based combination chemotherapy is a preferred option for patients who can tolerate it.[3] For patients with platinum-resistant disease or subsequent relapse, the preferred treatment is monotherapy with a non-platinum agent. Options include liposomal doxorubicin, topotecan, oral etoposide, or a taxane.[15] For patients unable to tolerate cytotoxic chemotherapy, hormonal therapies such as tamoxifen and aromatase inhibitors are potential treatment options for patients whose tumors are positive for estrogen receptors.[16,17]

For patients harboring a *BRCA1/2* mutation, medications targeting PARP enzymes may be an effective therapeutic option.[18] PARP is a family of enzymes that mediate DNA repair mechanisms that parallel *BRCA1/2* genes. PARP inhibition in the setting of *BRCA1/2* mutations can cause tumor cells to lose 2 important DNA repair mechanisms leading to DNA damage, apoptosis, and cell death. The purpose of this article is to review the pharmacology, clinical efficacy, safety, and monitoring of the currently available PARP inhibitors indicated for the treatment of ovarian cancer.

PARP INHIBITORS

The Food and Drug Administration (FDA) has approved 3 PARP inhibitors as monotherapy for the treatment of relapsed ovarian cancer: niraparib (Zejula, Tesaro), olaparib (Lynparz, AstraZeneca), and rucaparib (Rubraca, Clovis Oncology). Niraparib was FDA-approved in May 2017.[19] Olaparib was first approved in 2014 under accelerated approval, and in August 2017, it was granted full FDA approval for ovarian cancer as well as for *BRCA*-mutated breast cancer.[20,21] Rucaparib was approved in 2016 under accelerated approval.[22] Although all are approved for the management of relapsed ovarian cancer, the 3 agents have different specific FDA-approved indications (Table 1).

PHARMACOLOGY

Cellular DNA maintenance and DNA repair mechanisms include single-strand break (SSB) and double-strand break (DSB) repair pathways that help to maintain genomic stability. The *BRCA1/2* genes produce proteins involved in DSB repair; therefore, *BRCA1/2* mutations force the cell to utilize alternative cellular genome repair pathways such as SSB repair.[7] PARP enzymes are involved in the rate-limiting, base-excision step of the SSB repair process. In the setting of *BRCA1/2* mutations, PARP inhibition can be cytotoxic to *BCRA1/2*-deficient cells while preferentially avoiding damage to unmutated cells.[23,24] *BRCA1/2* mutation status combined with 90% of high-grade serous ovarian cancer harboring p53 mutations provides a setting for inducing synthetic lethality.[25] Synthetic lethality refers to producing a lethal state through the cumulative effects of mutations in 2 or more genes.[26] Clonal expansion of malignant tissue harboring *BRCA1/2* mutations thus produces a fortuitous environment for the setting of PARP inhibitor–induced synthetic lethality, while simultaneously producing an inherent tumor-specific targeting effect. Exploitation of this mechanism ultimately leads to selective cell death and collective tumor degradation.

CLINICAL EFFICACY

Niraparib

ENGOT-OV16/NOVA is a randomized, placebo-controlled, phase 3 trial evaluating the safety and efficacy of niraparib as maintenance therapy in patients with relapsed, platinum-sensitive ovarian cancer.[27] Patients were enrolled into 2 different cohorts based on either the presence or absence of a germline *BRCA* mutation. Within 8 weeks of their last dose of platinum-based chemotherapy, patients were randomized to receive maintenance therapy with either placebo or niraparib 300 mg orally once daily until disease progression or intolerable toxicity. The primary endpoint was PFS; secondary endpoints included chemotherapy-free interval, time to first and second subsequent therapy, and overall survival (OS).

Of the 546 patients who were enrolled and received treatment, 201 had a germline *BRCA* mutation and 345 had no germline *BRCA* mutation. Patients receiving niraparib experienced a statistically significant improvement in PFS compared to those receiving placebo ($P < 0.001$). In the germline *BRCA*-mutant group, the median PFS in the niraparib and placebo arms were 21.0 months and 5.5 months, respectively (hazard ratio [HR], 0.27; 95% confidence interval [CI], 0.17–0.41). The median chemotherapy-free interval was significantly longer with niraparib compared to placebo in patients with a germline *BRCA* mutation (22.8 versus 9.4 months, [HR, 0.26; 95% CI, 0.17–0.41; $P < 0.001$]) and without a germline *BRCA* mutation (12.7 versus 8.6 months, [HR, 0.50; 95% CI, 0.037–0.67; $P < 0.001$]). Compared to placebo, niraparib also significantly prolonged the time until first subsequent treatment in patients with both a germline *BRCA* mutation (21.0 versus 8.4 months, [HR, 0.31; 95% CI, 0.21–0.48; $P < 0.001$]) and in those without (11.8 versus 7.2 months, [HR, 0.55; 95% CI, 0.41–0.72; $P < 0.001$]).

The authors of the study concluded that compared to placebo, niraparib significantly prolonged the median PFS in patients with relapsed, platinum-sensitive ovarian cancer when administered as maintenance therapy following a platinum-based chemotherapy regimen, and it was this trial that led to the FDA approval of niraparib as maintenance therapy in this setting.

Olaparib

Olaparib was evaluated in a prospective, multicenter, nonrandomized phase 2 study in the treatment of patients with germline *BRCA1/2* mutations and advanced, recurrent ovarian cancer that had been treated with at least 3 prior lines of chemotherapy.[28] Patients received olaparib 400-mg capsules orally twice daily. Also, patients included in this study were either platinum-resistant or -sensitive but not considered suitable for further platinum-based chemotherapy. Endpoints evaluated in this study included overall response rate (ORR), duration of response, and PFS. A total of 137 patients were included in the analysis of the data for this study. The ORR observed was 34% of patients; 2% had a complete response (CR) and 32% had a partial response (PR) based on Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 criteria.[29] The median PFS in those who were platinum-sensitive and platinum-resistant was 9.4 months and 5.5 months, respectively. The median duration of treatment was 158 days. The authors concluded that olaparib produced antitumor activity in patients with a germline *BRCA1/2* mutation and advanced ovarian cancer that had been treated with 3 or more prior lines of chemotherapy.

Olaparib was evaluated as maintenance therapy in relapsed, platinum-sensitive ovarian cancer in a randomized, double-blind, placebo-controlled phase 2 study, referred to as Study 19.[30] Patients were randomized within 8 weeks of their last dose of platinum-based chemotherapy to either olaparib 400 mg capsules orally twice daily or placebo. The primary endpoint was PFS. Patients had to have received at least 2 prior lines of therapy with platinum-based chemotherapy to be eligible for the study. A total of 264 patients received treatment in this

Table 1 PARP Inhibitor Overview

Generic (Brand)	Niraparib (Zejula)	Olaparib (Lynparza)	Rucaparib (Rubraca)
Manufacturer	Tesaro	AstraZeneca	Clovis Oncology
Cost (AWP)	100-mg capsules (90): $15,930.00 USD	50-mg capsules (112): $3,888.20 USD 100-mg tablets (60): $6,943.23 USD 150-mg tablets (120): $13,886.46 USD	200-mg tablets (60): $8,821.20 USD 250-mg tablets (60): $8,821.20 USD 300-mg tablets (60): $8,821.20 USD
FDA-Approved Indications	Maintenance treatment of recurrent ovarian cancer in patients who are in a complete or partial response to platinum-based chemotherapy	(Capsules & Tablets) Germline *BRCA*-mutated advanced ovarian cancer in patients who have received 3 or more lines of chemotherapy (Tablets) Maintenance treatment of adult patients with recurrent, epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum therapy, regardless of *BRCA* status	Germline and/or somatic *BRCA*-mutated advanced ovarian cancer in patients who have received two or more prior lines of chemotherapy
Elimination Half-Life	36 hours	Capsules: 11.9 +/- 4.8 hours Tablets: 14.9 +/- 8.2 hours	17–19 hours
Metabolism	Carboxylesterases to an inactive metabolite, which subsequently undergoes glucuronidation	Primarily hepatic: via oxidative metabolism (CYP3A4: major), minor glucuronide and sulfate conjugation	Primarily hepatic: via oxidative metabolism (CYP2D6: major) (CYP1A2/CYP3A4: minor)
Elimination	Urine (~48%) Feces (~39%)	Urine (~44%) Feces (~42%)	Not specified by manufacturer
Precautions	• Hypertension and hypertensive crisis have been reported. Antihypertensives and niraparib dose adjustment may be indicated. • Patients may experience bone marrow suppression, GI toxicity, and CNS fatigue. • Increased risk for secondary AML/MDS (rare)	• Rare cases of pneumonitis have occurred, some fatal. • Major CYP3A4 substrate, provides increased potential for drug interactions • Monitor for increased toxicity in patients with renal impairment. • Patients may experience bone marrow suppression, GI toxicity, and CNS fatigue. • Increased risk for secondary AML/MDS (rare)	• High-fat meal affects drug exposure: C_{max} ↑20%, AUC ↑ 38%, and T_{max} delayed by 2.5 hours. Still approved to take with or without regard to food • Patients may experience bone marrow suppression, GI toxicity, and CNS fatigue. • Increased risk for secondary AML/MDS (rare)

AML = acute myeloid leukemia; AUC = area under the curve; AWP = average wholesale price; C_{max} = maximum concentration; CNS = central nervous system; GI = gastrointestinal; MDS = myelodysplastic syndrome; T_{max} = time to maximum concentration; USD = U.S. dollar. RED BOOK prices effective August 15, 2018.

study: 136 received olaparib and 128 received placebo. Only 22.8% and 21.7% of patients in the olaparib and placebo groups, respectively, had a known germline *BRCA* mutation. The median PFS in the olaparib and placebo groups was 8.4 months and 4.8 months, respectively (HR, 0.35; 95% CI, 0.25–0.95; $P < 0.001$). An updated analysis to OS was recently published and median OS was 29.8 months with olaparib and 27.8 months with placebo, which did not meet statistical significance.[31] The authors concluded that olaparib maintenance therapy following platinum-based chemotherapy improved PFS in patients with relapsed, platinum-sensitive ovarian cancer; however, olaparib did not meet statistical significance in improving OS compared to placebo.

A new tablet formulation of olaparib was evaluated for efficacy as maintenance therapy in the international, multicenter, double-blind, randomized, placebo-controlled, phase 3 SOLO-2 trial in the treatment of platinum-sensitive, relapsed ovarian cancer patients with a germline *BRCA1/2* mutation who had received at least two lines of previous chemotherapy.[32] A total of 295 patients were stratified by response to previous platinum chemotherapy (complete versus partial) and length of platinum-free interval (6 to 12 months versus ≥ 12 months) and randomly assigned 2:1 to olaparib 300-mg tablets twice daily or matching placebo until unacceptable toxicity or disease progression. The primary endpoint assessed was PFS; OS will be assessed once the data matures. The median PFS was significantly longer at 19.1 months in the olaparib arm compared to 5.5 months in the placebo arm (HR, 0.3; 95% CI, 0.22–0.41; $P < 0.0001$). The authors concluded that olaparib maintenance provided a significant PFS improvement in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation.

Based on ORR and duration of response as demonstrated in Domcheck et al., olaparib was approved in 2014 under accelerated approval for monotherapy in patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy.[20, 28] Continued approval was to be contingent upon verification and description of clinical benefit in confirmatory trials. Results from the 2017 SOLO-2 randomized trial along with the 2016 updated analysis of Study 19 support the new FDA approval of olaparib tablets for maintenance treatment of adult patients with recurrent epithelial ovarian cancer, who are in complete or partial response to platinum-based chemotherapy and also support the conversion from accelerated approval to full approval of olaparib capsules and tablets for the original indication.[21,31,32] Olaparib capsules are scheduled to be phased out of the U.S. market and will only be available through the Lynparza Specialty Pharmacy Network.[21]

Rucaparib

The safety and efficacy of rucaparib were evaluated in the ARIEL2 study, an international, multicenter, 2-part, open-label, phase 2 trial in patients with relapsed, platinum-sensitive ovarian cancer.[33] Rucaparib 600 mg orally twice daily was administered continuously until disease progression. A total of 206 patients were enrolled and divided into 3 distinct patient subgroups: *BRCA1/2* mutant; *BRCA* wild-type and LOH high; and *BRCA* wild-type and LOH low. Patients with either a germline or somatic *BRCA* mutation were included. The primary efficacy outcome was PFS. Secondary outcomes included ORR, duration of response, and safety.

The primary endpoint of median PFS was 12.8 months, 5.7 months, and 5.2 months in the *BRCA*-mutant group, LOH high group, and LOH low group, respectively. This difference in median PFS was found to be statistically significantly longer in the *BRCA*-mutant group (HR, 0.27; 95% CI, 0.16–0.44; $P < 0.0001$) and the LOH high group (HR, 0.62; 95% CI, 0.42–0.90; $P = 0.011$) in comparison to the LOH low group. Patients in the *BRCA*-mutant and LOH high groups experienced high ORRs when compared to the LOH low group (80%, 29%, and 10%, respectively). The median duration of response was longer in patients in the *BRCA*-mutant group (9.2 months; 95% CI, 6.4–12.9; $P = 0.013$) and LOH high group (10.8 months; 95% CI, 5.7–not yet reached; $P = 0.022$) when compared to the LOH low group (5.6 months; 95% CI, 4.6–8.5).

The authors of ARIEL2 concluded that patients with germline or somatic *BRCA1/2* mutants and *BRCA* wild-type with LOH high relapsed, platinum-sensitive ovarian cancer can have longer PFS with rucaparib compared to patients with *BRCA* wild-type and LOH low ovarian cancer. The findings of this trial led to the FDA approval of rucaparib for the treatment of *BRCA1/2*-mutant relapsed, platinum-sensitive ovarian cancer that had been previously treated with at least 2 prior lines of therapy. Being a 2-part trial, the second phase of ARIEL2 is currently ongoing and will evaluate OS as an endpoint.

PHARMACOKINETICS

Niraparib

Niraparib has an oral bioavailability of about 73%.[34] Peak plasma concentrations are achieved within 3 hours following administration. Niraparib has an apparent volume distribution of approximately 1,220 ± 1,114 L and is 83% bound to plasma proteins. Carboxylesterases are the primary enzymes implicated in the metabolism of niraparib. Niraparib is metabolized by carboxylesterases to an inactive metabolite that is subsequently metabolized via glucuronidation. Niraparib is primarily eliminated via the urine and feces at 47.5% and 38.8%, respectively.

Olaparib

Olaparib capsules and tablets undergo rapid absorption following oral administration.[35] Peak plasma concentrations are achieved within 1 to 3 hours after administration of the capsule and within 1.5 hours after the tablet is given. Steady-state concentrations are achieved within 3 to 4 days following continuous twice-daily administration. The oral bioavailability of tablet formulation is higher than the capsule formulation and, therefore, they are not interchangeable on a mg-per-mg basis. The steady-state exposure following the 300-mg tablet given twice daily was 77% higher compared to that following the 400-mg capsule given twice daily.

Administering olaparib capsules or tablets with a high-fat meal has demonstrated a slower rate of absorption, but has not been shown to affect the degree of absorption. Olaparib capsules and tablets have similar distribution. The capsule has a mean volume of distribution of 167 ± 196 L following a single dose of olaparib 400 mg and is 82% bound to plasma proteins *in vitro*. Similarly, the tablet has a mean volume of distribution of 158 ± 136 L following a single dose of olaparib 300 mg and

Table 2 Dosing, How Supplied, and Dose Adjustments for PARP Inhibitors

Generic (Brand)	Niraparib (Zejula)	Olaparib (Lynparza)	Rucaparib (Rubraca)
Manufacturer	Tesaro	AstraZeneca	Clovis Oncology
Initial Dosing	300 mg orally once daily	Capsules: 400 mg orally twice daily Tablets: 300 mg orally twice daily	600 mg orally twice daily
How Supplied	Capsules: 100 mg	Capsules: 50 mg Tablets: 100 mg, 150 mg Do not substitute capsules for tablets on a mg-per-mg basis	Tablets: 200 mg, 250 mg, 300 mg
Renal Impairment	CrCl 30–90 mL/min: No adjustment suggested CrCl < 30 mL/min: Not studied ESRD: Not studied	CrCl 51–80 mL/min: No adjustment suggested CrCl 31–50 mL/min: Capsules: Reduce to 300 mg twice daily Tablets: Reduce to 200 mg twice daily CrCl < 30 mL/min: Not studied ESRD: Not studied	CrCl > 30 mL/min: No adjustment suggested CrCl < 30 mL/min: Not studied ESRD: Not studied
Hepatic Impairment	Mild (Child-Pugh Class A): No adjustment suggested Moderate to severe (Child-Pugh classes B and C): Not studied	Mild (Child-Pugh Class A): No adjustment suggested Moderate to severe (Child-Pugh classes B and C): Not studied	Mild (Child-Pugh Class A): No adjustment suggested Moderate to severe (Child-Pugh classes B and C): Not studied
Dose Adjustment for Toxicity	First dose reduction: 200 mg daily Second dose reduction: 100 mg daily	Capsules: First dose reduction: 200 mg twice daily Second dose reduction: 100 mg twice daily Tablets: First dose reduction: 250 mg twice daily Second dose reduction: 200 mg twice daily	First dose reduction: 500 mg twice daily Second dose reduction: 400 mg twice daily Third dose reduction: 300 mg twice daily

CrCl = creatinine clearance; ESRD = end-stage renal disease.

is 82% bound to plasma protein *in vitro*.

CYP3A4 is the primary enzyme responsible for the metabolism of olaparib capsules. Olaparib tablets are metabolized by CYP3A4 and CYP3A5. Olaparib capsules and tablets are extensively metabolized: 15% and 6% is excreted as unchanged drug in the urine and feces, respectively. Following a single dose of olaparib 400-mg capsule and 300-mg tablet, the terminal half-life is 11.9 ± 4.8 hours and 14.9 ± 8.2 hours with a plasma clearance of 8.6 ± 7.1 L/h and 7.4 ± 3.9 L/h, respectively.

Rucaparib

The pharmacokinetics of rucaparib has been found to be linear and dose-proportional across varying dosing levels ranging from 240 mg to 840 mg orally twice daily.[36] Rucaparib has an oral bioavailability of approximately 36%.[37] The median time to peak plasma concentrations is 1.9 hours following oral administration and the mean steady-state plasma concentration is about 1,940 ng/mL. When administered with a high-fat meal compared to when administered under fasting conditions, the area under the curve (AUC) and maximum concentration (C_{max}) were noted to increase by 38% and 20%, respectively, as well as resulting in a delayed time to peak plasma concentrations by 2.5 hours. At steady-state concentrations, rucaparib demonstrates a volume of distribution of 113 L to 262 L and is 70% bound to plasma proteins. Rucaparib is primarily metabolized by CYP2D6 and is also metabolized to a lesser degree by CYP3A4 and CYP1A2. After administration of a single 600-mg dose of oral rucaparib, the mean elimination half-life is approximately 17 to 19 hours. Following continuous dosing, the clearance of rucaparib ranges from 15.3 L/h to 79.2 L/h.

DRUG INTERACTIONS

Niraparib

Formal drug interaction studies have not yet been conducted with niraparib.[34] Niraparib is a substrate of carboxylesterases and UDP-glucuronosyltransferases, and it does not appear to have a strong or moderate inhibitory or induction effect on CYP enzymes.

Olaparib

Olaparib capsules are a substrate of CYP3A4 and olaparib tablets are a substrate of CYP3A4 and CYP3A5.[35] Coadministration of olaparib capsules with strong and moderate CYP3A4 inhibitors has demonstrated increases in the AUC of olaparib by 2.7-fold and 2-fold, respectively. Coadministration of olaparib tablets with the same strong and moderate CYP3A4 inhibitors resulted in increases in the AUC of olaparib by 170% and 121%, respectively. Administration of olaparib in combination with a strong or moderate CYP3A4 inhibitor should be avoided. If avoidance is not possible, olaparib should be dose-reduced. Grapefruits, grapefruit juice, Seville oranges, and Seville orange juice should also be avoided during olaparib therapy due to their ability to inhibit CYP3A4. Coadministration with strong or moderate CYP3A4 inducers can lead to decreased systemic exposure to olaparib and should be avoided if possible. If coadministration of CYP3A4 inducers cannot be avoided during olaparib therapy, then one should be aware of the potential for decreased efficacy with olaparib in this setting.

Rucaparib

Rucaparib is a minor substrate of CYP2D6, CYP1A2, and CYP3A4, and it demonstrates a low metabolic turnover in liver microsomes *in vitro*.[37] There are currently no known pharmacokinetic drug interactions associated with rucaparib; however, drug interaction studies are ongoing.

ADVERSE EVENTS

The adverse-event profiles of niraparib, olaparib, and rucaparib are relatively similar. The most common adverse events to occur in clinical trials with these agents include anemia, nausea, fatigue, diarrhea, and abdominal pain.[34,35,37] All 3 PARP inhibitors may cause laboratory abnormalities such as decreases in hemoglobin, absolute neutrophil count, platelets, and lymphocytes. In addition, olaparib may increase serum creatinine, and both rucaparib and niraparib may cause elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT).[35]

All the PARP inhibitors have warnings and precautions regarding the development of myelodysplastic syndrome or acute myeloid leukemia secondary to treatment.[34,35,37] PARP inhibitors should be discontinued if myelodysplastic syndrome or acute myeloid leukemia develops.

Niraparib has 2 additional warnings compared to olaparib and rucaparib: bone marrow suppression and cardiovascular events.[34] Approximately 29%, 25%, and 20% of patients receiving niraparib may experience grade 3 or higher thrombocytopenia, anemia, and neutropenia, respectively. Hematological toxicity with niraparib can be managed with dose delays and dose reductions. Cardiovascular events such as hypertension and hypertensive crisis have also been noted in patients receiving niraparib. Hypertension secondary to niraparib can be managed with antihypertensives or with dose reductions to niraparib.

Olaparib also has a warning regarding the development of pneumonitis.[35] Although pneumonitis is a rare event with olaparib therapy, being reported in less than 1% of patients taking olaparib in clinical trials, it can be a serious and potentially fatal adverse event. If a patient develops a confirmed case of pneumonitis while on olaparib, then the drug should be discontinued.

SPECIAL POPULATIONS

Pregnancy and Lactation

PARP inhibitors have the potential to cause embryo-fetal harm during use.[34,35,37] Because of a lack of data in pregnant women, highly effective contraceptive methods are recommended during therapy and post-therapy. With niraparib and rucaparib, contraception should be used for up to 6 months following the last dose of therapy. With olaparib, contraception should be used for up to 1 month following therapy discontinuation.

It is not known whether PARP inhibitors are excreted into breast milk.[34,35,37] Due to the lack of data and potential risk for harm, it is advised that women do not breastfeed during therapy and for a certain timeframe post-therapy. With niraparib and olaparib, women should not breastfeed for at least 1 month after the last dose of therapy. With rucaparib, women should not breastfeed for at least 2 weeks after the last dose of therapy.

Geriatric Patients

In the original clinical trials, reporting of adverse events were not stratified by age group.[27,28,30–33] There were no differences reported in clinical efficacy and safety in patients who were ≥ 65 years of age. Dockery et al. completed a data analysis of several prospective trials that evaluated olaparib at the indicated dose of 400-mg oral capsules twice daily.[38] The patients were separated into 2 groups: an "older" group, age ≥ 65 years, and a "younger" group, age < 65 years. The older population was further stratified into age groups by 5-year increments. A similar toxicity profile was noted across all age cohorts. The incidence of dose interruption and dose reduction did not differ between age groups. It was noted, however, that the oldest age group (≥ 75 years) required dose interruption and/or reduction more frequently, particularly from hematological toxicities. To our knowledge, this is the only published report on adverse effects stratified by age with the use of PARP inhibitors. The PARP inhibitors should be used cautiously at full doses in the elderly population (specifically age ≥ 75 years).

Monitoring Parameters

Considering the warnings and precautions associated with PARP inhibitors, there are monitoring parameters that must be employed by physicians taking care of patients on these medications (Table 3). Laboratory parameters, such as a comprehensive metabolic panel, liver function tests, and a complete blood count (CBC), should be monitored periodically because PARP inhibitors commonly cause some laboratory abnormalities, as previously described.[34,35,37]

In patients receiving any PARP inhibitor, because of the risk of developing myelodysplastic syndrome or acute myeloid leukemia, a CBC should be conducted at baseline.[34,35,37] In the event of developing hematological toxicity while on a PARP inhibitor, treatment should be interrupted until recovery of blood counts. If blood counts have not recovered within 4 weeks of discontinuation, patients should be referred to a hematologist for evaluation for the development of myelodysplastic syndrome or acute myeloid leukemia. A workup such as a bone marrow biopsy with analysis along with blood sampling for cytogenetics testing may be necessary. PARP inhibitor therapy should be

Table 3 Monitoring Parameters for PARP Inhibitors

PARP Inhibitor (Generic Name)	Indication for Monitoring	Labs and Monitoring Schedule
Niraparib[34]	Bone marrow suppression AML/MDS	Monitor CBC weekly for first month, then monthly for the following 11 months, then periodically
	Cardiovascular events	Monitor BP and HR monthly for first year of therapy, then periodically
Olaparib[35]	Bone marrow suppression AML/MDS	Monitor CBC at baseline, then monthly
	Pneumonitis	Monitor for signs and symptoms of pneumonitis
Rucaparib[37]	Bone marrow suppression AML/MDS	Monitor CBC at baseline, then monthly

AML = acute myeloid leukemia; BP = blood pressure; CBC = complete blood count; HR = heart rate; MDS = myelodysplastic syndrome.

discontinued if patients develop myelodysplastic syndrome or acute myeloid leukemia.

Patients receiving niraparib should have additional CBC monitoring every week for the first month of treatment.[34] After the first month of treatment, a CBC should be checked at least monthly for the next 11 months of treatment, and then periodically thereafter. Due to the concern for hypertension and hypertensive crisis in patients taking niraparib, blood pressure and heart rate should be monitored at least monthly for the first year of therapy and then periodically. Patients with pre-existing cardiovascular comorbidities such as hypertension, coronary insufficiency, and arrhythmias should be monitored closely if initiated on niraparib.

With the risk of developing pneumonitis secondary to olaparib therapy, patients should be closely monitored for the development of pulmonary symptoms indicative of pneumonitis.[35] Patients developing dyspnea, cough, fever, wheezing, or any radiological pulmonary abnormality should have their olaparib therapy interrupted. The development of this symptomatology should warrant investigation into possible olaparib-induced pneumonitis. If pneumonitis is confirmed, olaparib should be discontinued.

CONCLUSION

Although management of ovarian cancer presents a challenge in maintaining durable response, PARP inhibition has provided an alternative option in both treatment and maintenance therapy. Although patients with *BRCA1/2*-mutated disease represent only a fraction of relapsed cases, improvements in PFS and chemotherapy-free intervals in the maintenance of both mutated and unmutated disease is encouraging. Niraparib demonstrated efficacy in this particular setting and warrants possible exploration of PARP inhibitors as post-platinum maintenance therapy regardless of mutational status. While the outcomes for olaparib may appear less impressive, the trial population included both a smaller portion of *BRCA1/2*-mutated and more heavily pre-treated patients in comparison to the niraparib trial. Choice of maintenance treatment may also be guided by patient comorbidities, with niraparib and olaparib carrying respective unique side effects. This may be because of differences in target binding affinity on a molecular level, but it ultimately allows flexibility in maintenance options for patients.

Olaparib and rucaparib represent new options in the treatment of *BRCA1/2*-mutated disease. The study population for olaparib in the treatment of ovarian cancer was largely heavily pre-treated, receiving at least 3 lines of therapy, while including both platinum-resistant and -sensitive disease. Rucaparib appeared to have slightly improved outcomes compared to olaparib, but only in analyzed platinum-sensitive patients who had received 2 lines of therapy. Maturation of the OS data from the second phase of the ARIEL2 study may provide additional insight for rucaparib. Trial design differences led to their slight differences in respective indications, while also producing a possible niche for utilizing olaparib in platinum-resistant disease. Ovarian cancer patients with advanced disease may be subject to polypharmacy, and differences in drug metabolism may also serve to direct treatment choice. Both olaparib and rucaparib provide an additional line of treatment in this therapeutic setting, regardless of minor differences.

For formulary development, there are cost differences in the average wholesale price (AWP) between the 3 available PARP inhibitors (Table 1). In terms of agents for maintenance therapy, niraparib is more expensive than olaparib. In terms of treatment for advanced *BRCA1/2*-mutated ovarian cancer, olaparib capsules are less expensive than rucaparib. Because of their differences in approved indications, studied patient populations, pill burden, and lack of head-to-head comparisons, a cost-effectiveness analysis may be difficult to ascertain, although olaparib tablets are the least expensive choice for treatment and maintenance therapy.

PARP inhibitors being developed as an oral treatment or maintenance therapy for relapsed ovarian cancer represent an advance in the management of this disease state. Although further analysis of PARP inhibitors in ovarian cancer is needed, this new class of drugs is currently being evaluated in ongoing trials in breast, lung, colorectal, and prostate malignancies. PARP inhibitors (niraparib, olaparib, and rucaparib) offer a new, targeted therapeutic option in the management of relapsed *BRCA1/2*-mutant ovarian cancer.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin* 2017;67:7–30. doi: 10.3322/caac.21387. Epub 2017 Jan 5.
2. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. *CA Cancer J Clin* 2011;61:183–203. doi: 10.3322/caac.20113. Epub 2011 Apr 26.
3. Hennessy BT, Coleman RL, Markman M. Ovarian cancer. *Lancet* 2009; 374:1371–1382.
4. Howlader N, Noone AM, Krapcho M, et al. (eds.) SEER Cancer Statistics Review, 1975–2014, National Cancer Institute. Bethesda, MD. Available at: http://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER website, April 2017.

5. Kurman RJ, Shih leM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer—shifting the paradigm. *Hum Pathol* 2011;42(7):918–931. doi: 10.1016/j.humpath.2011.03.003.
6. Girolimetti G, Perrone A, Santini D, et al. BRCA-associated ovarian cancer: From molecular genetics to risk management. *Biomed Res Int* 2014;2014:787143. doi: 10.1155/2014/787143. Epub 2014 Jul 22.
7. Yoshida K, Miki Y. Role of BRCA1 and BRCA2 as regulators of DNA repair, transcription, and cell cycle in response to DNA damage. *Cancer Sci* 2004;95(11):866–871.
8. Ovarian cancer. American Cancer Society. Available at: www.cancer.org. Accessed October 9, 2017.
9. Goff BA, Mandel LS, Drescher CW, et al. Development of an ovarian cancer symptom index: Possibilities for earlier detection. *Cancer* 2007;109(2):221–227.
10. Fleming GF, Seidman J, Lengyel E. Epithelial ovarian cancer. In: Barakat RR, Markman M, Randall ME, eds. *Principles and Practice of Gynecologic Oncology*, 6th ed. Philadelphia: Lippincott Williams; 2013:757–847.
11. Bookman MA, Brady MF, McGuire WP, et al. Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: A phase III trial of the gynecologic cancer intergroup. *J Clin Oncol* 2009;27:1419–1425.
12. Du Bois A, Lück HJ, Meier W, et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;95:1320–1329.
13. Recurrence. Ovarian Cancer Research Fund Alliance. Available at: https://ocrfa.org/patients/about-ovarian-cancer/recurrence. Accessed October 15, 2017.
14. Harrison ML, Gore ME, Spriggs D, et al. Duration of second or greater complete clinical remission in ovarian cancer: Exploring potential endpoints for clinical trials. *Gynecol Oncol* 2007;106(3):469–475.
15. Elit L, Hirte H. Palliative systemic therapy for women with recurrent epithelial ovarian cancer: Current options. *Onco Targets Ther* 2013;6107–6118.
16. Markman M, Iseminger KA, Hatch KD, et al. Tamoxifen in platinum-refractory ovarian cancer: A gynecologic oncology group ancillary report. *Gynecol Oncol* 1996;62(1):4–6.
17. Smyth JF, Gourley C, Walker G, et al. Antiestrogen therapy is active in selected ovarian cancer cases: The use of letrozole in estrogen receptor-positive patients. *Clin Cancer Res* 2007;13(12):3617–3622.
18. Lee J-M, Ledermann JA, Kohn EC. PARP inhibitors for BRCA 1/2 mutation-associated and BRCA-like malignancies. *Ann Oncol* 2014;25:32–40. doi: 10.1093/annonc/mdt384. Epub 2013 Nov 12.
19. FDA News Release. FDA approves maintenance therapy for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers. Available at: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm548948.htm. Accessed October 28, 2017.
20. FDA News Release. FDA approves Lynparza to treat advanced ovarian cancer. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427554.htm. Accessed January 27, 2017.
21. FDA News Release. FDA approves olaparib tablets for maintenance treatment in ovarian cancer. Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm572143.htm. Accessed October 10, 2017.
22. FDA News Release. FDA grants accelerated approval to new treatment for advanced ovarian cancer. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm533873.htm. Accessed January 21, 2017.
23. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res* 2012;72:5588–5599. doi: 10.1158/0008-5472.CAN-12-2753.
24. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of BRCA2-deficient tumors with inhibitors of poly(ADP-ribose) polymerase. *Nature* 2005;434:913–917.
25. The Cancer Genome Atlas Network. Integrated genomic analyses of ovarian carcinoma. *Nature* 2011;474:609–615. doi: 10.1038/nature10166.
26. Bingliang F. Development of synthetic lethality anticancer therapeutics. *J Med Chem* 2014 Oct 9;57(19):7859–7873.
27. Mirza MB, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016;375:2154–2164.
28. Domchek SM, Aghajanian C, Shapira-Frommer R, et al. Efficacy and safety of olaparib monotherapy in germline BRCA1/2 mutation carriers with advanced ovarian cancer and three or more lines of prior therapy. *Gynecol Oncol* 2016;140(2):199–203.
29. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–247.
30. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med* 2012;366:1382–1392.
31. Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: An updated analysis from a randomized, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol* 2016;17:1579–1589.
32. Pujade-Lauraine E, Ledermann J, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017. Published online. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(17)30469-2/abstract.
33. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): An international, multicentre, open-label, phase 2 trial. *Lancet Oncol* 2017;18:75–87.
34. Zejula (niraparib) [prescribing information]. Waltham, Massachusetts: Tesaro Inc; August 2017.
35. Lynparza (olaparib) [prescribing information]. Wilmington, Delaware: AstraZeneca Pharmaceuticals LP; August 2017.
36. Kristeleit R, Shapiro GI, Burris HA, et al. A phase I-II study of oral poly(ADP-ribose) polymerase inhibitor rucaparib in patients with germline BRCA1/2-mutated ovarian carcinoma or other solid tumors. *Clin Cancer Res* 2017 Mar 6 pii: clincanres.2796.2016. doi: 10.1158/1078-0432.CCR-16-2796. [Epub ahead of print].
37. Rubraca (rucaparib) [prescribing information]. Boulder, Colorado: Clovis Oncology; December 2016.
38. Dockery LE, Tew WP, Ding K, Moore KN. Tolerance and toxicity of the PARP inhibitor olaparib in older women with epithelial ovarian cancer. *Gynecol Oncol* 2017. Published online. Available at: https://doi.org/10.1016/j.gyno.2017.10.007 ■