Rubraca (Rucaparib) Second PARP Inhibitor Approved for Patients with Advanced, BRCA-Positive Ovarian Cancer

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Epithelial carcinoma of the ovary is one of the most common gynecologic malignancies.1 The National Cancer Institute estimates that 22,280 women were diagnosed with ovarian cancer in 2016 and 14,240 women died from the disease.2

A history of ovarian cancer in a first-degree relative (ie, a mother, a daughter, or a sister) is the most important risk factor for ovarian cancer.1 BRCA genes play an important role in facilitating DNA repair and in preventing cancer.2 Mutations in the BRCA genes can lead to certain cancers, including ovarian cancer. Approximately 15% of patients with ovarian cancer have a mutation in the BRCA1 or BRCA2 gene.3

Regardless of mutation status, systemic treatment for advanced ovarian cancer most often includes platinum-based cytotoxic chemotherapy.4 Patients typically receive between 3 and 6 cycles of carboplatin and paclitaxel (or another platinum-based regimen), followed by completion surgery and postoperative chemotherapy.4 Maintenance therapy (or postremission therapy) with pazopanib (Votrient) or bevacizumab (Avastin) can be considered in some clinical circumstances.4

Patients with advanced ovarian cancer that is refractory to platinum-based chemotherapy and who can continue to receive systemic chemotherapy are often considered for single-agent docetaxel, nab-paclitaxel, gemcitabine, topotecan, pemetrexed, capecitabine, vinorelbine, or oral etoposide; the prognosis is poor for these patients.4

In December 2014, the US Food and Drug Administration (FDA) granted accelerated approval to olaparib (Lynparza), an inhibitor of poly ADP-ribose polymerase (PARP), for the treatment of women with advanced ovarian cancer who received ≥3 chemotherapies and who have deleterious or suspected deleterious germline BRCA mutation, as detected by the FDA-approved companion diagnostic test BRACAnalysis CDx.5,6 Results from a clinical trial of olaparib in 137 patients with BRCA mutation–positive ovarian cancer who had received ≥3 chemotherapies regimens demonstrated an investigator-assessed overall response rate of 34% and a median duration of response of 7.9 months.6

Described as a “milestone in the development of personalized treatment of recurrent ovarian carcinoma,” PARP inhibitors function by impeding DNA repair.7

Rubraca Approved for Relapsed Ovarian Cancer

On December 19, 2016, the FDA granted accelerated approval to the second oral PARP inhibitor rucaparib (Rubraca; Clovis Oncology) for the treatment of women who have received ≥2 chemotherapy regimens and whose tumors are associated with deleterious BRCA mutation–associated (germline and/or somatic) advanced ovarian cancer, as detected by the FDA-approved companion diagnostic test FoundationFocus CDxBRCA.8,9 The FDA approved this indication under its priority review status, and has also granted rucaparib a breakthrough therapy and an orphan drug designation for this indication.8

“Today’s approval is another example of the trend we are seeing in developing targeted agents to treat cancers caused by specific mutations in a patient’s genes. Women with these gene abnormalities who have tried at least two chemotherapy treatments for their ovarian cancer now have an additional treatment option,” stated Richard Pazdur, MD, Director of the FDA’s Office of Hematology and Oncology Products.8

Mechanism of Action

Rucaparib is an inhibitor of PARP, an enzyme that is involved in repairing damaged DNA. By blocking PARP in cancer cells with damaged BRCA genes, DNA repair is less likely; this leads to cancer-cell death and, potentially, to a slower rate of overall tumor growth.9

Dosing and Administration

For patients with advanced ovarian cancer who have received ≥2 chemotherapies and whose tumors have deleterious BRCA mutations, the recommended dosage of rucaparib is 600 mg, orally, twice daily with or without food. Treatment should continue until disease progression or until unacceptable toxicity.9

Patients who miss a dose of rucaparib should take their next dose at its scheduled time. Vomited doses should not be replaced.9

Rucaparib is available as 200-mg and 300-mg tablets.9
Rucaparib Distribution

Rucaparib can be delivered directly to patients through several specialty pharmacies, including Avella, Biologics, CVS Specialty, and US Bioservices. Practices and institutions with in-office pharmacies can order rucaparib from ASD Healthcare, Cardinal Health, and McKesson.

Study 10 and ARIEL2 Clinical Trials

The efficacy of rucaparib was established in Study 10 and in the ARIEL2 study, 2 open-label, single-arm, multicenter clinical trials of 106 patients with advanced BRCA mutation–positive ovarian cancer who received at least 2 previous chemotherapy regimens. Data from these studies were combined for an integrated efficacy and safety analysis. The presence of a BRCA mutation in patients was confirmed using the FDA-approved test FoundationFocus CDxBRCA.

Rucaparib monotherapy was administered at a dosage of 600 mg orally twice daily until disease progression or until unacceptable toxicity. The overall response rate and the duration of response were assessed by investigators and by independent radiologists using the Response Evaluation Criteria in Solid Tumors, version 1.1. The patients’ median age in the 2 clinical trials was 59 years (range, 33-84 years). The majority of women were Caucasian (78%), and all had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. All patients had received at least 2 previous platinum-based chemotherapy regimens, and 43% had received 3 or more chemotherapy regimens. Overall, 18 (17%) of the 106 patients had deleterious BRCA mutations detected in their tumor tissue, and not in whole blood samples. Tumor BRCA mutation status was verified retrospectively in 96% of the 67 patients for whom a tumor tissue sample was available.

The investigator-assessed overall response rate (complete or partial response) was 54% (95% confidence interval [CI], 44-64; Table), and the duration of response lasted for a median of 9.2 months (95% CI, 6.6-11.6). In patients with platinum-sensitive ovarian cancer who received rucaparib, the investigator-assessed overall response rate was 66% (95% CI, 54-76). In patients with platinum-resistant ovarian cancer who received rucaparib, the overall response rate was 25% (95% CI, 9-49). The overall response rates were similar between patients who harbored a BRCA1 mutation and those who harbored a BRCA2 mutation.

Adverse Events

The safety of single-agent rucaparib, at the recommended dose of 600 mg twice daily, has been studied in 2 open-label clinical trials. These studies included 377 patients with ovarian cancer whose median age was 62 years (range, 31-86 years). All patients had an ECOG performance status of 0 or 1; 38% of patients had BRCA mutation–positive ovarian cancer; and 45% of patients received ≥3 previous lines of chemotherapy. The median time from diagnosis with ovarian cancer was 43 months (range, 6-197 months).

The median duration of treatment with rucaparib was 5.5 months (range, 0.1-28 months). Dose reduction or interruption of rucaparib because of adverse events was required in 62% of patients. The most frequent adverse events leading to a dose reduction or an interruption of rucaparib therapy were anemia (27%) and fatigue or asthenia (22%). The discontinuation of rucaparib because of adverse reactions was required in 10% of patients. Fatigue or asthenia (2%) were the most common events leading to treatment discontinuation.

Adverse reactions (all-grade) that were observed in ≥35% of the 377 patients who received rucaparib included asthenia or fatigue (77%; 11% grade 3 or 4), nausea (77%; 5% grade 3 or 4), vomiting (46%; 4% grade 3 or 4), anemia (44%; 25% grade 3 or 4), constipation (40%; 2% grade 3 or 4), dysgeusia (39%; 0.3% grade 3 or 4), and decreased appetite (39%; 3% grade 3 or 4). Increases in creatinine levels and liver enzyme (ie, alanine transaminase [ALT] and aspartate transaminase [AST]) levels were also observed in more than 50% of the patients who received rucaparib. An increase in ALT or AST levels led to treatment discontinuation in 1 of 377 patients.

Rucaparib has no contraindications.

Table 10 and ARIEL2: Efficacy of Rucaparib in Patients with BRCA Mutation–Positive Ovarian Cancer

<table>
<thead>
<tr>
<th>Investigator assessment rucaparib (N = 106)</th>
<th>Independent review rucaparib (N = 106)</th>
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</thead>
<tbody>
<tr>
<td>Objective response rate, %</td>
<td>54 (95% CI, 44-64)</td>
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<tr>
<td>Complete response, %</td>
<td>9</td>
</tr>
<tr>
<td>Partial response, %</td>
<td>45</td>
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<tr>
<td>Median duration of response, mo</td>
<td>9.2 (95% CI, 6.6-11.6)</td>
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CI indicates confidence interval.
Source: Rubraca (rucaparib) tablets prescribing information; December 2016.

Warnings and Precautions

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Of 377 patients, MDS or AML was reported in 2 patients with ovarian cancer who received rucaparib; the duration of treatment with rucaparib in these 2 patients before the diagnosis of MDS or AML was 57 days and 539 days, respectively. Both patients had also received platinum therapies and other DNA-damaging agents.
In addition, AML was reported in 2 patients with ovarian cancer who were enrolled in a blinded, randomized clinical trial that evaluated rucaparib versus placebo. The duration of treatment before the diagnosis of AML was 107 days in 1 patient and 427 days in the other patient; both patients had received platinum therapies and other DNA-damaging agents.9

Complete blood counts should be evaluated at baseline and monthly during rucaparib therapy. Rucaparib should not be initiated until the patient has recovered from any hematologic toxicity caused by previous chemotherapy.9

Rucaparib should be interrupted if prolonged hematologic toxicity occurs. If blood counts do not recover to grade 1 or less after 4 weeks, bone marrow analysis and cytogenetic testing is warranted. If a diagnosis of MDS or AML is confirmed, rucaparib should be discontinued.9

Embryo-fetal toxicity. Based on its mechanism of action, rucaparib can cause fetal harm when administered to a pregnant woman.9

Use in Specific Populations

Pregnancy. Pregnancy testing is recommended for females of reproductive potential before starting treatment with rucaparib, because the drug can cause fetal harm when administered during pregnancy. Females of reproductive potential should use effective contraception during treatment with rucaparib and for 6 months after the final dose.9

Lactation. Women should not breast-feed during treatment with rucaparib and for 2 weeks after the last dose.9

Pediatric use. The safety and effectiveness of rucaparib have not been established in pediatric patients.9

Geriatric use. No overall differences in the safety of rucaparib were observed between patients aged ≥65 years and younger patients. The effectiveness of rucaparib in patients with BRCA mutation–positive ovarian cancer who were aged ≥65 years could not be assessed because of the small sample size.9

Renal impairment. Dose adjustment of rucaparib is not required in patients with mild or moderate renal impairment. Recommendations for starting dose adjustment are not available for patients with severe renal impairment.9

Hepatic impairment. No dose adjustment of rucaparib is recommended for patients with mild hepatic impairment. Recommendations for starting dose adjustment are not available for patients with moderate or severe liver disease.9

Conclusion

Rucaparib, the second PARP inhibitor approved by the FDA for women with BRCA mutation–positive relapsed advanced ovarian cancer, demonstrated measurable and durable responses in this patient population. Researchers are evaluating the activity of rucaparib monotherapy and rucaparib-based combination therapies in other subsets of patients with advanced ovarian cancer, as well as in other solid tumors, including prostate cancer and pancreatic cancer.10

References