

Real-World Delivery of Rucaparib to Patients with Ovarian Cancer: Recommendations Based on an Integrated Safety Analysis of ARIEL2 and Study 10

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ABSTRACT

Treatment options for women with recurrent ovarian cancer who have received two or more prior lines of chemotherapy have recently expanded with the U.S. Food and Drug Administration (FDA) and European Commission (EC) approvals of the poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib. As more oncologists begin to use rucaparib and other PARP inhibitors as part of routine clinical practice, awareness of possible side effects and how to adequately manage toxicities is crucial. In this review, we summarize the safety and tolerability of rucaparib reported in an integrated safety analysis that supported the FDA's initial approval of rucaparib in the treatment setting. Additionally, drawing on clinical data and our personal experience with rucaparib, we provide our recommendations on the management of common side effects observed with rucaparib, including anemia, blood

creatinine elevations, alanine aminotransferase and aspartate aminotransferase elevations, thrombocytopenia, gastrointestinal-related events (e.g., nausea, vomiting), and asthenia and fatigue. These side effects, many of which appear to be class effects of PARP inhibitors, are often self-limiting and can be managed with adequate interventions such as treatment interruption and/or dose reduction and the use of supportive therapies. Supportive therapies may include blood transfusions for patients with anemia, prophylactic medications to prevent nausea and vomiting, or behavioral interventions to mitigate fatigue. Understanding and appropriate management of potential side effects associated with rucaparib may allow patients with ovarian cancer to continue to benefit from rucaparib treatment. *The Oncologist* 2020;25:e109–e119

Implications for Practice: Rucaparib was recently approved in the U.S. and European Union for use as treatment or maintenance for recurrent ovarian cancer. This review focuses on the safety and tolerability of rucaparib in the treatment setting. Similar side effects are observed in the maintenance setting. Drawing on the authors' clinical experience with rucaparib, rucaparib prescribing information, and published supportive cancer care guidelines, this review discusses how to optimally manage common rucaparib-associated side effects in patients with advanced ovarian cancer in the real-world oncology setting. Adequate management of such side effects is crucial for allowing patients with ovarian cancer to remain on treatment to receive optimal efficacy benefit.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the eighth most common cancer among women, accounting for an estimated 295,000 new cases worldwide in 2018, and is the leading cause of

death from gynecologic malignancy in the western world [1, 2]. Most patients are diagnosed at an advanced stage, and despite high initial responses to first-line treatment

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(typically cytoreductive surgery combined with platinum-based chemotherapy), overall 5-year survival for patients with advanced ovarian cancer remains poor, at only 29% [3].

Between 2006 and 2012, there were no new drug approvals for EOC. One barrier to progress has been the historical failure to recognize that EOC is not a single disease, resulting in the inappropriate or lack of selection of patients for clinical trials of targeted agents. However, EOC is now universally recognized as an umbrella term for several diseases with very distinct etiologies, molecular signatures, and clinical behaviors [4], and our approach to developing novel treatments for EOC must target and support these subgroups.

A successful example of this approach was the development and regulatory authority approvals of the poly(ADP-ribose) polymerase (PARP) inhibitors olaparib (Lynparza, AstraZeneca Pharmaceuticals, Wilmington, DE) and rucaparib (Rubraca, Clovis Oncology, Boulder, CO) for monotherapy treatment of EOC associated with a *BRCA* mutation [5, 6]. Initially approved by the U.S. Food and Drug Administration (FDA) in 2014, olaparib is indicated for patients with deleterious or suspected deleterious germline *BRCA*-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy [5]. In 2016, the FDA granted accelerated approval of rucaparib for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies [6]. In 2018, the European Commission (EC) approved rucaparib for treatment of adult patients with platinum-sensitive, relapsed or progressive, *BRCA*-mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy and are unable to tolerate further platinum-based chemotherapy [7]. Notably, the FDA- and EC-approved indications for rucaparib in the treatment setting include patients with either a germline or somatic *BRCA* mutation [6, 7], whereas olaparib is only approved by the FDA for patients with a germline *BRCA* mutation [5]. More recently, rucaparib, olaparib, and niraparib, another PARP inhibitor, have been approved as maintenance treatments for patients with ovarian cancer following a response to platinum-based chemotherapy [5–10].

The landmark approvals of these agents represent decades of research based on the concept of synthetic lethality [11]. In particular, PARP inhibitors cause an accumulation of double-strand DNA breaks that cannot be repaired by ovarian cancer cells with homologous recombination deficiency [11–23]. High-grade serous ovarian cancers (HGSOCs), the most common histological subtype of EOC [4], which have been shown to harbor a deleterious germline (24%) and/or somatic (9%) mutation in one or more genes in the homologous recombination repair pathway, with the most prevalent being a mutation in *BRCA1* (19%) or *BRCA2* (6%) [24].

Many women across the world are currently receiving PARP inhibitors in the treatment or maintenance setting outside of clinical trials as part of routine clinical practice by oncologists who may have little or no experience with

managing their toxicity. This challenge can be compounded by the length of time that many of these women remain on treatment, as some toxicities may occur late or persist with prolonged use of PARP inhibitors.

In this review, we discuss the results of an integrated safety analysis of the two early phase rucaparib trials on which the FDA based its initial approval of rucaparib for use in the treatment setting, provide an overview of the safety and tolerability of rucaparib, and discuss how to optimally manage common PARP inhibitor-related side effects in the real-world oncology setting in patients with advanced EOC, with specific reference to rucaparib.

We draw from published and nonpublished clinical trial data for rucaparib and the experience and knowledge of oncologists who led or participated in these clinical trials. We note that these recommendations do not replace any guidance outlined in approved prescribing information for rucaparib. Although we focus on clinical trials of rucaparib in the treatment setting, a similar safety profile has been observed with rucaparib in the maintenance setting; therefore, we have included an overview of the safety data from the phase III study ARIEL3, which supported the subsequent approval of rucaparib in the maintenance setting [25]. Many of the side effects discussed also appear to be class effects of PARP inhibitors. Thus, the management strategies outlined below may be broadly applicable.

Rucaparib: Efficacy in the Treatment Setting

Rucaparib (formerly known as CO-338, AG-014447, and PF-01367338) is a rationally designed, orally administered, small molecule inhibitor of PARP1, PARP2, and PARP3. The recommended dose and schedule of rucaparib is 600 mg (two 300 mg tablets) taken orally twice daily (BID) with or without food. The initial FDA approval was based on an integrated efficacy analysis of 106 patients with HGSOC and a *BRCA* mutation participating in Study 10 (NCT01482715) or ARIEL2 (NCT01891344) [6, 26]. All patients were treated with platinum previously and were sensitive, resistant, or refractory to platinum-based chemotherapy. Fifty-seven of 106 patients (53.8%) achieved a Response Evaluation Criteria In Solid Tumors version 1.1 best objective response (complete response, 8.5%; partial response, 45.3%), and 36 patients (34.0%) had stable disease [26]. The objective response rate was 64.6% in platinum-sensitive patients ($n = 79$) and 35.0% in those with platinum-resistant disease, a group of patients with very limited treatment options ($n = 20$) [7]. Rucaparib treatment was associated with a median progression-free survival of 10.0 months (95% confidence interval [CI], 7.3–12.5) and median duration of response of 9.2 months (95% CI, 6.6–11.6) in all 106 patients [26].

MATERIALS AND METHODS

We searched PubMed for pivotal studies of rucaparib in the treatment setting and identified data published by Oza and colleagues [26], which summarizes the integrated efficacy and safety analyses that supported the initial FDA approval of rucaparib in the treatment setting [6]. Here we discuss data from the integrated safety analysis of 377 patients with advanced EOC enrolled in Study 10 or ARIEL2

who received at least one dose of oral rucaparib 600 mg BID, irrespective of their *BRCA* mutation status and prior treatment lines [26]. The designs for the two clinical trials included in the integrated safety analysis are summarized in Table 1 and described in more detail elsewhere [26–28].

Upon request, Clovis Oncology, Inc., provided additional safety data for the integrated safety population ($n = 377$), including baseline comorbidities, concomitant medications, treatment duration and dose intensity, treatment-related adverse events (AEs), serious AEs (SAEs), and dose modifications (interruptions or reductions) for AEs of interest.

Recommendations for AE management provided in this manuscript are based on our own clinical experience, as well as recommendations from the National Comprehensive Cancer Network (NCCN) and American Society for Clinical Oncology (ASCO) [29–32].

SAFETY PROFILE OF RUCAPARIB IN THE TREATMENT SETTING

Integrated Safety Population Patient Characteristics

Of the 377 patients with EOC enrolled, 143 (37.9%) had a *BRCA* mutation, of whom 108 (28.6%) had a germline mutation and 28 had a somatic mutation (7.4%; Table 2) [26]. Patients were predominantly white ($n = 302$; 80.1%), with a median age of 62 years (range, 31–86) and a median time since diagnosis of 42.7 months (range, 6.3–196.6). Approximately two-thirds ($n = 246$; 65.3%) were heavily pretreated, having received two or more platinum-based therapies.

At study entry, patients had a number of comorbidities and complications related to disease and prior treatment, the most common being gastrointestinal (GI) disorders (primarily constipation and abdominal pain), fatigue, hypertension, peripheral neuropathy, anxiety, insomnia, and arthralgia (data on file).

Tolerability and Toxicity of Rucaparib

The median number of rucaparib cycles started was six (range, 1–31), with 112 patients (29.7%) receiving treatment for 6–12 months and 61 (16.2%) remaining on treatment for >12 months (data on file). The median dose intensity (actual dose received/first dose received) was 0.92 (range, 0.1–1.3; data on file).

All patients had at least one AE, and the most common AEs experienced by $\geq 20\%$ of patients were fatigue (including asthenia), GI-related events (nausea, vomiting, abdominal pain, constipation, reduced appetite, and diarrhea), anemia/decreased hemoglobin, thrombocytopenia/decreased platelet count, increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST), dysgeusia, dyspnea, and increased blood creatinine (Table 3) [26].

The most common treatment-related AEs of any grade (incidence $\geq 20\%$) were asthenia/fatigue, anemia, increased ALT/AST, increased blood creatinine, GI-related events (nausea, vomiting, constipation, decreased appetite, abdominal pain, and dysgeusia), dyspnea, and thrombocytopenia/decreased platelet count (range, 20.7%–76.9%; data on file).

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Treatment-emergent grade ≥ 3 AEs were reported in 229 patients (60.7%) [26]; treatment-related grade ≥ 3 AEs were reported in 177 patients (46.9%; data on file). Treatment-emergent SAEs were reported in 104 patients (27.6%); treatment-related SAEs were reported in only 36 patients (9.5%), most commonly anemia/decreased hemoglobin and vomiting (data on file).

No patients had a rucaparib-related AE leading to death during the studies [26]. Of the nine deaths during the studies, eight were attributable to progressive disease and one was due to an episode of sepsis and clinical progression considered unrelated to rucaparib therapy.

Dose Modifications

The overall incidence of AEs leading to treatment interruption or dose reduction was 58.6% ($n = 221$) and 45.9% ($n = 173$), respectively (Table 4) [26]. In the integrated safety population, 102 patients (27.1%) required one dose reduction, and 80 (21.2%) required two or more dose reductions; 480 mg BID was the most common dose reduction level (Table 4; data on file). Dose reductions were not always directly related to a treatment-emergent AE.

The most common reasons for dose modification (i.e., reduction or interruption) were anemia/decreased hemoglobin ($n = 81$; 21.5%), asthenia/fatigue ($n = 78$; 20.7%), nausea ($n = 68$; 18.0%), vomiting ($n = 45$; 11.9%), increase in ALT/AST ($n = 39$; 10.3%), and thrombocytopenia/decreased platelets ($n = 37$; 9.8%) [26].

Only 37 (9.8%) patients discontinued therapy because of AEs, excluding disease progression [26]. The most common AEs leading to treatment discontinuation were asthenia/fatigue ($n = 9$; 2.4%) and nausea ($n = 5$; 1.3%) [26].

MANAGEMENT OF RUCAPARIB TOXICITY

General Advice

We recognize that side effects may occur during rucaparib treatment but would like to highlight that most AEs are manageable and are unlikely to lead to drug discontinuation if appropriate guidance is followed. Although dose reductions may be needed, it is important to consider other mechanisms to combat and/or reduce what may be chronic low-grade toxicities.

Patients should be made aware that if they are pregnant or become pregnant while receiving rucaparib, there is risk of fetal harm [6, 7]. Breastfeeding is contraindicated during treatment with rucaparib [6, 7]. Coadministration of rucaparib can increase systemic exposure of cytochrome P450 (CYP) 1A2, CYP3A, CYP2C9, or CYP2C19 substrates [6, 7, 33]. If clinically indicated, dose adjustments may be

Table 1. Overview of the phase I–II studies included in the integrated safety summary^a

| | Study 10 (NCT01482715) | ARIEL2 (NCT01891344) |
|---------------------------------|---|--|
| Study details | | |
| Design | Three-part, phase I–II, open-label, safety, PK, and efficacy study ^b | Two-part, phase II, open-label, safety, PK, and efficacy study |
| Locations | Canada, Israel, Spain, U.K., and U.S. | Australia, Canada, France, Spain, U.K., and U.S. |
| Key eligibility criteria | | |
| Diagnosis | <ul style="list-style-type: none"> Part 1: solid tumor (including lymphoma) Parts 2A and 2B: histologically confirmed diagnosis of high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer with a deleterious <i>BRCA</i> mutation (germline for Part 2A, germline or somatic for Part 2B) Part 3: advanced solid tumor with a deleterious germline or somatic <i>BRCA</i> mutation (including lymphoma) | Histologically confirmed diagnosis of high-grade serous or grade 2–3 endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer |
| Prior therapy | <p>Part 1</p> <ul style="list-style-type: none"> Progressed on standard treatment <p>Part 2A</p> <ul style="list-style-type: none"> Relapsed on 2–4 prior chemotherapy regimens Last treatment received was platinum based, to which patients were sensitive A maximum of 1 nonplatinum regimen; for patients who received 4 prior regimens, 1 regimen must have been nonplatinum <p>Part 2B^c</p> <ul style="list-style-type: none"> Relapsed on 3–4 prior chemotherapy regimens^d Documented treatment-free interval of ≥6 mo following the first chemotherapy regimen received <p>Part 3</p> <ul style="list-style-type: none"> Relapsed on ≥1 prior chemotherapy regimen | <p>Part 1</p> <ul style="list-style-type: none"> Relapsed on ≥1 prior platinum-based regimen Last treatment received was platinum-based, to which patients were sensitive <p>Part 2</p> <ul style="list-style-type: none"> Relapsed on 3–4 prior chemotherapy regimens^d Documented treatment-free interval of ≥6 mo following the first chemotherapy regimen received |
| Patient characteristics | <ul style="list-style-type: none"> ECOG PS 0–1 Life expectancy ≥3 mo LVEF > LLN (Part 1) | ECOG PS 0–1 |
| Laboratory values | | |
| Absolute neutrophil count | ≥1.5 × 10 ⁹ /L | ≥1.5 × 10 ⁹ /L |
| Platelets | >100 × 10 ⁹ /L | >100 × 10 ⁹ /L |
| Hemoglobin | ≥9 g/dL | ≥9 g/dL |
| ALT/AST | ≤3 × ULN; if liver metastases then ≤5 × ULN | ≤3 × ULN; if liver metastases then ≤5 × ULN |
| Bilirubin | ≤1.5 × ULN (<2 × ULN if hyperbilirubinemia from Gilbert's syndrome) | ≤1.5 × ULN (<2 × ULN if hyperbilirubinemia from Gilbert's syndrome) |
| Serum albumin | ≥30 g/L (3.0 g/dL) (Part 2B ^c) | ≥30 g/L (3.0 g/dL) (Part 2) |
| Serum creatinine | ≤1.5 × ULN | ≤1.5 × ULN |
| Treatment | | |
| Rucaparib oral dosage regimens | <p>Once or twice daily for 21-day cycles</p> <ul style="list-style-type: none"> Part 1^e: 40 mg once daily to 840 mg twice daily Parts 2^c and 3^e: 600 mg twice daily | All patients received 600 mg twice daily for continuous 28-day cycles ^f |

^aInformation from references 26–28.

^bPatients enrolled into Part 1, Part 2, or Part 3 of the study, not into multiple parts.

^cNo patients were enrolled in Study 10 Part 2B prior to the enrollment cutoff date of October 1, 2015, used for the integrated efficacy and safety analyses; thus, no data for patients enrolled in Part 2B were included in the analyses.

^dHormonal agents, antiangiogenic agents, and other nonchemotherapy agents administered as single-agent treatment were not counted as a chemotherapy regimen for the purpose of determining patient eligibility.

^eParts 1 and 3 featured a food-effects portion.

^fWith or without food.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; PK, pharmacokinetics; ULN, upper limit of normal.

considered for substrates of CYP1A2, CYP3A, and CYP2C9, particularly those with a narrow therapeutic index (e.g., tizanidine, cyclosporine, and warfarin, respectively).

If dose reductions are required, the guidance is to reduce the rucaparib dose level in 100-mg increments to a minimum of 300 mg BID [6, 7]. The first dose reduction level is 500 mg

Table 2. Baseline demographics, cancer history, and prior anticancer treatment in 377 patients receiving ≥ 1 dose of rucaparib 600 mg BID as monotherapy for EOC

| Parameter | Value (n = 377) |
|---|--------------------|
| White, n (%) | 302 (80.1) |
| Median age (range), y | 62 (31–86) |
| ECOG PS, n (%) | |
| 0 | 233 (61.8) |
| 1 | 144 (38.2) |
| Median time since cancer diagnosis (range), mo | 42.7 (6.3–196.6) |
| Cancer type, n (%) | |
| Epithelial ovarian | 305 (80.9) |
| Primary peritoneal | 39 (10.3) |
| Fallopian tube | 33 (8.8) |
| BRCA mutation, n (%) | |
| Germline | 108 (28.6) |
| Somatic | 28 (7.4) |
| Mutation of unknown origin | 7 (1.9) |
| No mutation | 234 (62.1) |
| Median number of prior chemotherapies (range) | 2 (1–7) |
| 1 Prior therapy, n (%) | 127 (33.7) |
| 2 Prior therapies, n (%) | 85 (22.5) |
| ≥ 3 Prior therapies, n (%) | 165 (43.8) |
| Median number of platinum-based therapies (range) | 2 (1–5) |
| 1 Prior platinum-based therapy, n (%) | 131 (34.7) |
| 2 Prior platinum-based therapies, n (%) | 144 (38.2) |
| ≥ 3 Prior platinum-based therapies, n (%) | 102 (27.1) |
| PFI from latest platinum regimen, n (%) | |
| <6 mo | 90 (23.9) |
| ≥ 6 –12 mo | 152 (40.3) |
| >12 mo | 129 (34.2) |
| Missing | 6 (1.6) |
| Platinum response (most recent therapy), n (%) | |
| Sensitive (recurrence after PFI ≥ 6 mo) | 283 (75.1) |
| Resistant (recurrence after PFI <6 mo) | 67 (17.8) |
| Refractory (progression on platinum, PFI <2 mo) | 26 (6.9) |
| Unknown | 1 (0.3) |

Adapted from Oza et al. [26].

Abbreviations: BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOC, epithelial ovarian cancer; PFI, progression-free interval.

BID (two 250 mg tablets). The second dose reduction level is 400 mg BID (two 200 mg tablets), and the third dose reduction level is 300 mg BID (one 300-mg tablet).

Management of the Most Common Investigational and Noninvestigational AEs

The following sections discuss the most common clinically relevant AEs associated with rucaparib in Study 10 and ARIEL2,

Table 3. Treatment-emergent AEs^{a,b} in patients receiving ≥ 1 dose of rucaparib 600 mg BID as monotherapy for EOC

| Event | Incidence (n = 377), n (%) | |
|---|-------------------------------|-----------|
| | Any grade ^c | Grade 3/4 |
| Investigational AEs | | |
| Anemia and/or low or decreased hemoglobin | 165 (43.8) | 94 (24.9) |
| ALT/AST increased | 156 (41.4) | 41 (10.9) |
| Thrombocytopenia and/or low or decreased platelet count | 79 (21.0) | 17 (4.5) |
| Blood creatinine increased | 79 (21.0) | 2 (0.5) |
| Neutropenia and/or low or decreased ANC ^d | 60 (15.9) | 32 (8.5) |
| Weight decreased ^d | 51 (13.5) | 4 (1.1) |
| Blood alkaline phosphatase increased ^d | 39 (10.3) | 4 (1.1) |
| Noninvestigational AEs | | |
| Nausea | 290 (76.9) | 19 (5.0) |
| Asthenia or fatigue | 289 (76.7) | 41 (10.9) |
| Vomiting | 174 (46.2) | 15 (4.0) |
| Constipation | 150 (39.8) | 6 (1.6) |
| Decreased appetite | 148 (39.3) | 10 (2.7) |
| Dysgeusia | 148 (39.3) | 1 (0.3) |
| Diarrhea | 130 (34.5) | 9 (2.4) |
| Abdominal pain | 119 (31.6) | 13 (3.4) |
| Dyspnea | 81 (21.5) | 2 (0.5) |
| Abdominal distension ^d | 70 (18.6) | 0 |
| Headache ^d | 69 (18.3) | 1 (0.3) |
| Dizziness ^d | 64 (17.0) | 2 (0.5) |
| Cough ^d | 60 (15.9) | 1 (0.3) |
| Urinary tract infection ^d | 58 (15.4) | 8 (2.1) |
| Abdominal pain upper ^d | 49 (13.0) | 2 (0.5) |
| Peripheral edema ^d | 43 (11.4) | 1 (0.3) |
| Back pain ^d | 43 (11.4) | 3 (0.8) |
| Insomnia ^d | 43 (11.4) | 0 |
| Pyrexia ^d | 41 (10.9) | 1 (0.3) |
| Upper respiratory tract infection ^d | 39 (10.3) | 0 |
| Photosensitivity reaction ^d | 38 (10.1) | 0 |

Adapted from Oza et al. [26] and data on file.

^aA treatment-emergent AE was defined as any AE occurring or worsening on or after the first dose of study drug and within 28 days after the last dose.

^bAEs are coded using Medical Dictionary for Regulatory Activities version 18.1.

^cOccurring in $\geq 10\%$ of patients; graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

^dData on file.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BID, twice daily; EOC, epithelial ovarian cancer.

along with recommendations and approaches that may reduce their incidence, severity, or longevity. We recognize that other less frequent AEs may occur during rucaparib

Table 4. Dose modifications in 377 patients receiving ≥ 1 dose of rucaparib 600 mg BID as monotherapy for EOC

| Event | Incidence (n = 377), n (%) |
|--|-------------------------------|
| Modifications or discontinuation due to AE ^{a,b} | |
| Dose reduction because of treatment-emergent AE | 173 (45.9) |
| Dose reduction because of treatment-related AE | 167 (44.3) |
| Dose interruption because of treatment-emergent AE | 221 (58.6) |
| Dose interruption because of treatment-related AE | 186 (49.3) |
| Discontinued treatment because of an AE ^c | 37 (9.8) |
| Discontinued treatment because of treatment-related AE | 30 (8.0) |
| Dose reductions on study (regardless of reason) ^d | |
| Only one dose reduction | 102 (27.1) |
| ≥ 2 Dose reductions | 80 (21.2) |
| Dose reduced to ≤ 300 mg BID | 35 (9.3) |

Contains data from Oza et al. [26] and data on file.

^aA treatment-emergent AE was defined as any AE occurring or worsening on or after the first dose of study drug and within 28 days after the last dose.

^bAEs are coded using Medical Dictionary for Regulatory Activities version 18.1.

^cExcludes patients who discontinued because of disease progression.

^dIn Study 10 and ARIEL2, treatment interruptions and dose reductions were permitted: for patients who received a 600 mg BID starting dose of rucaparib in Study 10 Parts 1 and 2A or ARIEL2 Part 1, dose reduction steps were in 120 mg BID increments (e.g., 600 mg BID to 480 mg BID) down to 240 mg BID; in Study 10 Part 3 and ARIEL2 Part 2, dose reduction steps were in 100 mg BID increments down to 300 mg BID.

Abbreviations: AE, adverse event; BID, twice daily; EOC, epithelial ovarian cancer.

therapy and recommend that these be managed in accordance with published and/or local guidelines where available.

Investigational AEs

Anemia. Anemia and/or a decrease from baseline in hemoglobin were the most common investigational AEs across the two studies, with an incidence of 43.8% (all grades; n = 165; Table 3; see also change from baseline data in Table 5) [26], and are emerging as general class effects for PARP inhibitors [5, 8–10, 25–28, 34–40].

Anemia of grade ≥ 3 , defined in these studies as a hemoglobin level < 8 g/dL or the need for red blood cell transfusion [26, 29, 41], was reported in 94 patients (24.9%) [26], and 18 patients (4.8%) had an SAE of anemia/decreased hemoglobin (data on file). The median time to onset of anemia was 54 days [26]. Only 63 patients (16.7%) had a treatment interruption, 65 (17.2%) had a dose reduction, and 4 (1.1%) had a discontinuation of rucaparib because of anemia/decreased hemoglobin (data on file).

Anemia was managed in Study 10 and ARIEL2 by rucaparib treatment interruptions and/or dose reductions and use of supportive care as recommended by NCCN guidelines [29]. Of 377

Table 5. Incidence of change from baseline in laboratory parameters in patients with EOC treated with rucaparib 600 mg BID

| Key laboratory parameter | All patients with OC (n = 377), ^a n (%) | |
|---|---|-----------------|
| | CTCAE grade 1–4 | CTCAE grade 3–4 |
| Hematologic | | |
| Decrease in hemoglobin (anemia) | 251 (66.6) | 88 (23.3) |
| Decrease in lymphocytes (lymphocytopenia) | 168 (44.6) | 26 (6.9) |
| Decrease in platelets (thrombocytopenia) | 147 (39.0) | 23 (6.1) |
| Decrease in absolute neutrophil count (neutropenia) | 132 (35.0) | 37 (9.8) |
| Clinical chemistry | | |
| Increase in creatinine | 347 (92.0) | 5 (1.3) |
| Increase in ALT ^b | 279 (74.0) | 47 (12.5) |
| Increase in AST ^b | 276 (73.2) | 17 (4.5) |
| Increase in cholesterol | 150 (39.8) | 9 (2.4) |

Adapted from Oza et al. [26].

^aAt least one worsening shift in CTCAE grade and by maximum shift from baseline.

^bIncrease in ALT/AST led to treatment discontinuation in 1 patient (0.3%).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; EOC, epithelial ovarian cancer; OC, ovarian cancer.

patients in the integrated safety summary population, 111 (29.4%) had one or more blood transfusion at a median time of 65 days (95% CI, 59–80) after rucaparib initiation (data on file).

Recommendations: a patient's hemoglobin levels should be monitored at least every 28 days during rucaparib treatment. For patients who develop anemia, other reversible causes such as iron, B12, and folate deficiencies should be investigated. Once other causes have been excluded, clinicians should consider treatment interruption as well as dose reduction to manage anemia and reduce the need for blood transfusions (Table 6). Patients should be offered transfusion of packed red blood cells as clinically indicated by their symptoms and local guidelines (Table 6).

Blood Creatinine Elevations. On-study elevation of serum creatinine was a common treatment-emergent AE, occurring in 79 patients (21.0%; Table 3; see also change from baseline data in Table 5). Early reports of mild to moderate creatinine elevations by clinical investigators within the first few weeks of treatment were investigated by the study sponsor. Subsequent in vitro studies have shown that rucaparib potently inhibits the drug transporters MATE1 and MATE2-K and moderately inhibits OCT-1 [6, 7]; these transporters play a role in renal secretion of creatinine. Inhibition of all three transporters has been demonstrated in vitro with olaparib [42], and MATE1 and MATE2-K inhibition has also been demonstrated in vitro with the PARP inhibitor veliparib [43]. Creatinine increases have also been reported following olaparib treatment for advanced EOC [5, 10].

Table 6. Clinical practice recommendations for managing AEs associated with rucaparib

| | Rucaparib-specific advice | ASCO and NCCN guidelines |
|-------------------------------|--|--|
| Investigational AEs | | |
| Anemia | <ul style="list-style-type: none"> • Monitor complete blood counts at least every 28 days [6, 7] • For grade ≥ 3, consider treatment interruption [6, 7] • Reduce rucaparib dose level if anemia persists^a | <ul style="list-style-type: none"> • Exclude nontreatment-related causes, such as iron, B12, and folate deficiencies [29] • Red blood cell transfusion^b [29] • Erythropoietic therapy [29] • Supplemental iron [29] |
| Blood creatinine elevations | <ul style="list-style-type: none"> • Mild to moderate elevations in creatinine are generally observed within the first few weeks of treatment [26] • Assess patients for acute kidney injury, exclude other causes^a • For grade ≥ 3, consider treatment interruption [6, 7] • No dose adjustment is needed for patients with mild to moderate renal impairment (CrCl 30–89 mL/min) <ul style="list-style-type: none"> – Dose recommendations for patients with CrCl <30 mL/min or patients on dialysis have not been determined [6, 7] | N/A |
| ALT/AST elevations | <ul style="list-style-type: none"> • Increases in ALT/AST levels are generally asymptomatic, reversible, and rarely associated with increases in bilirubin [26] • Elevations generally normalize over time with continued treatment [26] • In general, no intervention is required for mild to moderate elevations^a • Liver function should be monitored monthly^a | N/A |
| Thrombocytopenia | <ul style="list-style-type: none"> • Exclude heparin-induced thrombocytopenia^a • Platelet transfusion per local guidelines^a • For grade ≥ 3, treatment interruption; consider dose reduction^a | N/A |
| Noninvestigational AEs | | |
| Nausea and vomiting | <ul style="list-style-type: none"> • Vomited doses should not be replaced [6, 7] • The next dose should be taken at the regular time [6, 7] • Extra doses should not be taken [6, 7] • Consider alternatives to antiemetics^a: <ul style="list-style-type: none"> – Eat small, frequent meals – Eat food that is easy on the stomach – Eat full liquid foods – Eat food at room temperature – Avoid foods that induce nausea • Consider adjusting timing of rucaparib dose to later in the day^a • Suggested antiemetics: metoclopramide, prochlorperazine, or cyclizine^a • For grade ≥ 3 nausea and vomiting, exclude other causes (e.g., partial/complete bowel obstruction)^a | <ul style="list-style-type: none"> • The emetogenic potential of rucaparib is classified as moderate to high risk [30] <ul style="list-style-type: none"> – For moderate to high risk oral chemotherapy, provide prophylactic 5-HT₃ RA antagonist (continue daily) [30] – For breakthrough nausea/vomiting, add 1 additional agent from a different drug class (e.g., benzodiazepine, steroid) [30] |
| Diarrhea and constipation | <ul style="list-style-type: none"> • Exclude and/or treat possible underlying causes (e.g., infection, overflow from constipation)^a • Consider treatment interruption based on severity^a | <ul style="list-style-type: none"> • Uncomplicated cases: loperamide [31] • Complicated cases: IV fluids and antibiotics [31] |
| Asthenia and fatigue | <ul style="list-style-type: none"> • Expect patterns of fatigue^a • Fatigue does not necessarily indicate disease progression^a • Instruct patients on how to conserve energy and maintain an optimal level of physical activity^a | <ul style="list-style-type: none"> • General strategies [32]^a: <ul style="list-style-type: none"> – Self-monitor energy – Conserve energy – Use distraction – Find meaning in current situation – Seek advice from specialists • Pharmacologic intervention [32] <ul style="list-style-type: none"> – Use stimulant medications – Treat any underlying cause (eg, pain, emotional distress, anemia) as required – Optimize treatment for sleep disturbances, nutrition, and comorbidities • Nonpharmacologic intervention [32] <ul style="list-style-type: none"> – Engage in or maintain physical activity – Employ physical-based therapies – Use psychosocial interventions – Consult with nutritionist – Use CBT for sleep |

^aRecommendation based on the clinical experience of the authors.

^bInstitute for asymptomatic anemia with comorbidities (i.e., cardiovascular disease, chronic pulmonary disease, cerebral vascular disease), symptomatic anemia (i.e., dyspnea on exertion, sustained tachycardia, tachypnea, chest pain, lightheadedness, syncope, severe fatigue limiting day-time functioning), or patients at high risk (i.e., progressive decline in hemoglobin) [29].

Abbreviations: 5-HT₃ RA, 5-hydroxytryptamine receptor antagonist; AE, adverse event; ALT, alanine aminotransferase; ASCO, American Society of Clinical Oncology; AST, aspartate aminotransferase; CBT, cognitive-behavioral therapy; CrCl, creatinine clearance; IV, intravenous; N/A, not applicable; NCCN, National Comprehensive Cancer Network.

Overall in Study 10 and ARIEL2, 13 patients (3.4%) had a treatment interruption, 10 (2.7%) had a dose reduction, and 1 (0.3%) discontinued treatment because of increased blood creatinine levels (data on file). Pharmacokinetic analysis according to creatinine clearance (CrCl) as estimated by the Cockcroft-Gault method demonstrated that patients with mild renal impairment (CrCl, 60–89 mL/min; $n = 148$) and moderate renal impairment (CrCl, 30–59 mL/min; $n = 72$) had an approximately 15% and 32% higher steady-state area under the concentration-time curve for rucaparib, respectively, than patients with normal renal function (CrCl, ≥ 90 mL/min; $n = 143$) [6, 7].

Encouragingly, in keeping with the now known mechanism of action, serum creatinine levels decreased with interruption or discontinuation of rucaparib and increased again with resumption of treatment.

Recommendations: patients receiving rucaparib who develop an elevation of any grade in serum creatinine by definition and are suspected of having acute kidney injury (AKI) should first undergo the appropriate clinical assessments and investigations to exclude and treat other causes of AKI, such as dehydration or obstructive uropathy, which can occur in patients with advanced EOC who have a high burden of peritoneal or nodal disease. It may be appropriate to withhold rucaparib while these preliminary investigations are undertaken. Mild serum creatinine elevations do not require dose modification. Specifically, no dose adjustment is needed for patients with mild to moderate renal impairment (defined as CrCl, 30–89 mL/min; Table 6). In patients who have CrCl < 30 mL/min or require dialysis, dose recommendations have not been determined as no dedicated clinical studies of rucaparib have been conducted in these patients. We recommend monthly monitoring of renal function in patients taking rucaparib.

ALT/AST Elevation. A treatment-emergent AE of ALT/AST elevation occurred in 149 patients (41.4%; Table 3; see also change from baseline data in Table 5) [26]. ALT/AST elevations occurred early, within the first few weeks of rucaparib treatment, and were mostly asymptomatic, transient, and self-limiting [26]. Importantly, these elevations were rarely associated with bilirubin increases; none of the cases of ALT/AST elevation met Hy's Law criteria for drug-induced liver injury (i.e., ALT/AST $> 3 \times$ upper limit of normal [ULN], with concomitant bilirubin $> 2 \times$ ULN without substantial alkaline phosphatase elevations [i.e., $< 2 \times$ ULN] or another clear reason for elevation) [26, 44, 45]. In the early stages of ARIEL2 and Study 10, investigators were cautious about these AEs: 33 patients (8.8%) had a treatment interruption, 19 (5.0%) had a dose reduction, and 1 (0.3%) discontinued treatment because of increased ALT/AST (data on file). The mechanism of action or etiology of the ALT/AST elevations with rucaparib is currently unknown; however, ALT/AST elevations have also been observed with the PARP inhibitor niraparib [8, 9].

Recommendations: for patients taking rucaparib, we recommend that liver function be monitored monthly, including evaluation of bilirubin, alkaline phosphatase, and ALT/AST levels. For patients with elevations in ALT/AST, other causes of liver dysfunction should be ruled out first. In our experience following the final safety assessments, no intervention was

required to mitigate mild to moderate (e.g., grade 1–3) ALT/AST elevations provided all other causes were excluded (Table 6). Patients with grade 3 elevations should be monitored closely, and treatment should be interrupted if levels continue to rise or do not decline to grade ≤ 2 within 2 weeks [7]. Upon resolution to grade ≤ 2 , rucaparib can be resumed at the same or a reduced dosage. Grade 4 ALT/AST elevations require treatment interruption and dose reduction [7].

Thrombocytopenia. Seventy-nine patients (21.0%) experienced an AE of platelet count reduction from baseline, but only 17 (4.5%) had grade ≥ 3 thrombocytopenia [26]. Notably, in the NOVA trial of niraparib, thrombocytopenia was the most common grade ≥ 3 treatment-emergent AE, occurring in 124 of 367 patients (33.8%) [34].

Thirty-five patients receiving rucaparib (9.3%) had a treatment interruption, 18 (4.8%) had a dose reduction, and only 4 (1.1%) discontinued rucaparib treatment because of thrombocytopenia (data on file). There was one case of thrombocytopenia reported as an SAE (0.3%; data on file).

Recommendations: we recommend managing thrombocytopenia per local treating institution guidelines (Table 6). Treating physicians should first ensure that in vitro platelet clumping (pseudothrombocytopenia), which is common, has been differentiated from true thrombocytopenia by blood film. Physicians should also be alert to other possible causes, such as heparin-induced thrombocytopenia, a common concomitant medication for many patients with cancer. We recommend that rucaparib be held for grade ≥ 3 thrombocytopenia and the next cycle of rucaparib be delayed until recovery to grade ≤ 1 (platelet count of $\geq 75 \times 10^9/L$). Consider dose reduction in patients who fail to recover platelet count that results in retreatment delays.

Noninvestigational AEs

Nausea and Vomiting. The most common symptoms reported by patients receiving rucaparib were within the GI system ($n = 358$; 95%; data on file). The most common GI-related AEs were nausea and vomiting, representing the first and third most frequently occurring noninvestigational AEs, with incidence rates of 76.9% ($n = 290$) and 46.2% ($n = 174$), respectively [26]. Toxicity was mostly grade 1–2, with 19 (5.0%) and 15 (4.0%) patients having grade ≥ 3 nausea or vomiting, respectively [26]. Serious AEs of nausea and vomiting each occurred in four patients (1.1%; data on file). Nausea or vomiting led to a dose modification in 68 (18.0%) and 45 (11.9%) patients, respectively [26]. During the study, it was rare for patients to discontinue rucaparib because of nausea ($n = 5$; 1.3%) [26] and vomiting ($n = 3$; 0.8%), respectively (data on file).

Recommendations: in our experience, PARP inhibitors are generally moderately emetogenic, resulting in mild nausea that is most commonly reported during the first cycle. Given the continuous daily dosing of rucaparib, even mild nausea can have a negative effect on patient quality of life. Therefore, education prior to initiation is essential, and nausea should be promptly addressed. A prophylactic antiemetic should be considered. Rucaparib treatment may be held and/or reduced for grade 2 nausea not adequately controlled by concomitant medications and/or supportive care at the discretion of the treating physician.

In patients who have grade ≥ 3 nausea and vomiting, it is unlikely to be related to rucaparib, and these patients should be investigated and managed for other causes, including in particular evolving partial or complete bowel obstruction, which can occur in women with advanced EOC. The addition of antiemetics does improve rucaparib-related nausea and vomiting, but it is also worth considering alternative ways of managing what could be a chronic toxicity (Table 6). For example, in an approach initiated by the research clinical nurse specialists at the Northern Center for Cancer Care, starting rucaparib dosing later in the day sometimes improved rucaparib-related nausea and helped patients avoid use of antiemetics entirely (e.g., patient switching from an 8 a.m.–8 p.m. to a 10 a.m.–10 p.m. dosing schedule). For patients requiring antiemetics, the choice can be guided by the treating physician and/or local guidelines, but we suggest starting with agents such as regular metoclopramide, prochlorperazine, or cyclizine. Serotonin (5-hydroxytryptamine) antagonists, corticosteroids, and neurokinin-1 antagonists are rarely required but could be considered.

Diarrhea and Constipation. Across the two rucaparib studies, the incidence of any grade diarrhea was 34.5% ($n = 130$), with only nine patients (2.4%) experiencing a grade ≥ 3 toxicity [26]. Constipation was reported in a similar number of patients (any grade, $n = 150$ [39.8%]; grade ≥ 3 , $n = 6$ [1.6%]) [26]. Many patients with advanced EOC experience GI-related symptoms such as constipation alternating with loose stools and abdominal bloating or cramps, which are thought to be due to peritoneal bowel serosal disease. In these studies, 55 patients (14.6%) were taking one or more medication to treat constipation at baseline (data on file). It is hard to establish from these single-arm studies if the incidences of diarrhea and constipation were related to rucaparib or symptoms of the cancer. Results from the ARIEL3 study, in which patients with advanced EOC were randomized to maintenance treatment with either rucaparib or placebo, suggest a combination of both, as diarrhea and constipation were reported at relatively high levels in the placebo group and at increased incidence rates in the rucaparib group: diarrhea was reported in 118 of 372 patients (31.7%) receiving rucaparib and 41 of 189 (21.7%) receiving placebo, and constipation was reported in 136 of 372 patients (36.5%) receiving rucaparib and 45 of 189 (23.8%) receiving placebo [25].

Recommendations: patients who develop diarrhea while taking rucaparib should first undergo clinical assessments and investigations to exclude and treat any underlying causes, including infection, overflow from constipation, or medication-induced diarrhea. Patients may require intravenous fluids and the addition of antibiotics per ASCO guidelines [31]. Uncomplicated cases may be treated with loperamide. Rucaparib dose interruptions, followed by dose reductions, may be considered based on severity.

Asthenia/Fatigue. Asthenia/fatigue is emerging as a common side effect of PARP inhibitors [25–28, 34–40]. It was assessed during the rucaparib studies using an 11-point visual analog scale and was a common AE, reported (as any grade) in 289 patients (76.7%) [26]. The median time to

onset of asthenia/fatigue was 14 days (range, 1–288) (data on file). Grade ≥ 3 asthenia/fatigue was reported in 41 patients (10.9%) [26]. Any-grade asthenia/fatigue resulted in treatment interruptions in 43 patients (11.4%) and dose reductions in 53 (14.1%; data on file); 9 patients (2.4%) discontinued treatment altogether [26].

Recommendations: Although the majority of patients experienced only grade 1 or 2 fatigue while receiving rucaparib, the treating team should recognize that this is likely to be a chronic toxicity and not to dismiss it. Fatigue may be associated with underlying causes such as anemia, uncontrolled pain, poor nutrition, hypothyroidism, emotional distress, and sleep disturbances that are possible to treat.

Recommendations: Although the majority of patients experienced only grade 1 or 2 fatigue while receiving rucaparib, the treating team should recognize that this is likely to be a chronic toxicity and not to dismiss it. Fatigue may be associated with underlying causes such as anemia, uncontrolled pain, poor nutrition, hypothyroidism, emotional distress, and sleep disturbances that are possible to treat.

Informing patients of expected patterns of fatigue and discussing ways to conserve energy while maintaining an optimal level of physical activity is important before starting rucaparib (Table 6). While patients are on treatment, referrals for psychosocial interventions, nutrition consultation, and sleep therapy should be considered [32].

AEs of Special Interest

In the integrated safety population from Study 10 and ARIEL2, grade 1 or 2 photosensitivity reactions occurred in 38 patients (10.1%; data on file). No grade 3 or 4 events were reported.

Recommendations: The increased susceptibility to sunburn while receiving rucaparib may necessitate lifestyle and/or behavioral changes. Before initiating rucaparib therapy, patients should be counseled to avoid spending time in direct sunlight, to use appropriate sun protection when outdoors (e.g., wearing a hat and protective clothing), and to use sunscreen and lip balm with a sun protection factor of ≥ 50 [6, 7].

SAEs of Special Interest

Of the 1,077 patients from all clinical studies of rucaparib who received at least one dose of oral rucaparib, myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) was reported as an SAE in 5 patients (0.5%) during treatment and the 28-day safety follow-up period and in 10 patients (0.9%) who had long-term safety follow-up [7]. The duration of therapy with rucaparib in patients who developed MDS/AML varied from <1 month to approximately 29 months.

Recommendations: If MDS/AML is suspected, the patient should be referred to a hematologist for further investigations, including bone marrow analysis and blood sampling for

cytogenetics [6, 7]. If MDS/AML is confirmed by a hematologist, rucaparib should be discontinued [6, 7].

SAFETY PROFILE OF RUCAPARIB IN THE MAINTENANCE SETTING

Although the recommendations we have outlined above are based on data from and experience in the treatment setting, they can also be used in the management of rucaparib-associated side effects in the maintenance setting, in which similar AEs are observed. In the ARIEL3 study of rucaparib maintenance treatment, of 372 rucaparib-treated patients, 280 (75.3%) had nausea, 258 (69.4%) had asthenia/fatigue, 146 (39.2%) had dysgeusia, 139 (37.4%) had anemia/decreased hemoglobin, 136 (36.6%) had constipation, and 136 (36.6%) had vomiting of any grade [25]. Among rucaparib-treated patients, 70 (18.8%) reported anemia/decreased hemoglobin, 39 (10.5%) ALT/AST increased, 25 (6.7%) asthenia/fatigue, 25 (6.7%) neutropenia/decreased neutrophils, and 19 (5.1%) thrombocytopenia/decreased platelets of grade ≥ 3 [25].

CONCLUSION

Here we have discussed the most common clinically relevant scenarios that health care professionals will face when treating their patients with EOC with PARP inhibitors, specifically rucaparib. We have formulated practical recommendations for preventing and managing treatment-emergent AEs to maintain dose intensity, prolong treatment duration, and support quality of life. Our experience is based on multiple prior and ongoing clinical trials of rucaparib in conjunction with standard of care for patients with EOC, and our recommendations are aligned with and complement approved prescribing information and supportive cancer care guidelines published by ASCO and the NCCN [6, 7, 29–31].

Overall, rucaparib has a favorable benefit-risk profile and acceptable tolerability. The AEs and laboratory abnormalities that arise are usually self-limiting or can be managed with practical advice to the patient, treatment interruption and/or

dose reduction, and prophylactic or symptomatic therapies. This approach may allow patients with EOC to receive the optimal efficacy benefit from rucaparib and avoid premature treatment discontinuation.

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DISCLOSURES

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