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CASE SERIES

Recurrent Ovarian Cancer with BRCAness Phenotype: A Treatment Challenge

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ABSTRACT

Introduction: Ovarian cancer is a leading cause of death among women with gynecologic malignancies. The relapse rate is high after platinum-based therapy, with the effectiveness of subsequent treatment lines decreasing over time. Recent data suggest the benefit of maintenance therapy with niraparib in platinum-sensitive recurrent disease.
Case Presentations: We report a case series of five women with advanced ovarian cancer and BRCAness phenotype who responded favorably, and in some cases with long-term response, to maintenance therapy with niraparib. Toxicities were as expected and generally manageable. Two patients developed grade 2/3 hematological toxicity, which resolved with treatment suspension and subsequent dose reductions, and one patient reported a rare skin toxicity while responding to full-dose niraparib treatment, which was controlled with photoprotection and sunscreen.
Discussion and Conclusions: This case series highlights the role of PARP1/2 inhibitors as a new standard of care as maintenance therapy for recurrent platinum-sensitive high-grade ovarian cancer, irrespective of BRCA status.

Keywords: Advanced ovarian cancer; BRCAness; Maintenance therapy; PARP1/2 inhibitor; Platinum-sensitive

Key Summary Points

Multi-treated ovarian cancer patients can benefit from maintenance therapy with niraparib and maintain response with low doses of this agent more frequently than previously considered.

Niraparib has a manageable toxicity profile, with skin toxicity (including acral erythema) occasionally presenting.

The full range of PARP inhibitor toxicities will become clearer with increasing use of these agents in clinical practice.

Tumor marker CA-125 predicts disease progression and should be used in the follow-up of patients with ovarian cancer.

The results of this case series add relevant real-world evidence to data retrieved from clinical trials.

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INTRODUCTION

Ovarian cancer is one of the most common gynecologic cancers, ranking third after cervical and uterine cancer, and is a leading cause of death from gynecologic malignancy [1–3]. Most patients present at an advanced stage of disease and have a dismal prognosis [1]. In recent years, this tumor has been increasingly diagnosed in younger women (< 50 years) with no family history of the disease [1].

Major prognostic factors in ovarian cancer include stage at diagnosis, extent of surgery cytoreduction and debulking, sensitivity to platinum-based chemotherapy, and BRCA1/2 mutational status [4–6]. The absence of residual disease after debulking has been consistently associated with survival [7]. Patients with miliary residual disease after cytoreduction have lower rates of complete response to treatment, poorer prognosis, lower median progression-free survival (PFS), and shorter survival after relapse [8].

The concept of 'BRCAness' was introduced by Ashworth and colleagues to identify phenotypic changes in sporadic cancers that would imply similar treatment susceptibility to DNA-damaging agents [9]. These ovarian cancer patients with BRCAness syndrome are characterized by high response rates to first-line platinum-based treatment, high response rates to subsequent therapies, including platinum therapies, long treatment-free intervals beyond relapse, improved overall survival, and tumors that are usually, but not exclusively, serous in terms of histologic characterization [10].

In the era of personalized medicine, it is now possible to see beyond tumor type and target tumor phenotypes, molecular changes, and genetic variants with new drugs. The aim of this change of paradigm is to increase patients' survival with an improved quality of life by targeting a singular cancer type in a singular patient, replacing the days in which every cancer type was treated the same way with a new era in which treatment is directed at the molecular aberrations of each patient.

The standard upfront treatment in ovarian cancer includes cytoreductive surgery and, in most patients, platinum-based chemotherapy with or without bevacizumab [11, 12]. High response rates to first-line platinum-based chemotherapy are typically observed, but also high recurrence rates [13]. Sequential chemotherapy regimens are often used in the absence of other therapeutic options, with suboptimal results and cumulative toxicity [13]. Treatment effectiveness decreases over time, with resistance to platinum drugs being an ominous sign regarding survival and quality of life [2, 14]. Maintenance therapy with poly(-adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors has shown promising results in platinum-sensitive recurrent ovarian cancer after first-line treatment and regardless of BRCA1/2 status, improving the median PFS with manageable toxicities [15, 16]. Niraparib is an oral, highly selective PARP1/2 inhibitor approved as maintenance therapy in patients with recurrent ovarian cancer who respond to platinum-based chemotherapy, regardless of BRCA status [15, 17–19]. It has shown clinical benefit in treating patients with wild-type BRCA tumors in the NOVA [15] and QUADRA [18] clinical trials and in those with or without homologous-recombination deficiency in the PRIMA trial [16]. Regarding toxicities, niraparib is frequently associated with myelosuppression, fatigue, nausea and vomiting, decreased appetite, headache, hypertension, insomnia, and dizziness [15, 16, 18, 20]. Dose reductions were reported in 66.5% and 70.9% of patients in the NOVA and PRIMA trials and treatment discontinuations due to thrombocytopenia in 9.3% and 4.3%, respectively [15, 16].

We report here a series of five clinical cases of advanced ovarian cancer previously treated with chemotherapy-based regimens with good response and manageable toxicities to maintenance therapy with niraparib. Written informed consent for case description and use of photographs had been obtained previously from all patients, who had no involvement in the study other than being treated for their condition.

CASE PRESENTATIONS

Case 1

A fit and apparently healthy 55-year-old woman with no relevant medical or family history presented with a 3-week history of abdominal pain and distention. Computed tomography (CT) scan of the thorax, abdomen, and pelvis revealed multiple peritoneal implants (the largest being 5.3 × 4.2 cm in the pelvic cavity), bilateral ovarian masses (both 4.5 × 4 cm), and suspicious peri-aortic lymphadenopathies. Laboratory tests showed increased levels of cancer antigen 125 (CA-125; 750 U/mL) and normocytic/normochromic anemia (hemoglobin [Hb] 10.6 g/dL).

The patient underwent primary debulking surgery with hysterectomy, bilateral salpingo-oophorectomy, complete omentectomy, lymphadenectomy of the suspicious lymph nodes, excision of peritoneal implants and an implant located on the duodenum wall, and ascitic cytology. The anatomopathological examination led to the diagnosis of bilateral ovarian serous cystadenocarcinoma with multiple peritoneal pelvic and extra-pelvic implants, malignant ascites, and macroscopic residual tumor invading the margins (International Federation of Gynaecology and Obstetrics [FIGO] stage IIIC R2). Post-surgery CT scan revealed a paraduodenal mass with no other suspicious lesions, and laboratory tests showed a CA-125 of 338 U/mL.

The patient was proposed for adjuvant chemotherapy. She completed six 3-week cycles of gemcitabine 800 mg/m^2 on days 1 and 8 and carboplatin AUC 5 on day 1 in combination with bevacizumab 15 mg/kg body weight, which was maintained for 22 cycles. No relevant toxicities were reported. After five cycles, complete remission of the duodenal metastasis and CA-125 normalization were achieved. The patient did well for the first 15 months following the last platinum administration, then the CA-125 level began to rise (69.2 U/mL), and thorax, abdomen, and pelvis CT confirmed disease progression, with three de novo lymph nodes in the pelvic cavity. The patient started first-line palliative chemotherapy with 3-week cycles of paclitaxel 175 mg/m^2 and carboplatin AUC 6. After six cycles, complete imagiological response was achieved. However, the patient presented peripheral sensory neuropathy grade 3 on both feet and grade 2 on the hands, and chemotherapy was suspended.

Approximately 6 months later, disease progression was documented by biochemical (increased CA-125 to 140 U/mL) and imagiological methods, with multiple hepatic lesions, lymph nodes, and peritoneal implants. The patient started second-line palliative chemotherapy with 3-week trabectedin 1.1 mg/m^2 and pegylated liposomal doxorubicin 30 mg/m^2. After nine treatment cycles, partial response was achieved, but grade 3 neutropenia and grade 3 cholestasis prompted doxorubicin suspension, and the patient maintained only trabectedin monotherapy. After three cycles, disease progression was again documented, and the patient received doxorubicin monotherapy, but after three more cycles, the disease again progressed with peritoneal carcinomatosis and lymph nodes.

At this time, the patient was tested for germline BRCA mutations, with a negative result, and started on 3 weeks of gemcitabine 800 mg/m^2 on days 1 and 8 and carboplatin AUC 5 on day 1. After six cycles of gemcitabine and carboplatin with partial response and good tolerability, she started maintenance therapy with niraparib 300 mg daily. The patient has currently maintained niraparib therapy for 15 months, with stable disease and manageable toxicity (mainly grade 2 fatigue).

Case 2

A 71-year-old woman presented with a 3-month history of diarrhea and progressive abdominal distention. More recently, she developed orthopnea and epigastric discomfort. She denied nausea or vomiting. On physical examination, the woman exhibited signs of large-volume ascites and bilateral malleolar edema, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2.

Colonoscopy and endoscopy were performed, both without relevant findings. Thoracoabdominal-pelvic CT revealed peritoneal carcinomatosis and ascites but no signs of the primary tumor. Abdominal drainage was performed, and peritoneal fluid cytology revealed a carcinoma, not likely of pulmonary or intestinal origin (no CDX2 or TTF1 expression). CA-125 and CA-15.3 levels were elevated (395 and 321 U/mL, respectively). The gynecologic examination also showed no evidence of the primary tumor. Positron emission tomography (PET)/CT scan with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (18F-FDG) confirmed diffuse peritoneal carcinomatosis with uptake in numerous lymph nodes, including the left retro-clavicular, mediastinal, left internal mammary, left inter-aorta-cava, and right external iliac. Guided biopsy of one of these sites was proposed, but no visible lesion amenable to the procedure was identified on CT scan.

At this point, the form of presentation and exclusion of most common digestive tumors in a female patient favored the diagnosis of ovarian or primary peritoneal carcinoma. Although other etiologies could not be completely excluded, treatment of an occult primary tumor was started accordingly.

Considering the patient's age and PS, treatment with carboplatin AUC 2 and paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 28-day cycle was initiated. The last abdominal drainage was performed 4 days before treatment initiation and was not necessary again. Pelvic magnetic resonance imaging (MRI) was performed before cycle two, revealing only small-volume ascites and right external iliac nodes, the most prominent being 11×8 and 10×6 mm. After six cycles, tumor markers were within normal range, and the patient underwent exploratory laparoscopy, with identification of peritoneal carcinomatosis with ileum involvement. Histological testing suggested a carcinoma of gynecological origin, although a peritoneal primary could not be excluded. After 6 months of follow-up, abdominal-pelvic MRI showed numerous omental nodular lesions consistent with peritoneal carcinomatosis, right external iliac nodes (the largest being 23 mm), and a 14-mm nodule on the left flank. The patient received another six courses of the previous chemotherapy schedule, with complete response on MRI. At this point, niraparib therapy was started.

The patient remains on niraparib, having completed 17 months of treatment with no evidence of disease recurrence. At month 7, she reported insomnia and confusion episodes. After excluding cerebral metastases and electrolytic disturbances, the niraparib dose was reduced to 200 mg daily, with resolution of the complaints.

Case 3

A 62-year-old woman with a history of depression under treatment with escitalopram complained of decreased appetite, weight loss, and abdominal pain. Abdomen and pelvis CT revealed a left ovarian mass incarcerating part of the ileum and lombo-aortic and bilateral iliopelvic nodes, peritoneal carcinomatosis, and ascites. Guided biopsy of the major iliopelvic adenopathy revealed a lymph node metastasis morphologically and immunophenotypically compatible with high-grade serous ovarian carcinoma (CK7+, CK20-, PAX8+ , WT1+, p53+, RE+). Radiological assessment was concordant with non-resectable International Federation of Gynecology and Obstetrics (FIGO) stage IIIC ovarian cancer.

Perioperative platinum-based chemotherapy was started. After paclitaxel anaphylaxis during the first cycle, docetaxel was the taxane of choice. Interval cytoreduction was incomplete, with documented miliary disease throughout the entire parietal peritoneum. Even after postoperative platinum-based chemotherapy, persistent disease was identified in CT scan (peritoneal implants lining the liver capsule, diaphragm, and paracolic recesses). The patient was started on maintenance hormone therapy with exemestane. BRCA1/2 testing disclosed no pathogenic variants.

Nine months after the last platinum-based chemotherapy cycle, disease progression was observed by biochemical (CA-125) and radiological (new peritoneal implants and lymph nodes) methods, and platinum-based chemotherapy (cisplatin + gemcitabine) was

resumed. Complete biochemical and partial radiological response (only residual peritoneal implants and pathological densification on the right vaginal apex) was observed, and maintenance therapy with niraparib 300 mg/day was initiated 7 weeks after chemotherapy conclusion.

During the first 6 months of niraparib maintenance therapy, grade 1 constipation was the only adverse event reported, and no dose reductions were required. No rise in CA-125 level was observed, and abdomen and pelvis CT confirmed sustained response with at least stable disease, with no new lesions or any increase of previous ones. During the seventh month of treatment, the patient presented with erythema of the chest and scapular regions compatible with photosensitivity and sunburn (Fig. 1) and with erythema and edema of the palms compatible with acral erythema (Fig. 2). Since no other drug had been prescribed, adverse skin reactions were attributed to niraparib, probably exacerbated by sun exposure and alcoholic skin disinfection related to SARS-CoV2 infection prophylaxis. Photoprotection and the use of sunscreen were started. One month later, slight erythema was still present on the palms (Fig. 3), and previous areas of hypersensitivity displayed brown spots compatible with solar lentigines (Fig. 4a, b). Sun avoidance measures were reinforced, emollients

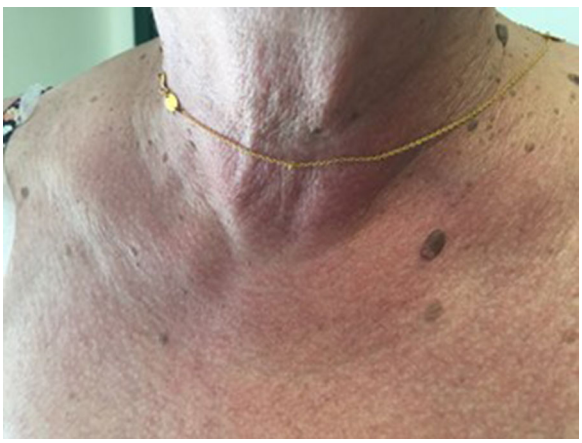

Fig. 1 Erythema of the chest and scapular regions compatible with photosensitivity and sunburn

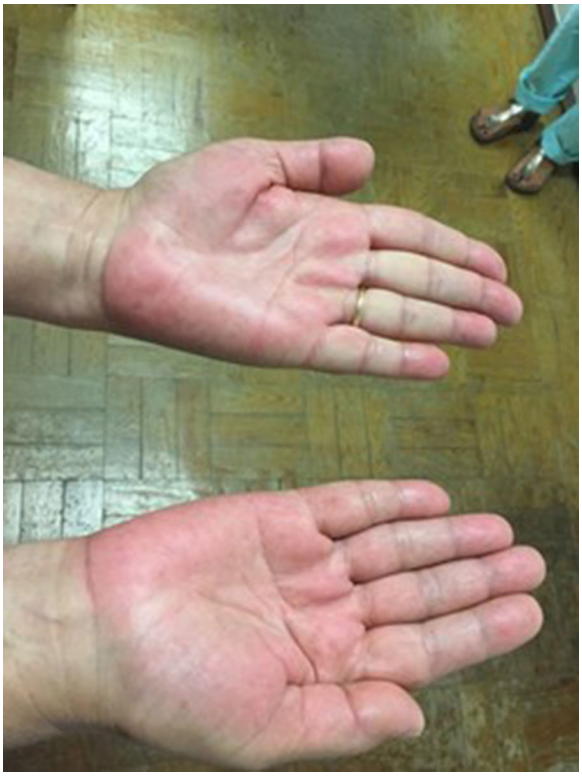

Fig. 2 Erythema and edema of the palms compatible with acral erythema

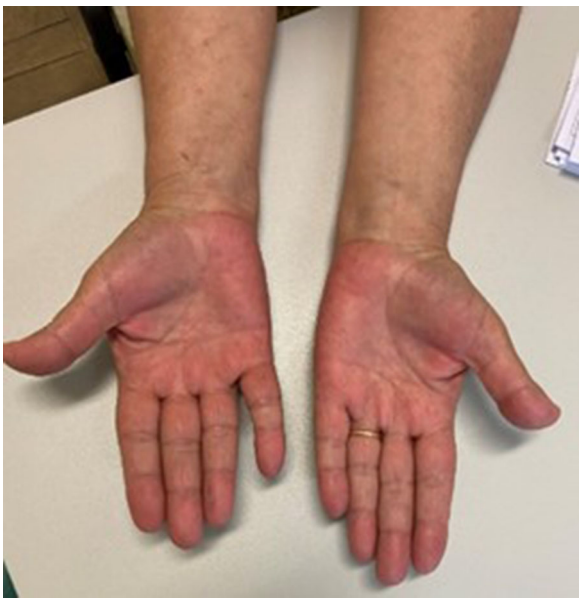

Fig. 3 Slight erythema of the palms

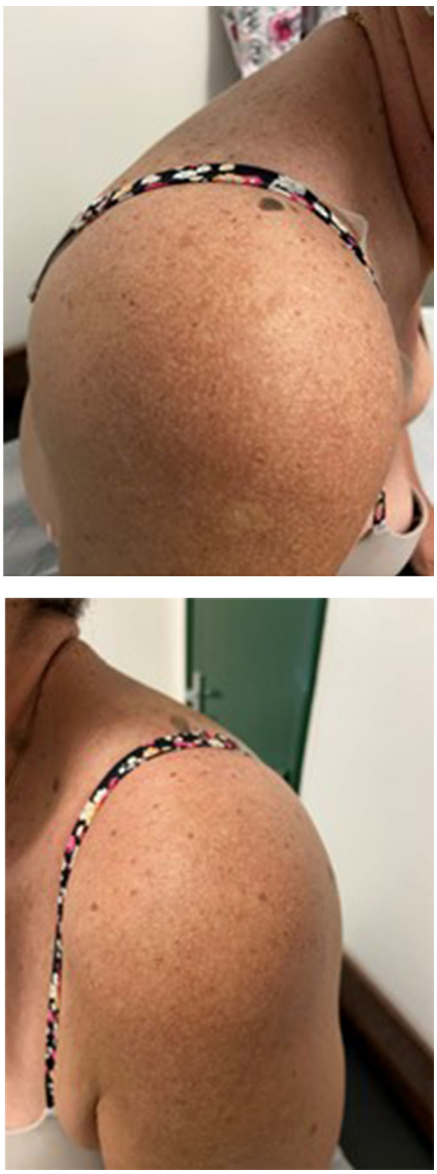

Fig. 4 **a**, **b** Previous areas of hypersensitivity displaying brown spots compatible with solar lentigines

were initiated, and niraparib maintenance was continued with no dose reduction.

The patient currently remains on niraparib 300 mg daily, with documented stable disease.

Case 4

A 66-year-old woman presented with a growing complex cyst on the right ovary. She had a personal history of atrial fibrillation and glaucoma, and a family history of colon cancer diagnosed in her sister at the age of 74 and urologic cancer diagnosed in a second-degree cousin of the father at the age of 80.

The patient underwent hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, pelvic and para-aortic lymphadenectomy, and appendectomy. The histopathological evaluation reported a borderline serous tumor on the right ovary, grade 1, with neoplastic cells identified in peritoneal washings. The patient was maintained under surveillance.

Ten months later, a rise in CA-125 level was observed (185 U/mL), with no associated symptoms. A thoracoabdominal CT scan was performed, revealing a growing solid and heterogeneous nodular lesion of 43 × 31 mm on the right side of the vaginal dome, suggestive of an implant. Results of vaginal cytology, upper gastrointestinal endoscopy, and colonoscopy were unremarkable. Lesion biopsy disclosed a low-grade serous ovarian cancer consistent with ovarian cancer metastases. A FDG-PET scan was performed, revealing an abnormal single focus with significant FDG avidity corresponding to a mass on the right pelvic region near the right external iliac vessels, also consistent with tumor recurrence. Pelvic MRI confirmed previous findings of a solid mass suggestive of a tumor implant, 5.2 × 4.0 × 3.2 cm, in close contact with but apparently without invasion of other pelvic organs. Genetic testing revealed no pathogenic BRCA 1/2 variants.

The patient underwent resection of the pelvic mass near the vaginal dome, with identification of clear-cell ovarian carcinoma in most of the sample and some areas displaying borderline serous tumor. Peritoneal washing was negative for malignant cells, and the patient was proposed for adjuvant chemotherapy.

Two months later, the patient underwent ureteroneocystostomy and segmental colonic resection with anastomosis for closure of an ureterocolic fistula, and 1 month later she started chemotherapy with weekly carboplatin + paclitaxel, completing the six protocol-defined cycles with no evidence of active disease. However, hematological toxicity was observed,

with grade 1/2 thrombocytopenia (69–76 $\times$ 10^9/L platelets) and grade 3 neutropenia (7.20–9.30 $\times$ 10^9/L neutrophils); this resulted in treatment cycle delay and the need for dose reduction. The CA-125 remained within the normal range after surgery and throughout chemotherapy. At this time, the patient was proposed for maintenance therapy with niraparib, starting on a daily dose of 200 mg due to previous toxicities.

Two months after starting niraparib, the patient developed grade 2 thrombocytopenia (73 $\times$ 10^9/L), and the drug was suspended for 3 weeks to enable hematological recovery. It was then resumed at the reduced dose of 100 mg daily, which the patient currently maintains.

The patient has been regularly evaluated since, remaining asymptomatic, with good PS and quality of life. Approximately 8 months after starting niraparib, she has no evidence of disease activity (normal CA-125 and radiological assessment with no signs of recurrence/metastases).

Case 5

A 53-year-old woman with no relevant personal or family history presented a pelvic mass during a routine gynecology appointment. She had no complaints or associated symptoms.

An ultrasound examinationt revealed a complex cystic and dense pelvic mass on both ovaries. Blood tests showed elevated CA-125 (1386 U/L). A subsequent thoracoabdominopelvic CT scan confirmed the presence of a complex pelvic mass with dimensions 16 $\times$ 14 $\times$ 13 cm, both cystic and solid, involving both ovaries and the uterus, as well as multiple nodules throughout the abdominal cavity compatible with peritoneal implants. Metastatic disease involving the liver (3 hypovascular nodes) and spleen (8 splenic hypovascular nodes) was also detected. CT-guided biopsy of a hepatic lesion revealed an adenocarcinoma CK7+, CK20-, intense and diffuse estrogen receptor-positive, Ca-125+, CDX2-, TTF1-, and P53-, and the patient was diagnosed with stage IV hormone receptor-positive, high-grade ovarian papillary serous cystadenocarcinoma.

The patient received three cycles of platinum-based (carboplatin + paclitaxel) neoadjuvant chemotherapy, followed by interval debulking surgery consisting of hysterectomy, bilateral salpingo-oophorectomy, removal of para-aortic, mesenteric and pelvic lymph nodes, resection of a metastatic nodule on the umbilical scar, right parietocolic biopsy, and splenectomy. The anatomopathological study revealed a high-grade tumor with peritoneal involvement and lymphovascular invasion, stage pT3cN0M1 R2. The patient completed three more cycles of adjuvant chemotherapy and 1-year maintenance with bevacizumab, with complete response shown on the PET-CT scan. Germinative and somatic BRCA testing were negative.

Two years and 6 months after diagnosis (1 year and 6 months after complete response), the disease relapsed with a right inguinal node, later confirmed by biopsy. New staging revealed no distant disease. The patient underwent another six cycles of carboplatin + paclitaxel, with complete biochemical and imaging response shown on the CT and PET-CT scan.

Two years after the first relapse, a progressive increase in the level of the CA-125 tumor marker was observed. New imaging and staging exams showed two hepatic metastases and a nodular lesion on the left flank in L2 plane, compatible with a peritoneal implant, and the patient underwent a second cytoreductive surgery. Anatomopathological study of the hepatic VI–VII posterior sectors, VIII sector, and peritoneal implant was compatible with high-grade ovarian papillary serous cystadenocarcinoma. Due to the high morbidity associated with these metastases and lesions, and known difficult surgery recovery, the patient did not complete adjuvant chemotherapy and was maintained on close surveillance.

Eight months after surgery, a new increase in CA-125 levels prompted a CT scan, revealing hepatic and pulmonary metastatic disease. The patient restarted chemotherapy with carboplatin + paclitaxel, completing a total of six cycles. On the last cycle, she developed grade 3 angioedema (CTCAE [Common Terminology

Criteria for Adverse Events] v5.0) attributed to paclitaxel, which resolved in < 24 h. Response assessment on CT scan revealed a very good response, with dimensional reduction or disappearance of hepatic and pulmonary metastases. In this setting, the patient started maintenance therapy with niraparib at a daily dose of 300 mg.

After starting niraparib 300 mg daily, the patient displayed good tolerability and no adverse reactions until the fourth week of treatment. At that time, she developed grade 3 thrombocytopenia, with oral mucosal bleeding and petechial lesions on the oral cavity and skin. Niraparib therapy was suspended, and the patient was admitted for surveillance due to the high risk of bleeding. She was discharged after 2 weeks, with recommendation of hemogram with full blood cell count every 3 days.

Twenty-eight days after suspension, the patient restarted niraparib at a daily dose of 200 mg. Two months later, she developed anemia, with Hb < 8 g/dL, and was in need of transfusion support; niraparib was suspended for another 28 days. During this period, the patient maintained normal CA-125 levels and stable disease on the CT scan.

Niraparib was restarted at the lowest daily dose of 100 mg, with no adverse events. The patient gradually became more active and resumed her everyday activities. Five months after starting the lowest niraparib dose, disease progression was documented, mainly on the lung metastasis, with a concomitant CA-125 increase.

Almost 7 years after diagnosis, the patient has good PS and performs her normal daily life. She has no intention of restarting chemotherapy, has started hormone therapy and undergoes monthly clinical and analytical evaluations.

DISCUSSION AND CONCLUSIONS

Ovarian cancer is the eighth most common cancer in women globally [3]. Approximately 90% of ovarian cancers are classified into five subtypes: high-grade serous, low-grade serous, mucinous, endometrioid, and clear-cell carcinoma [21].

The standard treatment for newly diagnosed advanced epithelial ovarian cancer is surgical cytoreduction and systemic platinum-based combination chemotherapy [22]. However, up to 85% of patients with advanced disease experience disease recurrence after completing chemotherapy [23], often requiring additional chemotherapy regimens. Despite an initially high response rate to platinum regimens, treatment effectiveness decreases over time [13]. Due to the lack of therapeutic options, platinum retreatment is usually used in patients with assumed platinum sensitivity, with suboptimal outcomes and cumulative toxicity [13].

Recent data have shown that, among patients with platinum-sensitive recurrent ovarian cancer, maintenance therapy with the oral PARP 1/2 inhibitor niraparib significantly increases PFS, regardless of the presence of BRCA germline mutations [15]. Phase III studies confirmed that PARP inhibitor activity extends beyond BRCA-mutated phenotype and can also benefit patients without BRCA mutations, especially when clinical characteristics such as platinum sensitivity and high-grade serous histology are present [24, 25]. National Comprehensive Cancer Network (NCCN) guidelines currently recommend niraparib as maintenance therapy for patients with platinum-sensitive ovarian cancer who have had ≥ 2 lines of platinum-based therapy and complete or partial response to the most recent line [22].

Despite presenting with advanced disease and the absence of BRCA mutations, most patients in this case series had a favorable response to maintenance therapy with niraparib. Patients 1 and 3 remained on the full 300 mg daily dose of niraparib with no evidence of disease recurrence for 15 and 11 months, respectively, after > 3 lines of palliative chemotherapy in the first case.

Around 70% of patients in clinical trials [15, 16] and 86% of patients in the real-life cohort where Case 3 is included (unpublished data) required dose reductions with niraparib, and this was also the case with Cases 2, 4, and 5 in this series. To date, Case 2 has completed 17 months of treatment with no evidence of

disease recurrence after the niraparib dose had been reduced to 200 mg daily at 7 months of treatment due to insomnia and confusion episodes. Case 4 has no evidence of disease activity 8 months after starting 200 mg daily dose of niraparib due to previous chemotherapy-related hematological toxicity and later reducing it to 100 mg daily due to grade 2 thrombocytopenia. Case 5 had a different clinical course compared with the remaining patients, as she had disease progression 5 months after starting the lowest niraparib dose (100 mg/daily). This patient had started treatment at the full daily dose of 300 mg, but after grade 3 thrombocytopenia and anemia requiring transfusion support, the niraparib dose was progressively reduced to 200 and 100 mg/daily, eventually with treatment discontinuation due to disease progression.

Toxicities related to niraparib were as expected and generally manageable. Case 1 reported mainly grade 2 fatigue, Case 2 reported insomnia and confusion episodes, and Cases 4 and 5 reported grade 2 and 3 hematological toxicity that resolved with treatment suspension and subsequent dose reductions. The only exception was Case 3, who developed rare skin toxicity while responding to full-dose niraparib treatment, with no other toxicities. Adverse skin reactions are commonly observed with various types of cancer treatment [26], but as far as the authors are aware, this is the first real-world report of photosensitivity and acral erythema associated with niraparib treatment. Photosensitivity was reported in 8.7% of patients in the NOVA trial and acral erythema in 0.4% of patients in the PRIMA trial [15, 16]. There is currently no evidence of an association between skin reactions and niraparib dose. Due to poor prognostic factors (miliary disease after cytoreduction, incomplete response to platinum-based therapies during primary treatment and relapse, and BRCA1/2 wild-type phenotype), it was decided to keep this patient under observation with full-dose treatment, while recommending avoidance of sun exposure and topical treatment. While a correlation has been reported between dose and tumor response for several targeted treatments [27–31], it has not been described for PARP inhibitors. Therefore, while reducing adverse events, namely hematological toxicity, niraparib dose reduction does not seem to impair treatment efficacy. Further follow-up of this patient and awareness of more cases of skin reactions with niraparib and other PARP inhibitor treatment will be important to clarify this issue. Increasing cases of photosensitivity related to new targeted drugs have been reported in the Dermatologic Clinic of Portuguese Institute of Oncology Lisbon, which, together with the increased use of alcoholic hand sanitizers during the SARS-CoV2 pandemic, may have had a role in the skin toxicity observed in this case.

The present case series highlights the effectiveness and favorable safety profile of maintenance therapy with niraparib in patients with recurrent ovarian cancer irrespective of BRCA status. In particular, it shows that the maintenance of response with low doses of niraparib may be more frequent in real-world setting than previously considered. This adds relevant real-world evidence to data retrieved from clinical trials. The cases depicted here also underline some less common features of the management of patients treated with niraparib, in the expectation that sharing knowledge and expertise will help improve these patients' outcomes. Lastly, and also importantly, the evidence of response in ovarian tumors without BRCA mutations and without determination of genetic or genomic alterations in homologous recombination repair pathways observed in this study suggests that inducing a BRCAness state in BRCA-proficient tumors may be a new therapeutic approach to be considered in the future.

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Compliance with Ethics Guidelines. Written informed consent for case description and use of photographs had been obtained previously from all patients, who had no involvement in the study other than being treated for their condition.

Data Availability Statement. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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