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Safety and Clinical characteristics of patients with Ovarian cancer: Rucaparib Real-world Evidence (The SCORE Study)

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Keywords: *BRCA* mutations, Ovarian cancer, PARP inhibitors, Platinum-sensitive, Real-world evidence, Rucaparib

Abstract

Background: Ovarian cancer is one of the leading causes of cancer-related mortality among women, often diagnosed at advanced stages. Recent advances in targeted therapy, particularly the use of Poly (ADP-ribose) polymerase (PARP) inhibitors like rucaparib, have improved treatment outcomes in this patient population. However, real-world data regarding the patient characteristics, criteria for rucaparib use and treatment patterns remain limited.

Aim and Objective: This study aimed to evaluate clinical characteristics, treatment patterns, and criteria for rucaparib selection among ovarian cancer patients in India, focusing on identifying predictors of treatment response and safety profile.

Materials and Methods: This multicenter, retrospective, observational study enrolled adult women with ovarian, fallopian tube, or primary peritoneal cancer across nine Indian sites from June 2023 to January 2024. Eligible patients had ECOG performance status scores 0-4 and received rucaparib as maintenance treatment and were categorized based on platinum sensitivity. Patient characteristics, prior treatments, genetic mutation status, and

adverse events (AEs) were recorded. Descriptive statistics summarized patient demographics, treatment patterns, and safety data.

Results: The study included 36 patients with a mean age of 57.1 years. Most patients (86.1%) had ovarian cancer, primarily high-grade serous carcinoma, and presented at advanced stages (III-IV) with metastasis. *BRCA* mutations were present in 66.7% of patients, and rucaparib was mainly administered to patients with platinum-sensitive or partially sensitive relapsed cancer. The most common adverse events reported were anemia (27.8%) and fatigue (22.2%). Dose adjustments due to toxicity were required in 16.7% of patients, with 16.7% discontinuing rucaparib due to adverse events.

Conclusion: Rucaparib was well-tolerated in Indian ovarian cancer patients, with anemia and fatigue as common adverse events. Patients with BRCA mutations and platinum-sensitive disease were the primary candidates for rucaparib, though additional factors may influence treatment selection. Further research is needed to refine patient criteria and optimize treatment strategies.

Keywords: *BRCA* mutations, Ovarian cancer, PARP inhibitors, Platinum-sensitive, Real-world evidence, Rucaparib

Introduction

Ovarian cancer ranks as the seventh most common cancer and the eighth leading cause of cancer-related death in women. The absence of a public screening program for early detection of ovarian cancer often leads to its diagnosis at an advanced stage, by which time the cancer has metastasized beyond the ovaries.[1] Less than half of ovarian cancer patients survive beyond 5 years, and 15% of women diagnosed with advanced ovarian cancer die within 2 months of diagnosis.[2] Data from the Global Cancer Observatory (GLOBOCAN) database has established ovarian cancer as the third most common gynecological cancer globally in 2020. The rising prevalence of obesity, metabolic syndrome, estrogen exposure, and nulliparity has made ovarian cancer more common among younger women i.e., <50 years.[3]

Surgical cytoreduction aiming for the complete removal of visible disease remains the mainstay of treatment followed by adjuvant chemotherapy. Genetic testing to identify mutations influencing treatment options is now standard practice for all women diagnosed with epithelial ovarian cancer. The 2020 NCCN guidelines recommend that a gynecologic oncologist should assess if a patient with suspected or confirmed ovarian cancer can undergo surgery or receive neoadjuvant chemotherapy and conduct a laparoscopic evaluation for debulking surgery feasibility.[4] The revised 2022 NCCN guidelines recommend intravenous platinum-based chemotherapy for most patients with epithelial ovarian cancer and stage I disease as first-line systemic therapy and intravenous platinum-based chemotherapy with or without bevacizumab for those with stage II-IV disease.[5] Current guidelines strongly advocate for upfront and recurrent tumor molecular genetic testing in ovarian cancer to identify specific molecular alterations

that can inform treatment strategies and potentially incorporate highly beneficial therapies like poly (ADP-ribose) polymerase (PARP) inhibitors for patients who would respond well to them. Given that patients with ovarian cancer patients with *BRCA* mutations could potentially benefit from frontline maintenance therapy with a PARP inhibitor, it is suggested that all women with ovarian cancer be offered germline testing for *BRCA* mutations and other cancer susceptibility genes.[6] The emergence of PARP inhibitors has revolutionized treatment for platinum-sensitive recurrent ovarian cancer, and new data suggest even earlier incorporation of these drugs into the treatment course may be beneficial.[7] Recommendations based on results of a systematic review of clinical trials conducted between 2011 and 2020 highlighted the use of PARP inhibitors as maintenance therapy for all epithelial ovarian cancer patients who previously achieved complete or partial response to platinum-based chemotherapy.[8] Three PARP inhibitors olaparib, niraparib, and rucaparib have been approved by the US FDA based on the improved progression-free survival seen in three randomized phase III trials (SOLO-2/ENGOT-OV21, NOVA/ENGOT-OV16, and ARIEL3, respectively) for maintenance therapy in recurrent platinum-sensitive ovarian cancer. While PARP inhibitors demonstrate efficacy, especially in patients with *BRCA* mutations, as shown across these registration studies, the chronic, albeit low-grade, toxicity of these PARP inhibitors warrants a more nuanced approach. Individualized treatment plans, carefully weighing the potential benefits of PARP inhibitors against their safety profile for each patient with ovarian cancer is necessary.[9]

Rucaparib was first approved by the US FDA in December 2016 for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have previously achieved complete or partial response to platinum-based chemotherapy. It is also indicated for use in the treatment of adult patients with a 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.[10] More recently, it also gained accelerated approval in 2020 for the second- or later-line treatment of adult patients with *BRCA* mutation-positive metastatic castration-resistant prostate cancer. While germline and somatic *BRCA* mutations have traditionally been the focus for PARP inhibitor selection, responses observed in patients with high homologous recombination deficiency - loss of heterozygosity (HRD-LOH) following rucaparib treatment suggest a broader potential benefit.[11] This highlights the importance of exploring more nuanced patient selection criteria beyond just *BRCA* status to identify optimal candidates for PARP inhibitor therapy.

Given the evolving landscape of PARP inhibitor use and the potential for broader patient benefit beyond *BRCA* mutations, identifying characteristics that predict optimal response to rucaparib is crucial. The present study addresses this gap by analyzing real-world data on rucaparib treatment patterns and patient outcomes in Indian ovarian cancer patients.

Materials and Methods

Study design

This was a multicenter, retrospective, open-label, registry-based post-marketing observational study designed to collate real-world evidence regarding patient characteristics and treatment patterns with rucaparib use in ovarian cancer patients in India. The study was conducted between June 2023 and January 2024 at nine sites across India.

Ethical considerations

This retrospective study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethics committee approval was obtained before study initiation (Approval no. SCORE/IND/04/2023 date 15th June 2023). Patient anonymity was maintained throughout the study. This study adhered to ethical principles outlined in the World Medical Association Declaration of Helsinki.

Study population

Adult women (>18 years old) diagnosed with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer (regardless of biomarker status) were included in the study. They also had to satisfy the inclusion criteria of ECOG performance status score 0-4 and receipt of rucaparib as maintenance therapy at any line of treatment. These platinum-sensitive, partially platinum-sensitive, or platinum-resistant.

Patients were excluded if they received other experimental drugs by participating in other clinical trials at the same time as this study, if they had a previous or current diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), or if they were pregnant, lactating, or planning pregnancy during the study.

Study intervention

In this study, the intervention administered was rucaparib. Patients received varying dosages of rucaparib i.e.,200 mg BD 300 mg BD, 500 mg BD, or 600 mg BD. This regimen continued until disease progression or if the patients experienced unacceptable toxicity. The study specifically focused on patients receiving rucaparib as maintenance treatment i.e., they would initiate rucaparib treatment no later than 8 weeks after completing their final dose of a platinum-based chemotherapy regimen.

Study endpoints

The primary endpoint was the proportion of women with specific demographic characteristics (e.g., age range, comorbidities) and cancer characteristics (e.g., stage, histology) among ovarian cancer patients receiving rucaparib. Secondary endpoints included incidence rate of adverse events (AEs) and progression-free interval (PFI) in women with ovarian cancer who received rucaparib. Changes in specific laboratory parameters (e.g., creatine clearance) following rucaparib treatment were also evaluated.

Data sources and collection

Data were extracted from the case record form (CRF) provided to the physicians in the participating hospitals (Supplementary Table 1). This form was based on the pre-defined outcome measures. Trained personnel at each participating site were responsible for quality of data extraction using the standardized form. Data quality control procedures were implemented to ensure data accuracy and completeness.

Data variables

A systemic examination of the general appearance, head and neck, cardiovascular system, respiratory system, gastrointestinal system, and nervous system, etc. was conducted. The following data were collected for each patient: demographics, family history of ovarian or breast cancer, characteristics of ovarian cancer (ovarian, fallopian tube, peritoneal), cancer stage, histology, results of genetic/molecular testing (e.g., *BRCA* mutation testing), sensitivity to platinum-based chemotherapy regimens (platinum-sensitive, partially platinum-sensitive, platinum-resistant), presence and number of metastatic sites, treatment history (prior chemotherapy regimens, response to previous treatments), details of rucaparib treatment (dosage, duration, treatment interruptions/discontinuations, reasons for discontinuation), and safety data (adverse events associated with rucaparib treatment).

Sensitivity to platinum chemotherapy was determined based on the patient's response to prior platinum-based chemotherapy regimens.[12]

The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were applied to evaluate tumor response as a complete response (CR), a partial response (PR), progressive disease (PD), and stable disease (SD).

Statistical analysis

Descriptive statistics are used to summarize patient characteristics and treatment patterns. Categorical variables are presented as frequencies and percentages. Continuous variables are presented as means, medians, and standard deviations (or interquartile ranges) depending on data normality. Data from all patients who received at least one dose of the study drug were included in the safety analyses. AEs were summarized with classification of serious AEs, AEs leading to treatment discontinuation or death, and Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher AEs.

Results

The study included a total of 39 patients from nine sites across India. Of the 39 patients, 3 were excluded from the analysis because they had other cancers i.e., 2 with breast cancer and 1 with cancer of unknown etiology. Therefore, the intention-to-treat population comprised 36 patients (Figure 1).

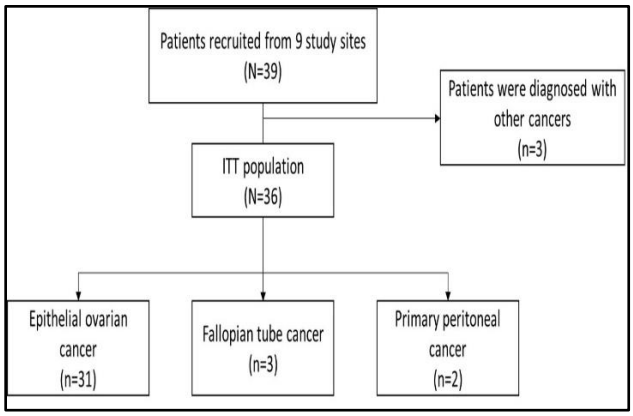

Figure 1: Patient disposition

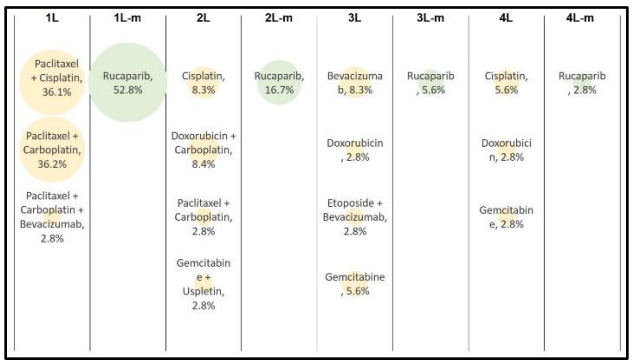

Figure 2: Treatment regimens administered to the patients

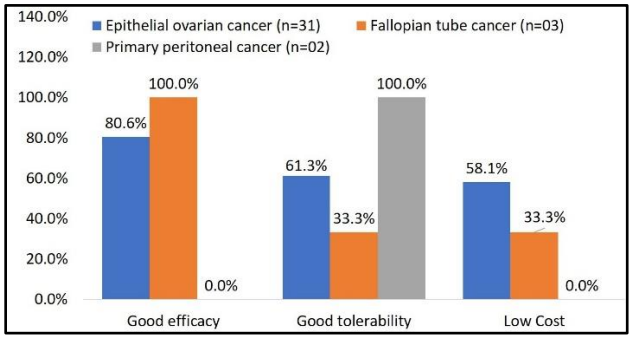

Figure 3: Reasons for selection of Rucaparib dose (n=36)

Table 1. Patient characteristics

Characteristic	Overall population (N=36)
Age, mean ± SD, years	57.1 ± 9.7
BMI, mean ± SD, kg/m^2	24.2 ± 5.4
Diagnosis, n (%)	
Ovarian cancer	31 (86.1)
Fallopian tube cancer	3 (8.3)
Peritoneal cancer	2 (5.6)
Histology type, n (%)	
HGSC	30 (83.3)
LGSC	1 (2.8)
Mixed	4 (11.1)
Mucinous	1 (2.8)
Cancer stage, n (%)	
IIa	1 (2.8)
IIb	1 (2.8)
IIc	2 (5.6)
IIIa	1 (2.8)
IIIb	6 (16.7)
IIIc	12 (33.3)
IV	13 (36.1)
Metastasis[a], n (%)	
Yes	25 (69.4)
One site	15 (41.7)
Two sites	9 (25.0)
Three sites	1 (2.8)
No	11 (30.6)
Lymph node positivity, n (%)	
Yes	31 (86.1)
No	4 (11.1)
Unknown	1 (2.8)
ECOG PS, n (%)	
1	25 (69.4)
2	8 (22.2)

3	3 (8.3)
Number of previous relapses, n (%)	
0	14 (38.9)
1	10 (27.8)
2	10 (27.8)
3	1 (2.8)
Missing data	1 (2.8)

[a] Sites of metastasis included: peritoneum (n=10, 27.8%), liver (n=7, 19.4%), omentum (n=7, 19.4%), lung (n=6, 16.7%), pleura (n=2, 5.6%), stomach (n=1, 2.8%), and bone (n=1, 2.8%)

Table 2. Treatment history

Variable	**Overall population (N=36)**
Surgery, n (%)	26 (72.2)
Neo-adjuvant treatment, n (%)	26 (72.2)
Number of prior lines of therapy, n (%)	
1	23 (63.9)
2	8 (22.2)
>3	4 (11.1)
Missing data	1 (2.8)
Number of prior platinum-based therapy, n (%)	
1	23 (63.9)
2	11 (30.6)
>3	2 (5.6)
Types of therapy, n (%)	
Chemotherapy	35 (97.2)
Bevacizumab	10 (27.8)
PARPi	4 (11.1)
Targeted therapy	2 (5.6)
PFI from latest regimen[b], n (%)	
< 6 months	10 (27.8)
6-12 months	8 (22.2)
>12 months	6 (16.7)
Unknown	10 (27.8)
Missing data	2 (5.6)
RECIST	
Complete response	5 (13.9)
Partial response	23 (63.9)
Stable disease	2 (5.6)
Progressive disease	3 (8.3)
Not evaluable	3 (8.3)

[a] chemotherapy included: paclitaxel (n=26, 72.2%), carboplatin (n=20, 55.6%), paclitaxel + carboplatin (n=20, 55.6%), cisplatin (n=2, 5.6%), paclitaxel + cisplatin (n=2, 5.6%), and carboplatin + bevacizumab (n=1, 2.8%)

[b] Before receiving the study drug, the patients had received platinum-based chemotherapy (n=31, 86.1%), non-platinum-based chemotherapy (n=4, 11.1%), or targeted therapy (n=1, 2.8%)

Table 3. Details of rucaparib treatment

Variable	Overall population (N=36)
Stage at which rucaparib was started, n (%)	
IIb	1 (2.8)
III	8 (22.2)
IIIa	2 (5.6)
IIIb	2 (5.6)
IIIc	8 (22.2)
IV	13 (36.1)
NR	1 (2.8)
NR	1 (2.8)
Rucaparib dosing technique, n (%)	
Escalation	25 (69.4)
De-escalation	11 (30.6)
1L maintenance rucaparib, n (%)	19 (52.8)
Stage at which 1L maintenance rucaparib was started, n (%)	
IIb	1 (5.3)
IIIc III	6 (31.6) 1 (5.3)
IV	8 (42.1)
NR	3 (15.8)

NR: Not reported.

Table 4: Rucaparib dose details

	Epithelial ovarian cancer	Fallopian tubecancer	Primary peritoneal cancer	Total
200 mg BD	4	0	0	4
300 mg BD	19	3	2	24
300 mg OD	2	0	0	2
500 mg BD	1	0	0	1
600 mg BD	5	0	0	5
Total	31	3	2	36

Table 5. Safety data associated with rucaparib therapy

Variable	Overall population (N=36)
Number of AEs, n (%)	
0	17 (47.2)
1	9 (25.0)
2	6 (16.7)
3	4 (11.1)
AE severity, n (%)	
Grade 1	1 (2.8)
Grade 2	4 (11.1)
Grade 3–5	3 (8.3)
AEs experienced by the patients, n (%)	
Anemia	10 (30.3)

Fatigue	8 (24.2)
Myelosuppression	4 (12.1)
Neutropenia	3 (9.1)
GI disturbances	5 (15.2)
AST/ALT elevation	2 (6.1)
Thrombocytopenia	1 (3.0)
Total AEs	33 (100.0)
Amendments to rucaparib therapy, n (%)	
None	24 (66.7)
Dosage reduced	6 (16.7)
Discontinued	6 (16.7)
Reasons for discontinuation of rucaparib therapy, n (%)	
Old age and comorbidity	2 (33.3)
Cost and comorbid obesity	1 (16.7)
Frailty	1 (16.7)
Grade 4 anemia	1 (16.7)
Myelosuppression	1 (16.7)

Patient demographics

The demographic characteristics of the included patients are shown in Table 1. The patients had a mean age of 57.1 ± 9.7 years and were predominantly diagnosed with ovarian cancer (n=31, 86.1%), followed by fallopian tube cancer (n=3, 8.3%) and peritoneal cancer (n=2, 5.6%). The majority of the patients had high-grade serous carcinoma (n=30, 83.3%), were diagnosed at a late stage i.e., stage IIIc (n=12, 33.3%) or stage IV (n=13, 36.1%), presented with metastasis (n=25, 69.4%), and had lymph node positivity (86.1%). A majority of the patients had ECOG PS status of 1 (69.4%).

Only 6 out of 36 patients had a family history of cancer, with breast cancer being the most common (n=3, 8.3%), followed by *BRCA*-positive fallopian tube cancer, lung cancer, and ovarian cancer (n=1, 2.8% each). Of note, all 3 patients with a family history of breast cancer developed an epithelial type of ovarian cancer. While 38.9% had no relapse, more than half of the patients (58.3%) had at least one relapse event.

Genetic mutation testing results

Testing for genetic mutations was conducted at the time of first diagnosis for 27 (75.0%) patients or at the time of first relapse for 8 (22.2%). Of note, CA125 mutation testing was conducted as part of the initial screening for 16 (44.4%) patients. A majority of the patients had CA125 mutations (n=17, 47.2%), with 5 patients (29.4%) having germline mutations in CA125 and 4 (23.5%) with somatic mutations. A majority of the patients had *BRCA* mutations (n=24, 66.7%), with almost half of the patients having germline mutations in *BRCA* (n=17, 47.2%) and some (n=7, 19.4%) with somatic mutations. Homologous recombination deficiency (HRD) was reported in 4 patients (11.1%), all of them being diagnosed with the epithelial type of ovarian cancer. Other mutations were reported in 28 (77.8%) patients.

Treatment history

In terms of treatment history, most patients (72.2%) had undergone surgery and received one prior line of therapy (63.9%) (Table 2). Chemotherapy was the dominant treatment type (97.2%). While 63.9% of patients achieved a partial response, nearly a third (27.8%) had their cancer progress within 6 months after their latest treatment.

Tumor response

RECIST criteria were used to evaluate response to treatment (Table 2). Complete response (CR) was achieved in 5 (13.9%) patients, whereas a majority (n=23, 63.9%) had achieved partial response (PR). The disease had progressed in 3 (8.3%) patients.

Details of rucaparib treatment

At the time of initiating rucaparib treatment at any line, most patients had advanced disease, with 8 (22.2%) in stage IIIc and 13 (36.1%) in stage IV (Table 3). The details of the Rucaparib dose used at any line of therapy are as per Table 4. Nearly two-thirds 69.4% of patients received rucaparib as an escalation therapy and 30.6% received it as de-escalation.

First-line maintenance rucaparib was administered to 19 (52.8%) patients, and the majority of these 19 patients had stage IV disease (n=8, 42.1%). First-line maintenance rucaparib was administered mainly as 300 mg BD (44.1%), 500 g BD (11.1%) or 600 mg BD (33.3%). When rucaparib was used as first-line maintenance therapy, it was mainly administered after paclitaxel + carboplatin in (36.2%) and paclitaxel + cisplatin in (36.1%).

Rucaparib was administered as a second-line maintenance therapy in 6 (16.7%) patients, third-line maintenance therapy in 2 (5.6%) patients and 1 (2.8%) patient received rucaparib as a fourth-line maintenance treatment. Data regarding all treatment regimens administered to the patients are shown in Figure 2.

As seen in figure 3, the reasons for selecting rucaparib in the study population were good efficacy (77.8%), good tolerability (61.1%), and low cost (52.8%).

Rucaparib safety

A total of 33 AEs were reported in 19 (52.8%) patients. Among the 8 AEs for which severity grading data were available, 4 AEs were of grade 2 and 3 AEs were of grade 3–4. Anemia (n=10, 27.8%), fatigue (n=8, 22.2%), and gastrointestinal disturbances (n=5, 13.9%) were the most common AEs reported by the patients. Other AEs included myelosuppression (n=4, 11.1%), neutropenia (n=3, 8.3%), AST/ALT elevation (n=2, 5.6%), and thrombocytopenia (n=1, 2.8%).

The mean ± SD serum creatine level was 1.18±0.31 mg/dL in the 5 patients with available data. Serum creatine clearance was 82.63±16.58 mL/min in the 24 patients with available data.

While no amendments to the rucaparib dosing were needed for 24 (66.7%) patients, the dosage had to be reduced in 6 (16.7%) patients and treatment discontinued in 6 (16.7%) patients (Table 5). Among patients who discontinued rucaparib therapy, the reasons were old age and comorbidities in 2 (33.3%), cost and comorbid obesity in 1 (16.7%), frailty in 1 (16.7%), grade 4 anemia in 1 (16.7%), and myelosuppression in 1 (16.7%).

Discussion

Rucaparib has emerged as a treatment of choice for several physicians worldwide in the management of ovarian cancer. However, since a one-size-fits-all approach may not be appropriate, it is important to identify patient groups who will maximally benefit from rucaparib treatment. This study was conducted to identify the characteristics of ovarian cancer patients in India who were prescribed rucaparib treatment at various stages of their disease.

The present study population primarily consisted of patients with epithelial ovarian cancer, particularly high-grade serous carcinoma. A substantial proportion of patients presented with advanced disease and metastasis. This is in line with the fact that most patients with ovarian cancer are diagnosed only in advanced stages.[13] While cytoreductive surgery followed by intravenous paclitaxel/platinum-based chemotherapy remains the standard first-line treatment for advanced HGSC, the majority of patients experience a recurrence of the disease within 3 years, posing a significant challenge.[14] A majority of the patients (72.2%) underwent surgical resection and neo-adjuvant treatment in this study. Among these patients, the majority i.e., 11/26 had platinum-sensitive (PFI >12 months) or partially sensitive (PFI >6 months) recurrent ovarian cancer. This is in line with results from the AGO-DESKTOP III trial, in which surgery was considered beneficial for patients with platinum-sensitive recurrent ovarian cancer who undergo complete resection.[15]

In the present study, almost a third (29.4%) of the patients had a resistant relapse and 23.5% had a partially sensitive relapse since the latest treatment regimen. Rucaparib was initiated in these patients as maintenance treatment.

The choice of systemic therapy depends on tumor histology, *BRCA* mutation status, platinum-free interval (PFI), and prior exposure to the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab. Analysis of patients from two phase 2 trials, Study10 and ARIEL2, including patients with *BRCA* mutation-positive HGSC ovarian cancer and prior platinum-based chemotherapy showed that the objective response rate was 54% and CR and PR were achieved in 9% and 43% patients, respectively.[16] The phase 3 ARIEL3 study conducted between April 2014 and July 2016 showed that rucaparib significantly improves progression-free survival in platinum-sensitive ovarian cancer patients.[17-18] In this trial, 21% of patients were found to respond exceptionally to rucaparib treatment i.e., they had a PFS ≥2 years. In terms of molecular markers, those with *BRCA1*, *BRCA2*, *RAD51C*, and *RAD51D* alterations and genome-wide loss of heterozygosity derived exceptional benefit.[19]

BRCA genetic screening plays a crucial role in ovarian cancer management, even though germline *BRCA* mutations occur in a minority of patients with HGSC ovarian cancer. While not everyone will have a germline mutation, many tumors harbor genetic aberrations in *BRCA* or other homologous recombination (HR) genes.[20] Identifying these mutations through genetic screening allows for improved preventive measures and targeted therapeutic development. *BRCA* mutations were noted in a majority (66.7%) of the patients in this study, and 47.2% and

19.4% had germline and somatic mutations, respectively. *BRCA* mutation status does not influence the decision to use a PARP inhibitor as maintenance therapy following platinum-based chemotherapy in patients with HGSC ovarian cancer.[21] However, the US FDA granted accelerated approval to rucaparib in 2016 for the treatment of advanced ovarian cancer patients with deleterious *BRCA* mutations (germline and/or somatic) who have received two or more prior chemotherapies.[22]

In the present study, *CA125* mutation testing was included as part of the initial screening for almost half of the patients (44.4%). *CA125* mutations were found in almost half of the study population, with 29.4% having germline mutations and 23.5% having somatic mutations. While *CA125* has been the most widely used biomarker for ovarian cancer in clinical practice, its high rates of both false positives and negatives limit its diagnostic potential and reliability in the early detection of ovarian cancer.[23] A retrospective cohort study conducted in the United Kingdom demonstrated a 12-fold higher odds of being diagnosed with early-stage ovarian cancer when the CA125 levels were normal than when abnormal.[24] These findings put CA125 screening out of favor, yet many clinicians follow a combined approach utilizing longitudinal CA125 monitoring and second-line transvaginal ultrasound to achieve earlier diagnosis of ovarian cancer.[25] Since there is no common baseline level for CA125, more frequent serial measurements, perhaps every 3 months, have also been suggested.[26]

Clinically meaningful efficacy benefits from rucaparib maintenance treatment are also dependent on response to last platinum-based chemotherapy or baseline disease.[27] In the ARIAL3 trial, patients with no measurable disease at baseline, CR to latest platinum chemotherapy, and longer penultimate PFI exhibited excellent response to rucaparib treatment. In the present study, almost all patients had received at least one line of platinum-based chemotherapy before initiating rucaparib. They had achieved CR (13.9%) or PR (63.9%) and predominantly had stage IIIc (22.2%) or stage IV (36.1%) disease at the time of initiating rucaparib. The ATHENA-MONO phase 3 trial showed that rucaparib was an effective first-line maintenance therapy option for ovarian cancer patients regardless of their genetic mutation results.[28] In the present study, rucaparib was administered as first-line maintenance therapy in 52.8% patients. The FDA has approved rucaparib as a single-agent maintenance therapy after patients have achieved CR or PR with platinum-based chemotherapy, and half of the patients (52.8%) in the present study were initiated on rucaparib as first-line maintenance. Of note, 42.1% of the patients who received rucaparib as first-line maintenance treatment had stage IV disease. The selection of rucaparib in the present study was mainly driven by its good efficacy, good tolerability, and cost-effectiveness. A cost-effectiveness study comparing PARPi showed that the high costs of orally administered PARPi were not compensated for by the reduced costs associated with infusions and managing toxicities associated with intravenous regimens with lower response and shorter median PFS.[29] However, further understanding of the economic benefits of rucaparib over platinum-based maintenance chemotherapy regimens warrants additional research and analysis.

The high efficacy of PARPi in ovarian cancer opens possibilities for treatment de-escalation. This approach is crucial in oncology because it allows to maintain effective treatment while minimizing adverse effects associated with conventional chemotherapy, while reducing financial burden caused by these expensive, yet powerful, drugs like PARPi. De-escalation strategies aim to find the optimal balance between achieving positive clinical outcomes and minimizing the downsides of treatment for patients.[30] Potential de-escalation strategies include administrating PARPi in the neo-adjuvant settings and potentially reduce surgical burden, reducing the intensity of post-operative chemotherapy following initial surgery when combined with PARPi, shortening the recommended duration of PARPi therapy for patients with a good response, administering PARPi immediately after surgery, forgoing maintenance therapy altogether when combined with PARPi, and continuing PARPi treatment combined with localized treatment even if oligo progression was noted.[31] In the present study, rucaparib was administered as escalation therapy in about 70% of the patients, but de-escalation was possible in 30.6% of patients.

Safety data from the phase III ARIEL3 study showed that AEs associated with rucaparib include anemia, elevations in blood creatinine, alanine aminotransferase, and aspartate aminotransferase, thrombocytopenia, gastrointestinal-related events, and asthenia and fatigue.[32] Most of these AEs are highlighted as manageable AEs that are unlikely to need treatment discontinuation. When dose reduction is deemed necessary, it is recommended that the dosage be reduced from the 600 mg daily dosage to 300 mg daily dosage in three steps (600 mg to 500 mg, 500 mg to 400 mg, and 400 mg to 300 mg).[32] To proactively manage treatment-emergent adverse events (TEAEs), particularly during early treatment phases, close patient follow-up is crucial. Additionally, educating patients about expected TEAEs, their monitoring methods, and management strategies is essential.[33] In the present study as well, anemia, fatigue, and GI disturbances were the most commonly observed AEs. Dose adjustments were needed in 16.7% of patients in this study. Rucaparib treatment also had to be discontinued in 16.7% patients, mainly due to AEs. Pooled evidence from clinical trials highlights a similar proportion of 16.2% of patients in which rucaparib had to be stopped due to TEAEs. Caution is advised regarding rucaparib dosing for patients with creatinine clearance <30 mL/min, as dose reduction may be necessary.[34] In the present study, no dose reduction for rucaparib treatment due to impaired kidney function was necessary as all patients in this study had a creatine clearance >30 mL/min.

Conclusion

Rucaparib was generally well-tolerated among Indian ovarian cancer patients in this real-world evidence study. The treatment demonstrated an acceptable safety profile, with manageable adverse events such as anemia and fatigue. Patients with BRCA mutations and platinum-sensitive disease were the primary candidates for rucaparib, though additional factors may influence treatment selection. However further research is needed to refine patient selection criteria beyond BRCA mutations, potentially including HRD-LOH status.

Optimizing treatment regimens, including potential escalation or de-escalation strategies, warrants further investigation to balance efficacy with minimizing AEs and treatment burden.

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Conflict of Interest

None.

Ethical No.

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