PARP Inhibition and its Evolving Use in the Treatment of Cancers:

What Managed Care Needs to Know for Improved Clinical and Economic Outcomes

A CME/CNE Approved Activity

JOURNAL of MANAGED CARE MEDICINE

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Instructions for CME/CNE: Activity is valid from April 1, 2019 to March 31, 2021.

A score of 70% must be achieved on the post-test to receive continuing education credits.
Read the monograph, answer the post-test, complete the evaluation form, and send the completed post-test and evaluation to:

By E-mail: Jeremy Williams at jwilliams@namcp.org

By Fax: Jeremy Williams at 804-747-5316

By Mail: Jeremy Williams
NAMCP CME Dept.
4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060

Authors:
Don S. Dizon, MD, FACP, FASCO is Director of the Women's Cancers, Lifespan Cancer Institute; Director of Medical Oncology at the Rhode Island Hospital; and Professor of Medicine at the Alpert Medical School of Brown University, Providence, RI.
Gary M. Owens, MD is President of Gary Owens and Associates, Ocean View, DE.
Shannon N. Westin, MD, MPH, FACOG is an Associate Professor in the Department of Gynecologic Oncology and Reproductive Medicine at the University of Texas MD Anderson Cancer Center, Houston, TX.

Learning Objectives:
1. Explain tumor biology mechanisms that provide the rationale for targeting PARP in the treatment of cancers.
2. Explore the role of PARP inhibitors in the current oncology treatment landscape including ovarian, breast and prostate cancer.
3. Compare PARP inhibitors in cancer therapy including mechanisms of action, delivery methods, dosing and scheduling, efficacy, safety, interactions, and ease of use.
4. Analyze the role of genetic testing and biomarkers for the identification of patients with various cancers to be treated with PARP inhibition, including those with BRCA-mutated disease.
5. Identify strategies for anticipating, recognizing, and managing adverse events of PARP inhibitor therapy in patients with ovarian, breast or prostate cancer.
6. Assess the managed care considerations of current and emerging PARP inhibitors by exploring where these agents fit into the current cancer management paradigm.

Faculty Disclosure:
Dr. Dizon has no relevant financial relationships to disclose.
Dr. Owens has no relevant financial relationships to disclose.
Dr. Westin serves as a consultant for AstraZeneca, Clovis, Genentech, Medivation, Merck, Ovation, Pfizer and Takeda. She has received grant/research support from AstraZeneca, Bayer, Clovis, Cotinga, Genentech, and Tesaro.

All material has been peer reviewed for bias.

Planning Committee Disclosure
Bill Williams, MD; Jacqueline Cole, RN, CPHQ, CMCN; and Jeremy Williams have no relevant financial relationships to disclose.

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Nurses who complete this activity and achieve a passing score will receive 1 hour in continuing nursing credit.
This activity has been approved by the American Board of Managed Care Nursing for 1.0 contact hours toward CMCN recertification requirements.

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Post-Test Questions

1. With which type of DNA is PARP involved?
   a. Base excision **b.** Mismatch
   c. Nucleotide excision **d.** Single-strand annealing
2. PARP inhibitors induce synthetic lethality in cells deficient in _____.
   a. Homologous recombination **b.** Mismatch repair
   c. Nonhomologous end joining **d.** Double-strand annealing
3. In addition to ovarian and breast cancer, which of the following cancers are PARP inhibitors likely to be effective, based on their mechanism of action?
   a. Colorectal **b.** Kidney
   c. Prostate **d.** Brain
4. Which of the following PARP inhibitors is FDA approved for maintenance in advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer with deleterious germline or somatic BRCA mutations who are in a complete or partial response to **first-line** platinum-based chemotherapy?
   a. Niraparib **b.** Olaparib
   c. Rucaparib **d.** Talazoparib
5. Which of the following is an accurate statement about the efficacy of PARP inhibitors as maintenance therapy in ovarian cancer?
   a. They significantly improve overall survival.
   b. They improve both progression-free survival and overall survival.
   c. The overall response rate is 80 percent or greater.
   d. They significantly improve progression-free survival.
6. Which two PARP inhibitors are FDA approved for treating germline BRCA-mutated HER2- negative metastatic breast cancer?
   a. Olaparib and rucaparib **b.** Rucaparib and niraparib
   c. Niraparib and talazoparib **d.** Olaparib and talazoparib
7. Median overall survival is significantly improved by PARP inhibitors in germline BRCA-mutated HER2- negative metastatic breast cancer.
   a. True **b.** False
8. Which of the following is an uncommon hematologic adverse effect of PARP inhibitors?
   a. Anemia **b.** Thromboctopeia
   c. Myelodysplastic syndrome **d.** Neutropenia
9. Which of the following is an accurate statement about management of adverse effects of PARP inhibitors?
   a. Dose reductions appear to reduce overall efficacy of PARP inhibitors and should be avoided.
   b. Complete blood counts should be monitored monthly for the first year of therapy.
   c. Therapy can be restarted once the adverse effect has improved to Grade 2.
   d. Myelosuppression with prior chemotherapy regimens does not predict hematologic issues.
10. Use of PARP inhibitors in patients with ovarian cancer and germline BRCA mutations or homologous recombination deficiency positive tumors is likely more cost-effective than use in all ovarian cancer patients who relapse.
    a. True **b.** False

Activity Evaluation and Improvement Process

Please rate this activity on the following scale:
4 - Excellent 3 - Good 2 - Fair 1 - Poor

1. Based on the content presented, I am better able to:

   Explain tumor biology mechanisms that provide the rationale for targeting PARP in the treatment of cancers.

   4 3 2 1

   Explore the role of PARP inhibitors in the current oncology treatment landscape including ovarian, breast and prostate cancer.

   4 3 2 1

   Compare PARP inhibitors in cancer therapy including mechanisms of action, delivery methods, dosing and scheduling, efficacy, safety, interactions, and ease of use.

   4 3 2 1

   Analyze the role of genetic testing and biomarkers for the identification of patients with various cancers to be treated with PARP inhibition, including those with BRCA-mutated disease.

   4 3 2 1

   Identify strategies for anticipating, recognizing, and managing adverse events of PARP inhibitor therapy in patients with ovarian, breast or prostate cancer.

   4 3 2 1

   Assess the managed care considerations of current and emerging PARP inhibitors by exploring where these agents fit into the current cancer management paradigm.

   4 3 2 1

2. The activity and presenters were free of bias.

   4 3 2 1

3. The activity was applicable to my position.

   4 3 2 1

4. How confident are you in managing patients based on this activity? (4 very confident - 1 not confident)

   4 3 2 1

5. Do you plan to change management strategies or patient care in your organization or practice based on the content presented?

   ☐ Yes ☐ No

6. If yes, what changes do you plan to implement in management strategies or patient care in your organization or practice?

   _____

   _____

   _____

7. Did the content of the activity help in meeting your above goal?

   ☐ Yes ☐ No

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4435 Waterfront Drive, Suite 101
Glen Allen, VA 23060
(804) 527-1905
fax (804) 747-5316

EDITOR-IN-CHIEF
J. Ronald Hunt, MD

PUBLISHER
Jeremy Williams

JOURNAL MANAGEMENT
Douglas Murphy
Communications Inc.
P.O. Box 71895
Richmond, VA 23255-1895
(804) 387-7580
fax (703) 997-5842

MANAGING EDITOR
Barry Barnum
barry.barnum@douglasmurphy.com

GRAPHIC DESIGN
Douglas Murphy Communications, Inc.

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PARP Inhibitor Monograph

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What Managed Care Needs to Know for Improved Clinical and Economic Outcomes

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Introduction

Poly (ADP-ribose) polymerase (PARP) inhibitors are relatively recent additions to the cancer treatment armamentarium. They have indications in ovarian and breast cancer and are being studied in prostate cancer and other cancers with homologous recombination DNA repair defects. Four agents are available – niraparib, olaparib, rucaparib, and talazoparib.

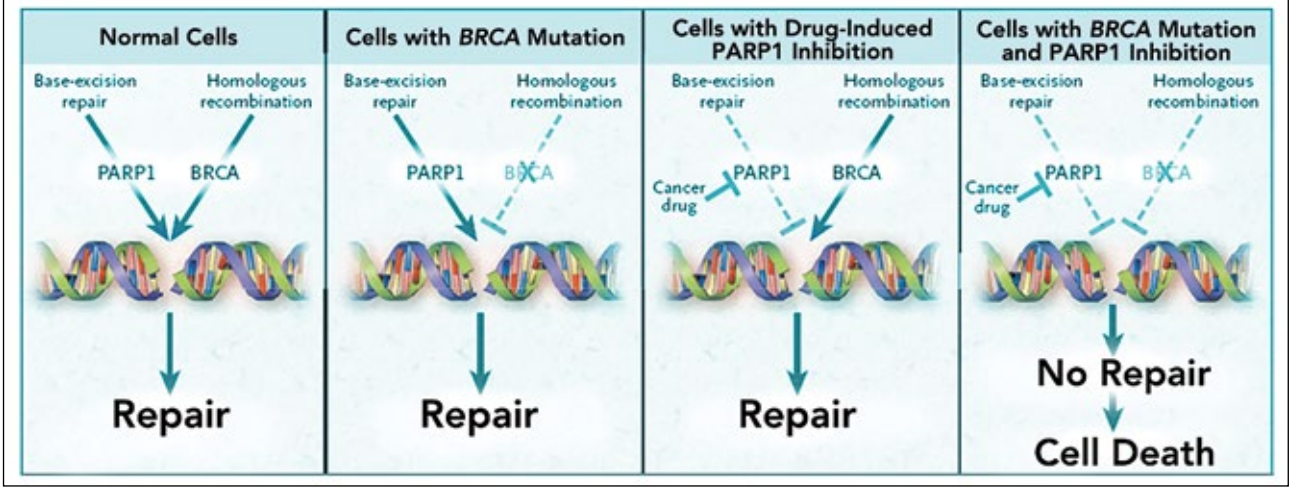
PARP and DNA Repair

DNA is not inert – rather, it is subject to assault from the environment, and any resulting damage, if not repaired, will lead to mutation and possibly disease. In addition to damage caused by the environment, the very process of DNA replication during cell division is prone to error and can result in mutations and single-and double-strand breaks in the DNA.[1] Repair of these errors is a multi-step process that starts with the detection of an abnormality in DNA structure. The abnormal DNA is removed, and normal DNA is synthesized. Thus, DNA repair mechanisms maintain genomic stability. Many mechanisms are involved in DNA repair, including base excision repair, mismatch repair, nucleotide excision repair, single-strand annealing, homologous recombination, and nonhomologous end joining.[2]

PARP and breast cancer gene protein (BRCA) are both involved in DNA repair.[3] BRCA is involved in repairing breaks in double-stranded DNA through homologous recombination, and PARP is involved in base excision repair. Cells with BRCA mutations have nonfunctional homologous recombination but can repair DNA through base excision repair (nonhomologous repair); however, use of this pathway alone results in genomic instability and increases the risk of developing breast, ovarian, prostate, and pancreatic cancer.

PARP inhibitors prevent repair of breaks in single-stranded DNA and induce synthetic lethality in cells deficient in homologous recombination (Exhibit 1). In cells with functional homologous recombination, the cell can still repair DNA when PARP inhibition is present. With in-vitro models, cells with BRCA mutations have 1,000 times greater sensitivity to PARP inhibitors than wild-type cells. Findings from studies published in 2000 led to the development

Exhibit 1: PARP Inhibitor Mechanism of Action



of clinical trials in patients with metastatic breast, ovarian, and other cancers, particularly in patients with germline BRCA mutations (gBRCAm).[5,6]

The mechanism for some PARP inhibitors is not only related to catalytic inhibition of PARP but also "trapping" of PARP-DNA complexes (chromatin binding). This is another way of increasing double-strand breaks in DNA and leads to cell death. Trapping explains the synergism of PARP inhibition with alkylating agents which also induce double-strand breaks. PARP trapping is not universal among all PARP inhibitors.[4] Niraparib has the highest trapping, followed by olaparib.

Genetic Testing

Because PARP inhibitors appear to be more efficacious in cancers with BRCA or other homologous recombination mutations, genetic testing before use is recommended for some of the indications. Mutations can occur and be germline (present in all cells) or somatic (present only in tumor cells). Genetic testing can be done for various reasons, including to select treatment, to identify need for primary prevention of breast and ovarian cancer in family members, and to consider secondary prevention strategies, such as mastectomy to prevent breast cancer. Preventing cases of cancer in family members can save significant health care dollars. For ovarian cancer, the Society of Gynecologic Oncologists recommends germline genetic testing at the point of diagnosis for those tumors with high-grade histology (which are the tumors that typically have BRCA mutations).[7] The National Comprehensive Cancer Network (NCCN) recommends testing all patients.[8] Testing at the time of diagnosis is now more important because of the availability of olaparib for first-line maintenance therapy. Previously PARP inhibitors were only indicated for recurrent disease. There is a companion diagnostic test (BRACAnalysis CDx®, Myriad Genetic Laboratories), which is part of the FDA-approved indications for olaparib, rucaparib, and talazoparib for certain indications to identify gBRCAm, but other genetic testing panels give similar information. For genomic testing (testing tumor samples), there is no consensus on testing in ovarian, breast, or prostate cancer at the time of diagnosis. It is likely these tests should be performed as part of a clinical trial, as they are not yet yielding sufficient information to point

Exhibit 2: PARP Inhibitors in Ovarian Cancer[9-14]

Agent	Trial	Dosing	Eligibility				Maintenance or Treatment	Efficacy
			ROC	HGS	Genetics	Plat Sens		
Niraparib	NOVA (n = 533)	300 mg QD	✓	✓	gBRCA+ gBRCA- HRD+	✓	Maintenance	15.5 months PFS difference (gBRCA+); 9.1 months (HRD), 5.4 months (gBRCA-)
Olaparib	SOLO-2 (n = 295)	300 mg BID	✓ ≥ 2 lines	✓	gBRCA+	✓	Maintenance	13.6 months PFS difference (gBRCA+)
	SOLO-1 (n = 391)	300 mg BID		✓	gBRCA+	✓	Maintenance	70% lower risk of disease progression or death compared to placebo 3-year PFS 60% vs 27% with placebo
	Phase II (n = 193)	400 mg BID	✓	✓	gBRCA+		Treatment	26% ORR 42% SD8w
Rucaparib	ARIEL-3 (n = 564)	600 mg BID	✓ ≥ 3 lines	✓	All comers	✓	Maintenance	11.2 months PFS difference (gBRCA+); 8.2 months (HRD); 5.4 months (ITT)
	Phase II (n = 106)	600 mg BID	✓ ≥ 2 lines	✓	✓		Treatment	54% ORR Median duration of response was 9.2 months

ROC = recurrent ovarian cancer
HGS = high-grade serous histology
HRD = homologous recombination deficiency
gBRCA+ = germline BRCA positive
gBRCA- = germline BRCA negative
SD8W = stable disease for 8 weeks
ITT = Intent to Treat
ORR = overall response rate

to an evidence-based tailored treatment. Although olaparib is the only FDA-approved PARP inhibitor for gBRCAm ovarian cancer as first-line maintenance, there is no reason to believe that somatic BRCA-mutated cancer would not respond, and these patients were included in the trial that led to FDA approval for first-line maintenance indication.

Ovarian Cancer

Exhibit 2 shows the efficacy of PARP inhibitors in ovarian cancer for maintenance or treatment from the Phase III trials.[9-14] Maintenance is given after response to platinum-based chemotherapy, and treatment is for recurrent disease instead of chemotherapy. The role of maintenance therapy is to delay disease progression, postpone the need for subsequent chemotherapy, and potentially improve the long-term survival of patients who achieve a response to platinum-based chemotherapy. In the maintenance trials, subjects had to have received two or more lines of prior chemotherapy and responded to the most recent platinum-based regimen. Progression-free survival (PFS) is improved mostly in patients with gBRCAm. PFS is also statistically improved in those with homologous recombination deficiency (HRD) and are BRCA mutation negative. Overall median survival data have not been reported for use of PARP inhibitors the in maintenance setting. Overall response rates (ORR) vary from 26 percent to more than 50 percent, depending on the number of prior lines of therapy the patient has undergone. These are high rates of response in second- and third-line settings compared with prior available treatments. Olaparib, niraparib, and rucaparib are all FDA approved for maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are experiencing a complete or partial response to platinum-based chemotherapy. Olaparib is also approved as maintenance treatment of adult patients with deleterious gBRCAm or somatic-mutated (sBRCAm) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are experiencing a complete or partial response to first-line platinum-based chemotherapy. This approval was based on a trial in newly diagnosed patients who responded to platinum-based chemotherapy, showing a 70 percent lower risk of disease progression or death with olaparib compared to placebo.[11] Olaparib and rucaparib are also FDA approved for treatment of recurrent gBRCAm ovarian cancer that has already been treated with three or more lines of chemotherapy. Exhibit 3 lists the FDA-approved indications for all of the PARP inhibitors.

The ideal patient for PARP inhibitor use in ovarian cancer has a functioning gastrointestinal tract, good performance status, no dose-delays or reductions due to myelosuppression with chemotherapy, high-grade serous histology, known genetic mutation impacting homologous recombination (BRCA or others), and good organ function.

Metastatic Breast Cancer

Because BRCA mutations are found in 5 to 10 percent of breast cancers, PARP inhibitors have been investigated as a treatment. Olaparib was compared to standard chemotherapy (vinorelbine, capecitabine,

Exhibit 3: PARP Inhibitor FDA Approvals

Agent	Dose	Treatment Indication	Maintenance Indication
Olaparib (Lynparza®)	300 mg BID	gBRCAm ovarian cancer ≥ 3 prior therapies gBRCAm metastatic HER2-negative, breast cancer	Platinum-sensitive ovarian cancer after response to platinum-based therapy First-line after platinum if gBRCAm or sBRCAm
Rucaparib (Rubraca®)	600 mg BID	gBRCAm/sBRCAm ovarian cancer ≥ 2 prior therapies	Platinum-sensitive ovarian cancer after response to platinum-based therapy
Niraparib (Zejula®)	300 mg QD	None	Platinum-sensitive ovarian cancer after response to platinum-based therapy
Talazoparib (Talzenna®)	1 mg QD	gBRCAm metastatic HER2-negative, breast cancer	None

gBRCAm = germline breast cancer gene mutation
sBRCA = somatic breast cancer gene
HER2 = human epidermal growth factor two

or eribulin) in metastatic breast cancer associated with gBRCAm and human epidermal growth factor receptor two (HER2)-negative metastatic breast cancer treated with up to two prior lines of prior chemotherapy for metastatic disease population in the OlympiAD trial.[15] This was an open-label, multicenter clinical trial that randomized 302 patients. The median PFS was seven months compared with 4.2 months for chemotherapy (p<.001). There was no difference in median OS between the two treatment groups (median, 19.3 vs 19.6 months). The overall response rate was 60 percent versus 29 percent.

Olaparib was FDA approved for breast cancer in 2018. It was the first FDA-approved treatment for patients with gBRCAm HER2-negative metastatic breast cancer. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy, or be considered inappropriate for endocrine treatment. Patients must be selected for therapy based on an FDA-approved companion diagnostic for olaparib.

In the EMBRACA trial, talazoparib was compared with chemotherapy (gemcitabine, vinorelbine, capecitabine, or eribulin) in advanced breast cancer with gBRCAm.[16] Median PFS was 8.6 months in the talazoparib group compared with 5.6 months in the chemotherapy group (p<.0001). Median OS was 22.3 months versus 19.5 months but was not statistically different (p = 0.11). Similar to the OlympiAD trial, the ORR was 62.6 percent compared with 27.2 percent. One adverse effect that stood out with this trial was alopecia in 25 percent of patients.

Prostate Cancer

Olaparib received an FDA breakthrough therapy designation in January 2016 for the treatment of patients with BRCA1/2 or ATM gene-mutated metastatic castration-resistant prostate cancer (mCRPC) based on results of a compelling Phase II trial of olaparib in patients with advanced castration-resistant prostate cancer (TOPARP-A).[17] This single-arm study included 50 men with mCRPC who had already received one or two prior chemotherapeutic regimens but were platinum-naïve. Subjects received olaparib 400mg twice a day. There was an ORR of 33 percent, and 22 percent had a PSA drop of at least 50 percent. Some DNA damage repair aberration was found in 33 percent of the subjects (BRCA2 in 7; ATM in 5; FANCA in 3; PALB2 in 1). This study found that men with mCRPC and genetic mutations in DNA damage repair genes had an ORR of 88 percent with olaparib treatment. The response rate in those without a DNA repair mutation was 6 percent. The median OS was 10.1 months. The adverse effects in men were similar to what is seen in women.

> The Breakthrough Therapy designation is intended to expedite the development and review of drugs to treat serious or life-threatening medical conditions when preliminary clinical evidence demonstrates that the drug may have substantial improvement over existing therapies on at least one clinically significant endpoint. The standard for breakthrough therapy designation is not the same as the standard for drug approval, and not all drugs receiving breakthrough therapy designation will receive approval for marketing.

Rucaparib also has FDA breakthrough therapy designation as a monotherapy treatment of adult patients with BRCA1/2-mutated mCRPC who have received at least one prior androgen receptor targeted therapy and taxane-based chemotherapy. The designation was based on initial efficacy and safety results from TRITON2, a Phase II study in men with mCRPC with BRCA 1/2 mutations (germline or somatic) or HRD. Forty-four percent of the subjects had a response to rucaparib.[18] As of February 2018, no PARP inhibitor has an FDA-approved indication for prostate cancer.

Adverse Effects

Proactively managing adverse effects is important for persistence and adherence. Even though PARP inhibitors are "just a pill," there are adverse effects. Patients need to know that certain adverse effects may occur. Typically, most adverse effects are easily managed with supportive care and dose reduction, with many adverse effects improving over time. Monitoring should be at least once a month during the first few cycles of therapy. It is important to manage expectations of patients and caregivers to alleviate key symptoms so that therapy can continue uninterrupted. Incorporating the nursing staff into the education process can help keep patients on therapy.

All of the PARP inhibitors can cause anemia, thrombocytopenia, and neutropenia. Niraparib appears to cause a higher rate of Grade 3 and 4 thrombocytopenia and neutropenia than the other agents. About one-third of patients require a dose reduction because of low platelets. The hematologic adverse effects tend to be worst early in therapy. Patients who weigh less than 77 kg or start with platelets less than 150,000 are more likely to have thrombocytopenia with niraparib and probably should be started on a lower dose than the usual starting dose.[19] Acute myelogenous leukemia (AML)

Exhibit 4: Dose Adjustments for Adverse Effects[20-23]

Olaparib Dose Reductions	Dose
Starting Dose	• 300 mg BID
First Dose Reduction	• 250 mg BID
Second Dose Reduction	• 200 mg BID

Niraparib Dose Reductions	Dose
Starting Dose	• 300 mg daily
First Dose Reduction	• 200 mg daily
Second Dose Reduction	• 100 mg daily

Rucparib Dose Reductions	Dose
Starting Dose	• 600 mg twice daily
First Dose Reduction	• 500 mg twice daily
Second Dose Reduction	• 400 mg twice daily
Third Dose Reduction	• 300 mg twice daily

Talazoparib Dose Reductions	Dose
Starting Dose	• 1 mg daily
First Dose Reduction	• 0.75 mg twice daily
Second Dose Reduction	• 0.50 twice daily
Third Dose Reduction	• 0.25 mg twice daily

and myelodysplastic syndrome (MDS) have occurred with PARP inhibitor therapy. The incidence is very low (<1% of patients), but patients who develop AML or MDS tend to do poorly. Before initiating a PARP inhibitor, prior chemotherapy adverse effects should have resolved to Grade 1 or less. The rate of myelosuppression is increased in heavily pretreated patients.

Complete blood counts (CBC) need to be monitored monthly with these agents. Those receiving niraparib should have weekly counts done the first month of therapy. If hematological toxicities are noted, the agent should be held until weekly CBC have recovered to Grade 1 or less. If the hematological profile recovers, the clinician can consider restarting at a reduced dose. If the hematological profile has not recovered to Grade 1 or less after four weeks without the PARP inhibitor, the patient should be referred to a hematologist for bone marrow analysis and cytogenetics. If AML or MDS develop, a PARP inhibitor should not be restarted.

PARP inhibitors also frequently cause nausea, vomiting, and decreased appetite. The emetogenic potential for PARP inhibitors is moderate to high (≥30% frequency of emesis). Antiemetic prophylaxis is recommended with an oral 5-HT3 antagonist (i.e., granisetron, ondansetron, or dolasetron). Patients can also be counseled on ways to minimize nausea and vomiting by eating smaller meals throughout the day, not skipping meals, eating foods that are easy on the stomach (white toast, plain or vanilla yogurt, clear broth), and eating a small amount of dry toast or crackers before getting out of bed, if early morning nausea is an issue.

Fatigue can be a major issue for patients on PARP inhibitors and is a common reason for dose reductions. Although there is not a great deal that can be done, the patient should be checked for anemia and encouraged to maintain good nutrition, stay well-hydrated, and maintain an optimal level of physical activity.

Increased creatinine with olaparib and rucaparib is secondary to effects on renal transport proteins and is not actual renal damage. Elevated transaminases can occur with rucaparib and may require dose reduction but is not generally associated with hepatic damage. Blood pressure can increase with niraparib that may be due to an effect on neurotransmitters. Rash or photosensitivity reaction can occur with rucaparib and olaparib.

In general, for Grade 1 level toxicities, the patient should be monitored for worsening. For Grade 2, again monitoring is appropriate, except for thrombocytopenia secondary to niraparib, which should be held and the dose reduced. For Grade 3 to 4 level effects, the medication should be held and then restarted at a lower dose. Transfusion and growth factors can be considered for treating hematological adverse effects. Exhibit 4 shows the FDA labeling recommendations for dose adjustments based on adverse effects.[20-23] Dose reductions do not appear to reduce overall efficacy. Patients need to be educated that managing adverse effects with dose reductions will not impact the benefit.

Quality of Life

Especially when a medication is used in the maintenance setting, it is important that, in addition to extending life, the agent does not cause harm to quality of life. Studies have shown that the quality of life on PARP inhibitor therapy is equivalent to placebo.[9-11] After the first two to three months of

Exhibit 5: Metabolism and Drug–Drug Interactions Among PARP Inhibitors[20-23]

PARP Inhibitor	CYP Enzymes Used for Metabolism	Drug–Drug Interactions	Effect on Cell Transporters
Rucaparib	• CYP2D6 (predominant) • CYP1A2 and CYP3A4 (lesser extent)	• Reversibly inhibits CYP1A2, CYP2C19, CYP2C9, CYP3A and induces CYP1A2	• Inhibits MATE1 and MATE 2-K OCT1 • Substrate of P-glycoprotein
Olaparib	• CYP3A4	• Inhibits CYP3A4 and induces CYP2C9 • Reduce dosage if strong or moderate CYP3A inhibitors are co-administered	• Inhibits MDR1, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2-K • Substrate of P-glycoprotein
Niraparib	• Carboxylesterases (non-CYP)	• Can induce CYP1A2 (weak)	• No interaction with the major hepatic or renal uptake transporters • Inhibits BCRP (weak) • Substrate of P-glycoprotein and BCRP
Talazoparib	• Mono-oxidation, dehydrogenation, cysteine conjugation of mono-desfluoro-talazoparib and glucuronide conjucation	• P-glycoprotein inhibitors • BCRP inhibitors	• Substrate of P-glycoprotein and BCRP

BCRP = breast cancer resistance protein

therapy, most patients feel that they are not receiving anything, primarily because these agents have much less toxicity than chemotherapy.

Selecting Which Agent to Use

Because there are no studies directly comparing the PARP inhibitors, one must use the data from individual trials to compare effectiveness that appears to be similar for each of the indications. Given comparable efficacy of the four available agents, other characteristics will need to inform choice such as whether they are being used for maintenance or treatment in the case of ovarian cancer, adverse effects, drug-drug interactions, dosing schedule, and formulary coverage. When considering likely adverse effects, niraparib may not be the best choice for patients with uncontrolled hypertension, or for patients with a history of significant myelosuppression with chemotherapy. The agents are all either dosed once or twice daily. For some patients, a once a day medication may be preferable for enhancing adherence. Ease of dose reductions to manage adverse effects is another selection issue; reductions are easier for niraparib, which only comes in one strength, while the others require a new prescription to achieve the recommended dose. The price of these agents is fairly consistent, so price itself is not necessarily a selection factor; however, formulary coverage by the individual patient's insurance will be a selection factor for clinicians.

Each PARP inhibitor is uniquely metabolized and has different potential for drug-drug interactions (Exhibit 5).[20-23] Rucaparib and olaparib are metabolized by the cytochrome p450 (CYP) system. Rucaparib is metabolized by CYP2D6, and it also induces and inhibits other CYP enzymes, but there are no known drug-drug interactions at this time. The package labeling states that for concomitant use of CYP1A2, CYP3A, CYP2C9, and CYP2C19 substrates the rucaparib dose should be adjusted, if clinically indicated. For olaparib, the drug is metabolized by the CYP3A4 enzymes. The package labeling recommends avoiding concomitant use of strong or moderate CYP3A inhibitors or inducers, and to reduce the olaparib dose if an inhibitor cannot be avoided. Niraparib is metabolized by carboxylesterases, and is not affected by the CYP system, so there are no known drug-drug interactions. Talazoparib is minimally metabolized by several non-CYP routes. All of the agents are substrates for P-glycoprotein (P-gp) and niraparib, and talazoparib are substrates for breast cancer resistance protein (BCRP). Co-administration with P-gp or BCRP inhibitors may increase PARP inhibitor exposure and increase risk for adverse effects. Only the package labeling of talazoparib contains recommendations on co-administration with P-gp or BCRP inhibitors, but this may also be an issue with the other agents. In the clinical studies, co-administration of talazoparib with P-gp inhibitors including amiodarone, carvedilol, clarithromycin, itraconazole, and verapamil resulted in an approximate 45 percent increase in talazoparib

exposure and an increase in the rate of dose reduction. The recommendation for concomitant BCRP inhibitors (gefitinib, imatinib mesylate, estrone, 17ß-estradiol, ritonavir, omeprazole, ivermectin, and cyclosporine) is to monitor for potential increased adverse reactions. The effect on renal transporter proteins MATE1, MATE2-K (rucaparib and olaparib) and OCT1/2 (olaparib) can increase serum creatinine without any actual kidney damage.

The mechanisms of action of the four different PARP inhibitors are notably different as far as how they interact with the different PARP molecules. There are differences in PARP trapping and some theoretic differences in mechanisms. Clinically, this has not been shown to be relevant; however, direct comparison studies have not been undertaken. The differences may be more evident in the adverse effect profile.

Payer Concerns with PARP Inhibitors

Total expenditures of antineoplastic agents across all channels grew from $26.8 billion in 2011 to $42.1 billion in 2016.[24] Antineoplastic spending increased 12.2 percent in 2016 (compared with the previous year). The United States (U.S.) spends almost as much for oncology treatment as the rest of the world.[25] Because of specific legal protections, oncology medication costs are, by and large, covered by insurance in the U.S., unlike in other countries.[26]

The oncology pipeline is rather robust, so more and more agents are reaching the market each year with typically high costs.[26] The average cost to deliver a life-year benefit has increased dramatically since 2013, rising from $50,000 to more than $200,000, suggesting that value per life-year is decreasing.[27] As costs have increased, payers have shifted some of the burden to patients with higher cost sharing/copays especially for oral oncology medications. A recent trial found that higher out-of-pocket costs were associated with higher rates of oral oncology prescription abandonment and delayed initiation across cancers. Abandonment rates were 10 percent for $10 or less copays, 13.5 percent for $50.01 to $100, 31.7 percent for $100.01 to $500, 41.0 percent for $500.01 to $2,000, and 49.4 percent for $2,000 and over.[28]

Like most new oncology agents, the PARP inhibitors have a high cost ($15,000 – $16,000 per month). There are multiple PARP inhibitors on the market, and the indications have expanded. Payers will be looking for opportunities to manage this class in markets where the current regulatory landscape will allow. Oral oncology medications are a protected class in Medicare Part D coverage. In many states, there is legislation that requires insurers to pay for oncology medications, even if used off-label, if there is certain evidence of benefit.

There are numerous unanswered questions about the PARP inhibitor class. Because of a lack of direct comparison data, it is unknown which PARP inhibitor works best and in which patients. It is also not known if the dramatic improvement in PFS translates to an overall survival benefit or even an improved cure rate.[29] The overall value of the class is unknown. There is concern that long-term use of agents that interfere with repair of double-stranded DNA breaks will result in a significant number of acute leukemia and myelodysplastic syndrome cases.[29] A low rate has been reported so far, but this class has not been used for many years.

Economic Analyses/Cost-Effectiveness

A few value or cost analyses of PARP inhibitor use in ovarian cancer for maintenance have been published since their introduction. No analyses have been published of the use of them in breast cancer. To assess the value of the maintenance therapies and biomarkers to direct treatment, Foote and colleagues used the American Society of Clinical Oncology (ASCO)'s Net Health Benefit (NHB) and the European Society of Medical Oncology (ESMO)'s Magnitude of Clinical Benefit Scale (MCBS) to evaluate the value of bevacizumab, a tyrosine kinase inhibitor (cediranib or pazopanib), or a PARP inhibitor as maintenance treatment in platinum-sensitive ovarian cancer.[30] The ASCO NHB calculations include clinical benefit (OS, PFS, or ORR), toxicity, symptom palliation, treatment-free interval, and quality of life (QOL). The ESMO MCBS grading includes clinical benefit, crossover, toxicity, QOL, and long-term PFS. This analysis found higher value assessments in women with germline- or somatic-BRCA mutations or tumor HRD positivity treated with a PARP inhibitor compared with the other agents. The value frameworks used do not consider costs.

There are some data to suggest that a PARP inhibitor is more cost effective than bevacizumab for maintenance in ovarian cancer (Exhibit 6).[31] Exhibit 7 shows data from three decision analysis models generated to compare the cost of observation versus the cost of PARP inhibitor therapy for patients with platinum-sensitive recurrent epithelial ovarian cancer with gBRCAm, evidence of HRD, and no germline BRCA1/2 mutation (non-gBRCAm).[32] This analysis found that while PARP inhibitors demonstrate clinical benefit as maintenance therapy, they are not cost effective at their current average wholesale prices, based on a traditional incremental

Exhibit 6: Incremental Cost-Effectiveness of PARP Inhibitors Compared with Bevacizumab for Maintenance in Ovarian Cancer[31]						
	g*BRCA*		non-g*BRCA*		HRD	
	PFS difference (months)	ICER	PFS difference (months)	ICER	PFS difference (months)	ICER
Olaparib	13.6	$231,567				
Niraparib	15.5	$244,322	3.1	$304,775	9.1	$255,609
Rucparib	11.2	$248,992			8.2	$278,552
Bevacizumab			4.0	$531,151		
ICER = incremental cost effectiveness ratio						

Exhibit 7: Incremental Cost-Effectiveness of PARP Inhibitors for Maintenance in Ovarian Cancer Compared with Observation[32]				
Strategy	**Cost per Patient ($)**	**PF-QALY Benefit per Patient (years)**	**Incremental Cost-effectiveness Ratio ($/PF-QALY)**	**Additional Annual Cost to U.S. Health System ($)**
Observation	$827	0.29	--	--
gBRCA testing/selective treatment	$44,221	0.48	$225,919/PF-QALY	$246,000,000
gBRCA testing + HRD testing/ selective treatment	$105,933	0.71	$262,463/PF-QALY	$590,000,000
Treat all	$165,703	0.74	$2,377,992/PF-QALY	$922,000,000

cost-effectiveness ratio (ICER) cutoff. The authors of this analysis suggest a preferred strategy of treatment of patients with gBRCAm alone or with HRD + tumors with PARP inhibitors over global treatment of all ovarian cancer patients.

The Institute for Clinical and Economic Review (ICER) published an assessment in 2017 that focused only on ovarian cancer and two populations of interest – treatment of recurrent, BRCA-mutated disease with deleterious BRCA mutation which has elapsed after multiple lines of chemotherapy, and maintenance therapy for platinum-sensitive disease (2 or more prior platinum-based chemotherapy regimens, complete or partial response to the most recent regimen). At the time of this review, olaparib did not have a first-line maintenance indication and talazoparib was not yet available. The review noted that differences in study populations in the six published studies precluded formal indirect comparisons. Differences in the study populations included different patient populations (e.g., BRCA mutation type, number of prior chemotherapies, platinum sensitivity) and different evaluation protocols for tumor assessment (e.g., different intervals between scheduled measurements of response, assessment by investigator versus blinded independent central review) were found. The review had several general findings, including that only single-arm data was available for treatment indication, PARP inhibitors provide a PFS benefit over historical comparators and placebo, maintenance therapy benefits are greatest in those with gBRCAm or HRD, data on overall survival are extremely limited, and that the toxicity profile for PARP inhibitors is favorable compared to standard chemotherapy. The cost- effectiveness findings from this review are shown in Exhibit 8.[33] The review concluded that olaparib for recurrent, BRCA-mutated ovarian cancer would be the most cost-effective use of the three PARP inhibitors. In order to meet value thresholds for maintenance therapy with olaparib and rucaparib for BRCA-mutated disease and for maintenance therapy with niraparib, discounts would be required.

Exhibit 8: ICER Cost-Effectiveness Summary[33]				
For Recurrent BRCA-Mutated Disease				
Drug Name	**WAC per Month***	**Price to Achieve $100,000–$150,000/QALY**	**Discount from WAC to Reach Threshholds**	**Net Price within Benchmark Range?**
Olaparib	$13,679	$8,930–$12,587	8% to 35%	✓
Rucaparib	$13,940	$5,091–$7,007	50% to 63%	✗
For Maintenance Therapy in Platinum-Sensitive Disease with BRCA Mutation				
Drug Name	**WAC per Month***	**Price to Achieve $100,000 – $150,000/QALY**	**Discount from WAC to Reach Threshholds**	**Net Price within Benchmark Range?**
Olaparib	$13,679	$3,682–$5,607	59% to 73%	✗
Niraparib⊥	$14,965	$3,952–$6,437	57% to 74%	✗
Rucaparib	$13,940	$3,053–$4,817	65% to 78%	✗

** WAC as of August 23, 2017*
⊥ For Niraparib in maintenance therapy without inherited BRCA mutation, no price would meet $100,000 or $150,000 per QALY, due to high cost relative to the small observed clinical benefit.

The review also noted that due to ovarian cancer association with high mortality rates and sparse treatment options, additional research into PARP inhibitors is vital and being an oral medication is a benefit. The potential of PARP inhibitors to improve upon existing therapeutic paradigms, and the fact that they provide additional options to patients and their providers, cannot be overlooked.

At this point, it does not appear that there is enough data for payers to select a preferred agent. Pricing alone may not offer the most comprehensive view of the class. Payers should evaluate the real-world utilization of PARP inhibitors and look at total cost of care for the different agents.

Future PARP Inhibitors

One agent is in late stage trials. Veliparib is being evaluated for BRCA-mutated breast cancer, ovarian cancer, and non-small cell lung cancer (NSCLC). It is also in very early animal trials for amyotrophic lateral sclerosis (ALS).[34] PARP inhibitors are being studied in combination trials with bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, and immunotherapy. Potential additional tumor types being or to be studied include prostate cancer, non-small cell lung cancer, pancreatic cancer, head and neck cancer, glioblastoma multiforme, and esophageal cancer.

Conclusion

PARP inhibitors have established efficacy in ovarian cancer and breast cancer for improving PFS; however, survival data are yet to mature to demonstrate any OS benefits. Clinical trials of this class in prostate cancer are ongoing. Overall, there are no comparative efficacy studies of PARP inhibitors for the various indications. The four current agents differ in indications and adverse effects, which are common, but generally manageable. Patient counseling is key to adherence and managing adverse effects. This is a class of agents that payers will need to observe closely for potential management opportunities because use of these agents will likely expand significantly in the future. Value frameworks are in development to help establish benefits.

Author Bio

Don S. Dizon, MD, FACP, FASCO is Director of the Women's Cancers, Lifespan Cancer Institute; Director of Medical Oncology at the Rhode Island Hospital; and Professor of Medicine at the Alpert Medical School of Brown University, Providence, RI.

Gary M. Owens, MD is President of Gary Owens and Associates, Ocean View, DE.

Shannon N. Westin, MD, MPH, FACOG is an Associate Professor in the Department of Gynecologic Oncology and Reproductive Medicine at the University of Texas MD Anderson Cancer Center, Houston, TX.

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