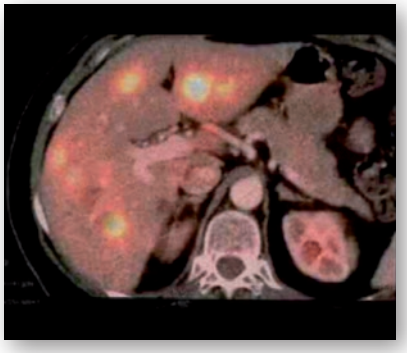

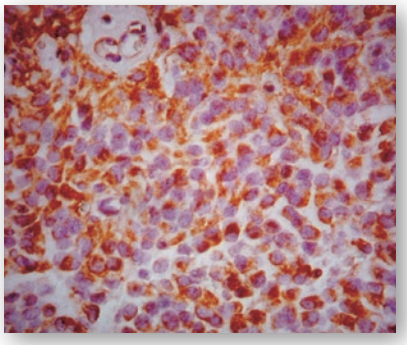

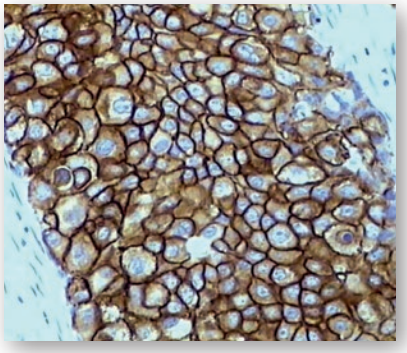

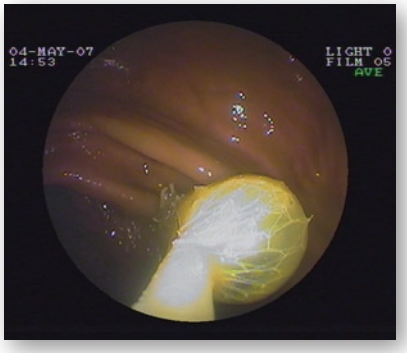

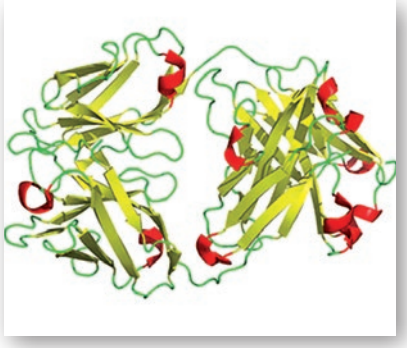

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Clinical Experience in Ovarian Cancer: What is there after PARP Inhibitors?

Introduction

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Given its location in the pelvis, the symptoms of ovarian cancer (OC) are insidious, causing delayed diagnosis in almost 75% of patients. Conventional first-line treatment schedules (carboplatin and paclitaxel with/without bevacizumab) obtain response rates of around 70-80%. In spite of this, the large majority of patients relapse and have a median progression-free survival (PFS) of between 12 and 18 months. Recent inclusion of PARP inhibitor (PARPi) as a first-line maintenance therapy has meant that the PFS[1,2] can be prolonged.

In recurrence disease, the main objective is to prolong survival with a preserved quality of life. This can be achieved through the administration of multiple lines of therapy with different treatment: platinum-based or platinum-free combinations, maintenance therapy with antiangiogenics or PARPi and single-agent chemotherapy. To determine which is the best therapeutic strategy, several factors are taken into account: treatment-free interval, patient's overall condition, histological and molecular characteristics of the tumor, number of lines, response obtained and cumulative toxicities of previous treatments, and type of relapse (tumor burden, symptoms…)[3]. However, one of the most relevant factors is undoubtedly the breast cancer (BRCA) status. This is not only because of its implications from a hereditary perspective but also because it is a prognosis factor and a predictor of response to PARPi and different types of therapies such as platinum, anthracyclines, or trabectedin.

The four clinical cases presented here illustrate how OC is currently managed and share common clinical and pathological features. All the patients are presented in advanced stages. Indeed, Stage IIIC is discovered by chance in one patient who was scheduled for prophylactic surgery. Furthermore, all histologies of the selected cases are high-grade papillary serous tumors and three patients are BRCA mutation carriers. It is possible that these histological and molecular characteristics, in conjunction with intelligent integration of all available therapeutic tools, have contributed toward patients attaining very prolonged survival.

From a therapeutic perspective, all the patients have been given trabectedin and pegylated liposomal doxorubicin (PLD) following multiple lines of platinum-based chemotherapy (at least two) and bevacizumab and PARPi. Importantly, the authors have used this platinum-free combination in very similar clinical scenarios:

- In the first instance, patients who have received several platinum-based lines, in addition to bevacizumab and PARPi, and who relapse with a treatment-free interval from last platinum (TFIp) of between 6 and 12 months. Platinum rechallenge in this situation does not tend to do well. In fact, the probability of achieving a response with platinum in this population is limited to 39-45%[4].

The rationale for using trabectedin + PLD comes from the results of the randomized Phase III study OVA-301, in which 672 relapsed OC patients receiving trabectedin + PLD or PLD monotherapy were included in the study. The results in the subgroup of patients with a TFIp between 6 and 12 months (n = 224) were especially revealing, since median overall survival (OS) was 22.4 months with the combination compared with 16.4 months with PLD monotherapy (hazard ratio [HR]: 0.64; 95% confidence interval [CI]: 0.47-0.86; p = 0.0027)[5]. Importantly, patients who received platinum as a subsequent line displayed an increased survival advantage of 9 months (27.7 vs. 18.7 months; HR: 0.58; 95% CI: 0.37-0.901; p = 0.0153)[5].

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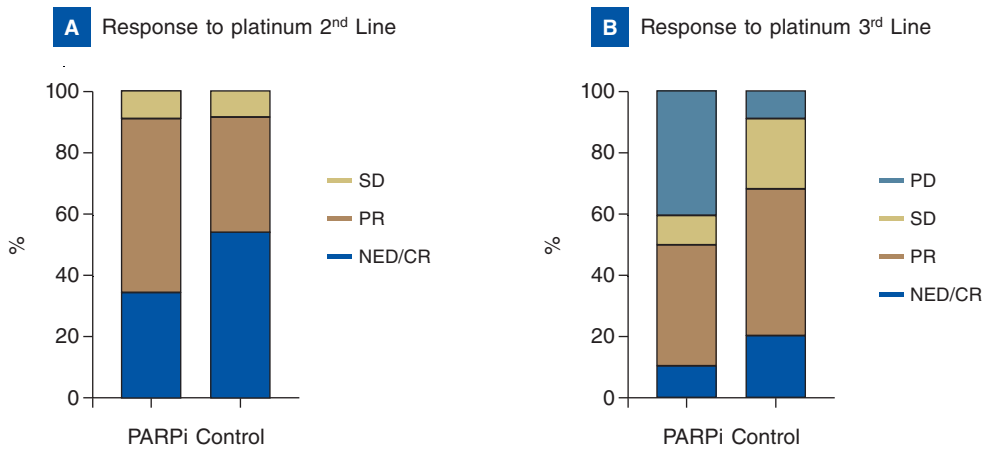

Figure 1. *Graphical overview of response to the second- and third-line chemotherapy for relapsed ovarian cancer in patients who did or did not receive prior PARP inhibitors maintenance therapy* (adapted from Baert et al., 2020)[16].

These observations led to the design of the Inovatyon study, a randomized Phase III trial that compared trabectedin + PLD versus platinum rechallenge in patients who relapse between 6 and 12 months to one or two previous platinum-based lines[6]. While there were no significant differences in the primary objective (similar OS in both arms: trabectedin/PLD: 21.5 months vs. carboplatin/PLD: 21.3 months; HR 1.10 [95% CI 0.92-1.32]; p = 0.284), the patients who benefited the most from trabectedin + PLD were precisely those who had received two prior lines and for whom the subsequent line had been platinum-based therapy.

- Second, trabectedin shows particular activity in patients/tumors with a BRCA mutation. This has been described in several preclinical studies and confirmed in the subgroup analysis of the OVA-301 study, in which BRCA-mutated patients benefited the most from trabectedin + PLD combination[7]. Furthermore, the results of the OVC-3006 randomized Phase III study[8] involving patients with platinum-sensitive recurrent OC receiving third-line treatment with trabectedin + PLD or PLD monotherapy has also shown a clinically relevant benefit with the combination in BRCA-mutated patients.
- Third, patients who develop platinum hypersensitivity or at risk of developing it. Hypersensitivity reactions to carboplatin are common in re-treatment of OC patients, with an increasing incidence ranging from 1 to 44%, depending on platinum exposure. It generally occurs from administration of the eighth cycle (< 1% occur before the fifth cycle, 6.5% in the sixth cycle, 27% from the seventh cycle, and up to 44% in the third line of treatment)[9,10]. A hypersensitivity reaction was observed in three of the four cases presented, being more frequent from the third line. In two of the cases, it led to platinum interruption and trabectedin + PLD was used in the following progression. In the other case, a protocol for desensitization and replacement with cisplatin was implemented following an assessment by the Allergology Department.

Last of all, there is some question as to whether patients who progress on PARPi are sensitive to further chemotherapy[2]. Although results of the Phase III olaparib[11] and niraparib[12] trials reported superiority of PARPi maintenance over placebo for median time to second progression (PFS2), a retrospective study from Italy[13] found that overall response rates (ORRs) were disappointing in platinum-sensitive patients with BRCA mutation who received chemotherapy after olaparib progression (n = 66 evaluable for response). Response rates of 22.2, 11.1, and 9.5% in patients with a TFIp of > 12, 6–12, and < 6 months, respectively, suggested cross-resistance[3]. Importantly, some of the mechanisms of resistance to platinum and PARPi are similar[14]. As such, there appears to be a decrease in the efficacy of platinum given after progression to PARPi, as several studies have recently indicated:

- In a real-world study involving 54 OC patients, benefit from subsequent platinum after PARPi in patients with TFIp 6-12 was similar to benefit from chemotherapy in the platinum-resistant group (5.1 months of median PFS in both groups and an ORR of 27.3 and 28.6%, respectively)[15].
- A recent retrospective study assessed the response to third-line platinum-based chemotherapy in 92 patients with and without prior PARPi treatment. Response to the second-line platinum-based chemotherapy was similar in both groups, however, the prior administration of PARPi significantly altered the response to third-line platinum-based chemotherapy (χ^2 14.19-df 3-p < 0.01) (Fig. 1 and Table 1)[16].

The study concluded that the response to platinum-based third-line chemotherapy is lower than

Table 1. *Response to the third-line platinum-based chemotherapy in patients with and without prior PARP inhibitors treatment*

	PARPi	%	Control	%
N	35		57	
3rd Line				
NED/CR	4	11%	12	21%
PR	14	40%	27	47%
SD	3	9%	13	23%
PD	14	40%	5	9%

Adapted from Baert et al., 2020[16].

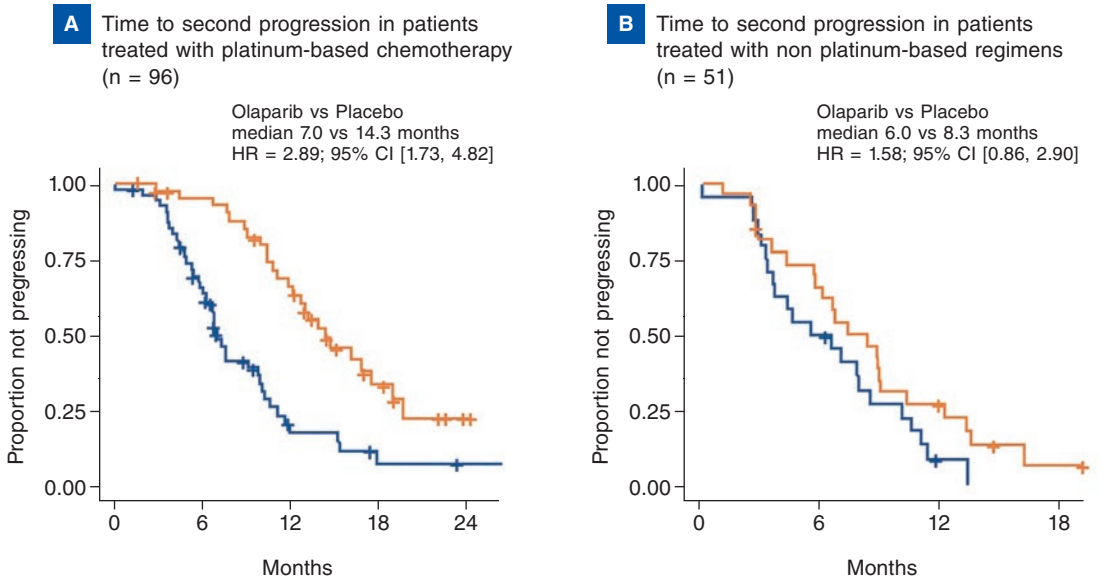

Figure 2. *Time to second progression in patients treated with platinum and non-platinum after progression on olaparib compared to placebo* (adapted from Frenel et al., 2020)[17].

expected in patients treated with PARPi maintenance after response to the second-line platinum-based chemotherapy, compared to patients who achieved a similar PFS and TFIp who did not receive a PARPi, indicating an altered sensitivity toward platinum-based chemotherapy after prior PARPi treatment[16].

– A subgroup analysis of the randomized Phase III study SOLO 2 evaluated the efficacy of subsequent chemotherapy for patients with BRCA1/2-mutated platinum-sensitive OC progressing on olaparib versus placebo[17]. The efficacy of subsequent chemotherapy (particularly platinum-based chemotherapy) appeared to be less in patients having received olaparib in maintenance compared to placebo (Fig. 2)[17].

Considering that PARPi maintenance therapy already represents a new standard in the first-line setting, these findings may have implications in terms of selecting treatment for recurrent disease[3]. Further insight is required to determine what treatments are more adequate to be used after progression on PARPi maintenance therapy.

In three of the four clinical cases presented below, the combination of trabectedin + PLD is administered as subsequent line after maintenance therapy with PARPi. In all cases, this combination provided a long-term clinical benefit with a manageable safety profile, confirming the maintenance of its activity despite unfavorable contexts such as the previous use of PARPi.

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Case study 1

Treatment with Trabectedin and Pegylated Liposomal Doxorubicin Following Niraparib in a Multi-treated Ovarian Cancer Patient

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Personal background

- A 59-year-old patient with no toxic habits, no known allergies to medication or cardiovascular risk factors
- Left side subtotal thyroidectomy due to thyroid nodules in December 2003
- Menarche aged 14 and menopause aged 52. Four pregnancies (three births and one pregnancy loss). Nine months of accumulated breastfeeding. Took oral contraception for 3 years before the pregnancies. Has had mass screening mammograms.

Family background

Two cases of breast cancer on the maternal side. Her sister took a germline genetic test in 2008 based on a background of breast cancer in the family. The result was a variant of uncertain significance in the BCRA2 gene (exon 11 V271V).

Signs and symptoms

Postprandial heartburn starting in December 2007 followed by abdominal distension. The patient was admitted to the hospital for observation after symptoms worsened.

Diagnosis

An abdominal ultrasound scan (January 3, 2008) showed a hyperechogenic nodular lesion 1.5 cm in diameter in the right-hand liver lobe, free peritoneal fluid, and hyperechogenic images in peritoneal fat (peritoneal carcinomatosis). The tumor markers (January 4, 2008) result was: CA125: 718.2 IU/mL and CA15.3: 70.3 IU/mL; alpha-fetoprotein, CEA, and CA19.9 were normal. Parietal peritoneum implants, nodular implants in the greater omentum, and abundant ascitic free fluid were observed in the abdominal computed tomography scan (CT scan) (January 7, 2008) but the primary tumor was not identified. Malignant cells consistent with ovarian carcinomas were detected in the peritoneal cytology (January 8, 2008).

Abdominal distension with ascites (not tense) and no other remarkable observations during the examination (January 9, 2008). Predominantly liquid tumors with undefined borders and marked mottled vascularization in both adnexa, suspected as malignant, were detected in the ultrasound scan performed on the same day. At presacral and retroperitoneal level, a bilobed cystic image with a thick 4 × 3 cm wall was observed with inconclusive criteria. A hyperechogenic image 1.5 cm in size was observed in the right-hand liver lobe. Small peritoneal tumor implants and substantial ascites were also detected.

Treatment

The patient underwent a laparotomy surgical procedure on January 25, 2008. The uterus was found to be normal and the ovaries, which were normal in size and were affected on the surface. The omentum was entirely unstructured and presented tumors, with miliary dissemination across the entire large and small intestine. Both diaphragmatic cupula and the parietal peritoneum were affected by miliary dissemination of the tumor. The patient underwent a total hysterectomy, double adnexectomy, removal of

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the omentum, and review of the uterine cavity. A residual tumor in excess of 2 cm remained (on the rectal wall, small intestine, diaphragmatic cupula, and entire parietal peritoneum). In the pathological anatomy, multiple areas of histological Grade 2 papillary serous carcinoma were observed at the level of the serosa of both sides of the myometrium, the peritubal serosa, and the external surface of both ovaries and omentum.

First line

The patient was referred to the Medical Oncology Department with a Grade 2 peritoneal ovarian serous carcinoma, in Stage IIIC, with suboptimal primary surgery and was eligible for chemotherapy. She received six cycles of carboplatin (AUC 5) and paclitaxel (175 mg/m^2) between February 2008 and June 2008, with a full biochemical response and no signs of disease based on images. A segregation analysis was performed and the patient was not a carrier of the family variant in BRCA2. In 2019, the germline analysis was repeated using a panel *(ATM, BRCA1, BRCA2, BRIP1, CHEK2, MLH1, MSH2, MSH6, NBN, PALB2, RAD51C, RAD51D, and TP53)* with no pathogenic findings.

Second line

In March 2009, after a TFIp of 9 months, the patient presented peritoneal tumor progression. Following six cycles of chemotherapy with the same schedule (carboplatin and paclitaxel from March 24, 2009, to July 18, 2009), a complete radiological and biochemical response was achieved.

Third line

Abdominal relapse was diagnosed in October 2013. A previously unseen nodule approximately 12 mm in size adjacent to the greater curvature was observed in the CT scan (this lesion had not been observed in the laparoscopy due to a presence of abundant fat). The CA125 was 634 IU/mL. It was believed that there was a relapse, apparently singular, 4 years and 4 months following the end of the second line of chemotherapy (carboplatin and paclitaxel). After the assessment of the Multidisciplinary Committee of Tumors, the performance of diagnostic laparoscopy and secondary debulking was proposed if a complete excision was feasible. A diagnostic laparoscopy is performed on November 29, 2013, and miliary implants in both diaphragmatic cupula and across the entire abdominal cavity were observed. A 2 cm nodule was detected in the area of the left infundibulum. Debulking surgery was ruled out. The result was infiltration by carcinoma.

The third-line treatment with carboplatin (AUC 5) and PLD (30 mg/m^2) was initiated. The patient was treated with six cycles between December 2013 and May 2014. There was a tumor marker decrease following the second cycle and, after the sixth cycle, there were no pathological findings in the CT scan.

Fourth line

Tumor progression was observed again in August 2014. An approximate 5 mm pulmonary nodule in the right lower lobe, a pathologic size lymphadenopathy in the right iliac system, and a pseudonodule image approximately 1 cm in size adjacent to the greater curvature were observed in the CT scan. The CA125 was 141.9 IU/mL.

It was considered that there was a relapse with a 3-month TFIp. A new line of treatment with paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 28 days) and bevacizumab (10 mg/kg, fortnightly) was started, being administered 41 cycles from August 26, 2014, to November 13, 2018. There was a tumor marker decrease following the fourth cycle and a full response in CT scan following the sixth cycle. The same treatment was continued but with changes to the schedule due to progressive mucocutaneous toxicity (Grade 2 mucositis, dermatitis and Grade 2 exudative onycholysis), initially to fortnightly and then every 21 days, being perfectly tolerated since then. This treatment continued until November 2018 when radiological progression was identified, even though the patient had displayed a progressive increase in CA125 from May 2018 (543 IU/mL). Peritoneal tumor implants were observed in the gastrosplenic ligament.

Fifth line

Given the evolution of the case and the absence of any relapse while receiving platinum, the decision to carry out retreatment with carboplatin (AUC 5) monotherapy was taken. The patient was given five cycles (from December 4, 2018, to March 5, 2019) before treatment is suspended due to a hypersensitivity reaction. The patient had achieved a partial response and maintenance therapy was advised with PARPi niraparib, 200 mg. This was sustained for 6 months until September 2019 when it was interrupted due to peritoneal tumor progression.

Sixth line

In October 2019, following reservoir placement, a new line of treatment with trabectedin (1.1 mg/m^2) + PLD (30 mg/m^2) begun. The patient received 10 cycles (from October 17, 2019, to July 16, 2020) and showed good tolerance to the treatment. The patient only suffered hematological toxicity (Grade 3 thrombocytopenia) meaning that the dose had to be decreased one level. Treatment was stopped in August 2020 due to peritoneal progression.

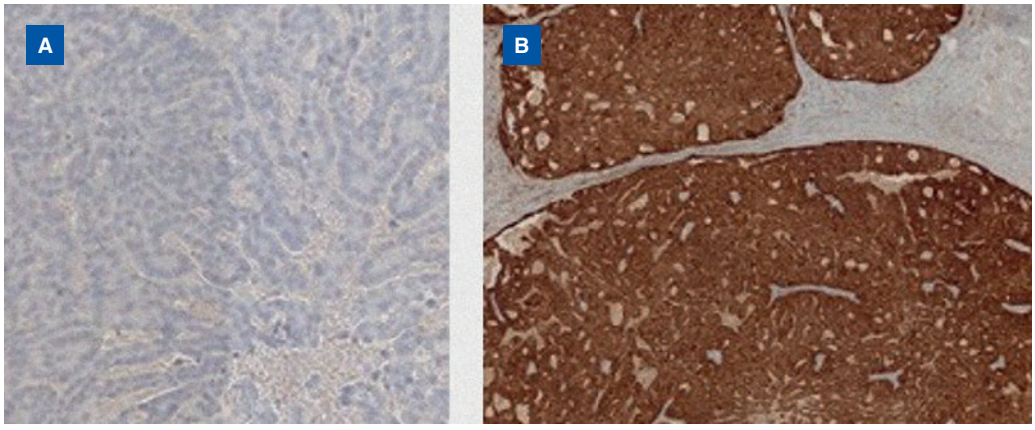

Figure 1. *Pathological anatomy.* ***A:*** *high-grade serous carcinoma;* ***B:*** *immunohistochemistry: aberrant P53, diffuse expression of P16 and negative estrogen receptors.*

Following lines of treatment

In October 2020, a peritoneal progression was observed and treatment with gemcitabine failed after two cycles with a poor tolerance.

After 2 months, a lymph node and peritoneal progression led to starting treatment with topotecan, however, a fast progression was detected after one cycle with again poor tolerance.

In March 2021, the patient received letrozole followed by an adrenal and lymph node progression in June 2021. Three cycles of ifosfamide were administered with poor tolerance.

In September 2021, a new lymph node and adrenal progression were treated with carboplatin and desensitization regimen. After two cycles with good tolerance but with symptomatic progression, active cancer treatment was terminated.

Until September 2021, the patient presented good general condition, with Eastern Cooperative Group (ECOG) 0/1 and with good quality of life.

In the last review performed in November 2021, a deterioration in relation to symptoms due to tumor progression was seen, with ECOG3. Currently the patient continuous palliative symptomatic treatment.

Discussion

This patient had advanced stage high-grade ovarian serous carcinoma. Although it was classified as Grade 2 in 2008, with the current dual grading system, it would be a high-grade serous carcinoma, as confirmed in the biopsy performed in the relapse (Fig. 1).

It is a long-standing case with a survival of over 10 years despite the unfavorable starting point, with suboptimal primary surgery and an initial relapse with a TFIp of 9 months. The patient has proven to be highly sensitive to platinum despite no germline mutation in BRCA1/2 or in other genes linked to ovarian cancer, although there was no somatic analysis to verify homologous recombination deficiency. However, the patient has not proven to be very sensitive to PARPi, having received niraparib during 6 months. The patient had received six cycles of carboplatin + PLD as third line and 10 cycles of trabectedin + PLD in the sixth line, after a TFIp of 6 months in the previous line, in which the patient had displayed a hypersensitivity reaction.

The disease was radiologically stabilized, with a biochemical response (Figs. 2 and 3) for 10 months and total tolerance to treatment. A score of 0 on the ECOG scale was maintained at all times. This treatment enabled decreasing the risk of a hypersensitivity reaction to platinum, bringing the opportunity of platinum rechallenge in a posterior line.

The PLD rechallenge used in this case is well aligned with the evidence recently published showing that prior treatment with PLD does not increase toxicities or negatively influence the efficacy of trabectedin + PLD[1]. Among the participants in a randomized Phase III study comparing trabectedin + PLD versus PLD, no difference was seen whether the patients were previously treated with PLD or not (median PFS 7.1 vs. 7.5 months [hazard ratio (HR) 0.853, 0.435-1.671] and overall response rates (ORR) 52.6 vs. 45.6% [HR 1.328, 0.468-3.819], respectively, observed in trabectedin + PLD treatment arm)[1].

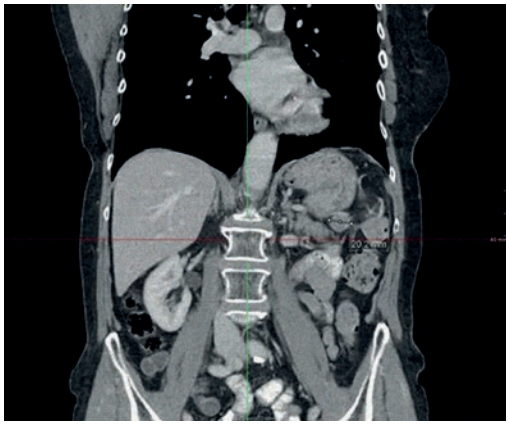

Figure 2. *CT scan: peritoneal tumor implants in the gastrosplenic ligament before treatment with trabectedin + PLD.*

In addition, several studies have shed light on whether the efficacy and safety profile of trabectedin + PLD combination is maintained when used late in the course of ovarian cancer disease. The prospective and monitored NIMES-ROC[2] study has recently evaluated trabectedin + PLD in 218 ovarian cancer patients mostly treated in third or later lines (72.5%). The median number of cycles administered was 6, reaching a maximum number of 24 cycles, with 57.8% of patients having received 6 or more cycles. Median PFS was 9.46 months (95% confidence interval [CI]: 7.9-10.9), with 68.8% of patients free from progression 6 months after treatment. An ORR and disease control rate of 37.2% and 64.2% were achieved, respectively. Treatment with trabectedin + PLD resulted in a median OS of 23.56 months (95% CI: 18.1-34.1), with almost half of the patients (49.5%) alive 2 years after treatment. The most common Grade 3/4 treatment-related adverse events (AEs) (> 5% of patients) were neutropenia (n = 66, 30.3%), anemia (n = 14, 6.4%), thrombocytopenia (n = 12, 5.5%), and asthenia (n = 11, 5.0 %). Interestingly, these rates of AEs observed in a population mainly treated in third or later lines were below the values observed in the OVA-301[3] randomized Phase III trial that tested trabectedin + PLD as the second-line treatment of ovarian cancer (Table 1), which seems to be related to the learning curve of the use of the combination after years of experience in clinical practice.

The most recent data that have been disclosed with trabectedin + PLD in ovarian cancer belong to the Inovatyon[4] randomized Phase III trial that compared trabectedin + PLD followed by platinum at progression versus carboplatin + PLD in patients who have relapsed between 6 and 12 months to one or two previous platinum-based therapies. The study did not meet its primary endpoint, showing a comparable survival between platinum rechallenge and trabectedin + PLD (median OS carboplatin + PLD: 21.3 months vs. trabectedin + PLD: 21.5 months; HR: 1.10; 95% CI: 0.92-1.32; p = 0.284). Importantly, a positive OS trend was observed with the administration of trabectedin + PLD to patients who have received two previous lines of therapy (HR: 0.87; 95% CI: 0.63-1.22; p = 0.426), despite only representing 30% of patients included in the study[5].

Available clinical data show that trabectedin + PLD is a clinically significant treatment for ovarian cancer

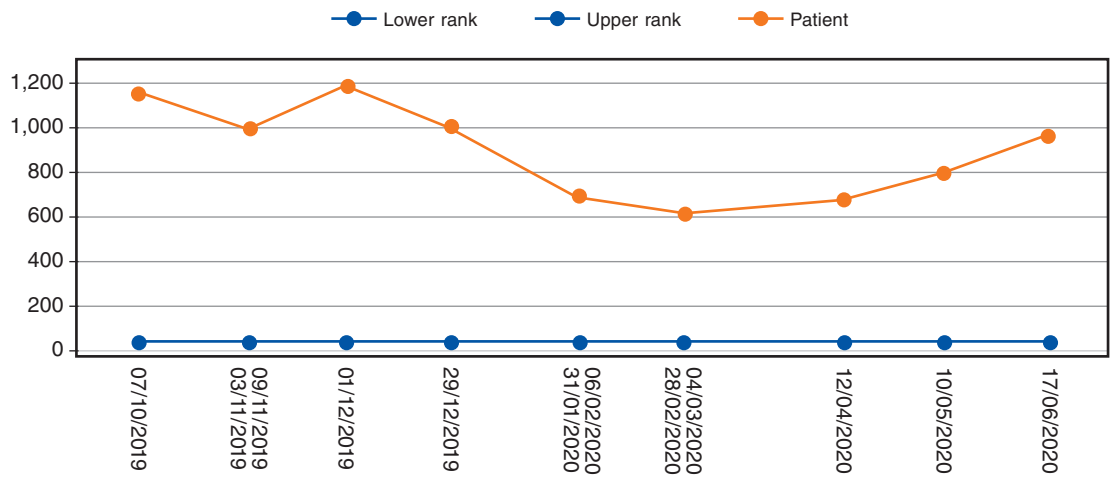

Figure 3. *CA125 evolution during treatment with trabectedin + PLD.*

Table 1. *Key safety findings with trabectedin + PLD in large prospective studies performed in patients with advanced ovarian cancer (OVA-301 randomized Phase III study[2] and NIMES-ROC observational Phase IV study[1])*

	OVA-301[2] Randomized Phase III n = 333	**NIMES-ROC[1] Observational Phase IV n = 218**
Line of treatment	2nd line in 100% of patients	≥3rd line in 72.5% of patients
Median age	56 years	61 years
Most common Grade 3/4 AEs n (%)		
Neutropenia	209 (62.7%)	66 (30.3%)
Anemia	41 (12.3%)	14 (6.4%)
Thrombocytopenia	61 (18.3%)	12 (5.5%)
Fatigue	20 (6%)	11 (5%)
AEs leading to trabectedin discontinuation	69 (20.7%)	10 (4.6%)
AEs leading to PLD discontinuation		11 (5%)
Deaths attributed to treatment-related AEs	5 (1.5%)	0 (0%)

patients with sensitive relapses, showing remarkable efficacy with adequate safety when administered third line or subsequently.

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Case study 2

Long-term Survival in a Patient with Advanced Ovarian Cancer

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Presentation

A 56-year-old patient was diagnosed with Stage IIIC hereditary ovarian cancer and received multiple lines of treatment, achieving long-term survival.

Personal background

- Hypercholesterolemia treated with rosuvastatin (10 mg/day)
- Hypothyroidism treated with levothyroxine (50 mg/day)
- High blood pressure treated with irbesartan (150 mg)/hydrochlorothiazide (12.5 mg)
- Allergic to iodinated contrasts
- Surgical intervention for abdominal abscesses aged 18 and hemorrhoidectomy aged 49
- No toxic habits
- Gynecological background:
  - Menarche at 14 years of age
  - 2G2P0A
  - Has not taken oral contraceptives
  - Menopause at 51 years of age.

Family background

Paternal aunt diagnosed with breast cancer at 53 years of age who died aged 60.

Signs and symptoms

In July 2015, the patient had abdominal pain, fever, and rectal bleeding. A colonoscopy was performed and a polyp in sigma was detected. A biopsy of the polyp revealed an intestinal-type adenocarcinoma infiltrating the submucosa. A sigmoid colon bowel resection, removal of adhesions with the bladder, lymphadenectomy, and omentectomy were performed. Several small implants were observed in the small intestine that was biopsied (suboptimal surgery).

Diagnosis

In the anatomopathological study, infiltration of the visceral peritoneum and, focally, of the muscularis propria of the intestinal wall by a high-grade serous carcinoma was observed. The carcinoma detected, likely of ovarian origin, also affected the greater omentum. Seven out of the 19 removed glands were infiltrated with neoplastic cells. The CA125 tumor marker was high: 78 IU/mL.

Stage IIIC ovarian serous carcinoma peritoneal carcinomatosis was diagnosed. The patient's performance status was good (Eastern Cooperative Group [ECOG] 0) and she weighed 63 kg.

A genetic test was carried out since the patient met clinical criteria for being at high risk of hereditary breast and ovarian cancer syndrome. A pathogenic mutation in the BRCA1 gene consisting of deletion of exons 11 and 15 (both inclusively) was identified.

Treatment

First line

In September 2015, first-line treatment with neoadjuvant aim was initiated. Following four cycles of carboplatin (AUC 5) + paclitaxel (175 mg/m^2) + bevacizumab (7.5 mg/m^2) every 21 days, levels of CA125 returned to normal. The most notable toxicity was Grade 2 anemia.

The patient underwent surgery in January 2016 and had a hysterectomy, double adnexectomy, and peritonectomy (optimal surgery) along with the administration of intraperitoneal chemotherapy (paclitaxel). The pathological anatomy showed a full pathological response.

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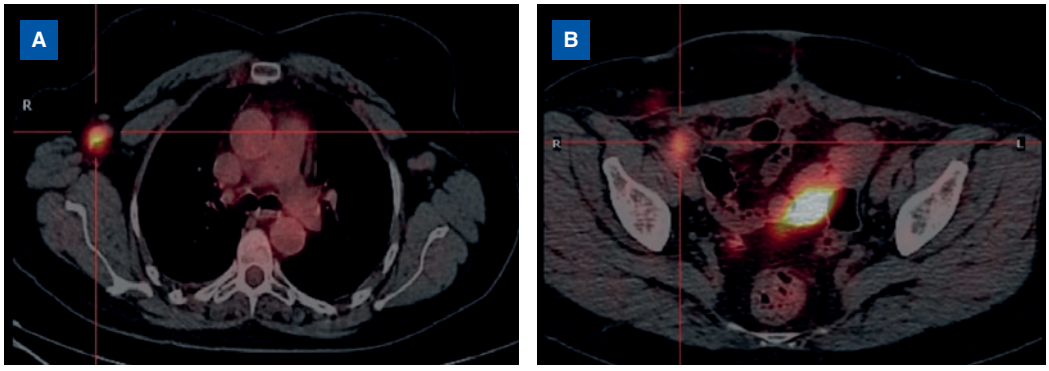

Figure 1. *Positron emission tomography-computed tomography (April 2017): axillary lymphadenopathies in the common right iliac system, the external iliac systems, and inguinal regions, enlarged in size and with an increase in metabolic activity suspected as malignant.*

Following surgery, two further cycles of chemotherapy were administered with the same schedule (carboplatin + paclitaxel + bevacizumab) and the patient continued with maintenance bevacizumab every 21 days until January 2017.

Second line

Following a 15-month interval free from disease, in April 2017, elevation of the tumor marker was detected (CA125: 98.9 IU/mL) and the positron emission tomography-computed tomography (PET-CT) showed axillary lymphadenopathies in the common right iliac system, bilateral lymphadenopathies in the external iliac systems, and bilateral lymphadenopathies in the inguinal region, enlarged in size and with an increase in metabolic activity suspected as malignant (Fig. 1).

Faced with this supradiaphragmatic and infradiaphragmatic progression in glands, histologically confirmed by axillary biopsy, the second line of chemotherapy was initiated with carboplatin (AUC 5) on day 1 + gemcitabine (1000 mg/m^2) on days 1 and 8 every 3 weeks.

In the second cycle, the patient had an allergic reaction to carboplatin. A desensitization protocol was implemented from the third cycle in collaboration with the allergology department. Following five cycles, normalization in the tumor marker and partial radiological response was observed and, as such, maintenance treatment with olaparib was prescribed (eight 50 mg capsules every 12 h) in September 2017.

Third line

In November 2018, following 14 months of maintenance treatment with olaparib, CA125 elevation (56.6 UI/mL) was detected and the CT scan showed signs of oncological progression at pelvic inguinal gland level. A left inguinal adenopathy was biopsied that was positive for metastatic papillary serous carcinoma. The third-line treatment was initiated with carboplatin (AUC 5) + gemcitabine (1000 mg/m^2) + bevacizumab (7.5 mg/kg) + atezolizumab (1200 mg)/placebo (blind not revealed) every 21 days as part of the Atalante clinical trial. In the second cycle, the patient had an anaphylactic reaction to carboplatin administered in the desensitization protocol. It was replaced with cisplatin since allergy tests for cisplatin were negative. Following six cycles, CA125 returned to normal and a partial radiological response was observed. The patient continued maintenance treatment with bevacizumab + atezolizumab/placebo.

Fourth line

In September 2019, following a 6-month progression-free interval, a peritoneal and glandular progression with multiple lymphadenopathies affecting the middle and lower retroperitoneum was detected. Over 20 clearly pathological lymphadenopathies between 0.8 and 2.2 cm in size with small mesenteric nodules 0.5-0.9 cm in size consistent with peritoneal implants were accounted.

The fourth-line treatment with trabectedin (1.1 mg/m^2) + PLD (30 mg/m^2) every 21 days was initiated. Tolerance was good with only Grade 1 anemia, Grade 1 asthenia, and Grade 1 nausea/vomiting. Partial response was attained (Fig. 2B) following the fifth cycle, along with the return to normal CA125 levels.

Fifth line

In March 2020, following nine cycles of treatment with trabectedin + PLD, an elevation in the tumor marker (CA125: 176 IU/mL) and radiological progression at glandular level were observed.

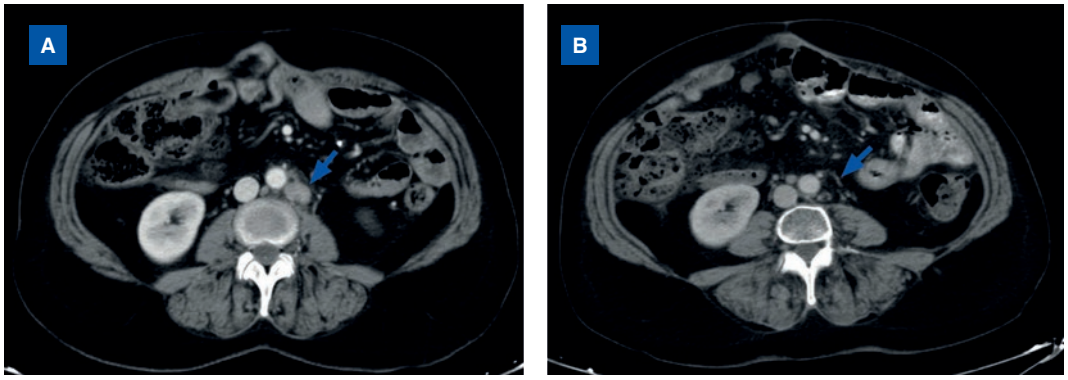

Figure 2. *CT scan.* ***A:*** *September 2019: progression at glandular level with multiple lymphadenopathies affecting the middle and lower retroperitoneum. Over 20 lymphadenopathies ranging from 0.8 to 2.2 cm in size were observed (arrow).* ***B:*** *December 2019: absence of lymphadenopathies after five cycles of trabectedin + PLD arrow.*

Weekly paclitaxel (80 mg/m^2) was administered as the fifth-line therapy. Tolerance was good and there was an initial reduction of CA125 levels (55.7 IU/mL). A partial response was shown in the CT scan after cycle 3, followed by a rapid posterior elevation of CA125. New progression disease at glandular level was observed following the fifth cycle.

The patient is now 61 years old. She is symptom free and in good functional state (ECOG 0). She has already begun treatment (sixth line) with weekly intravenous (IV) topotecan, 4 mg/m^2 on days 1, 8, and 15 every 4 weeks.

Discussion

The patient has a mutation in the BRCA1 gene and was diagnosed with Stage IIIC ovarian cancer at 56 years of age. The evolution of the disease has correlated very well with the levels of CA125 (Fig. 3). Neoadjuvant chemotherapy was administered followed by interval debulking surgery including peritonectomy. The patient responded well to the first three lines of treatment with platinum. Following an allergic reaction to carboplatin, the desensitization protocol enabled platinum rechallenge in the second and third line of treatment. The patient was given maintenance therapy in the first and second line with bevacizumab and olaparib, respectively. The patient participated in the Atalante clinical trial in the third line of treatment.

After three consecutive platinum-based lines, the patient faced limited sensitivity to platinum and fourth-line therapy with trabectedin + PLD was initiated. She received nine cycles and achieved a partial response with good tolerance. To date, the patient has received five lines of treatment (Table 1) and accumulated an OS over 5 years. Several circumstances have contributed toward this extended survival: BRCA1 mutation, optimal surgery, sensitivity to platinum, and the ability to administer it despite the allergic reaction to carboplatin, the maintenance treatments with antiangiogenics and PARPi, in addition to good response to trabectedin + PLD.

In alignment with this case, it was observed in two randomized Phase III trials comparing trabectedin + PLD versus PLD monotherapy that the combination is particularly effective in platinum-sensitive ovarian cancer patients carrying a BRCA mutation:

- In an exploratory analysis conducted as from the OVA-301 study, 31 platinum-sensitive patients were BRCA mutated. Treatment with trabectedin + PLD led to superior median PFS ([13.6 vs. 5.5 months; HR (95% CI): 0.13 (0.04, 0.43), p = 0.0001]) and median OS ([27.4 vs. 18.7 months; HR (95% CI): 0.36 (0.16, 0.80), p = 0.0093]) compared to PLD monotherapy[1].
- An additional randomized Phase III study (OVC-3006)[2] comparing trabectedin + PLD versus PLD alone was conducted in the third-line setting with 576 randomized patients. Patients were eligible if they had progressed ≥ 6 months after the 1st line platinum and obtained a complete or partial response to the second-line platinum. A *post hoc* exploratory analysis[3] has found that only 57.8% of the total population had a TFIp ≥ 6 months (333 platinum-sensitive patients). Despite the limited number of patients that preclude a reliable efficacy estimation, a marked treatment benefit was observed with trabectedin + PLD in platinum-sensitive patients with BRCA mutation[3]:
  - Median PFS trabectedin + PLD (n = 48): 10.3 months versus PLD (n = 52) 7.6 months; HR 0.61 (0.37-1.02); p = 0.053.
  - Median OS trabectedin + PLD: 47.8 months versus PLD: 20 months; HR: 0.34 (0.17-0.67); p = 0.0012.

With regard to safety, the patient only experienced anemia, asthenia, and nausea, all Grade 1. The safety profile of trabectedin + PLD has been largely assessed. In the randomized Phase III OVA-301 study that compared trabectedin + PLD versus

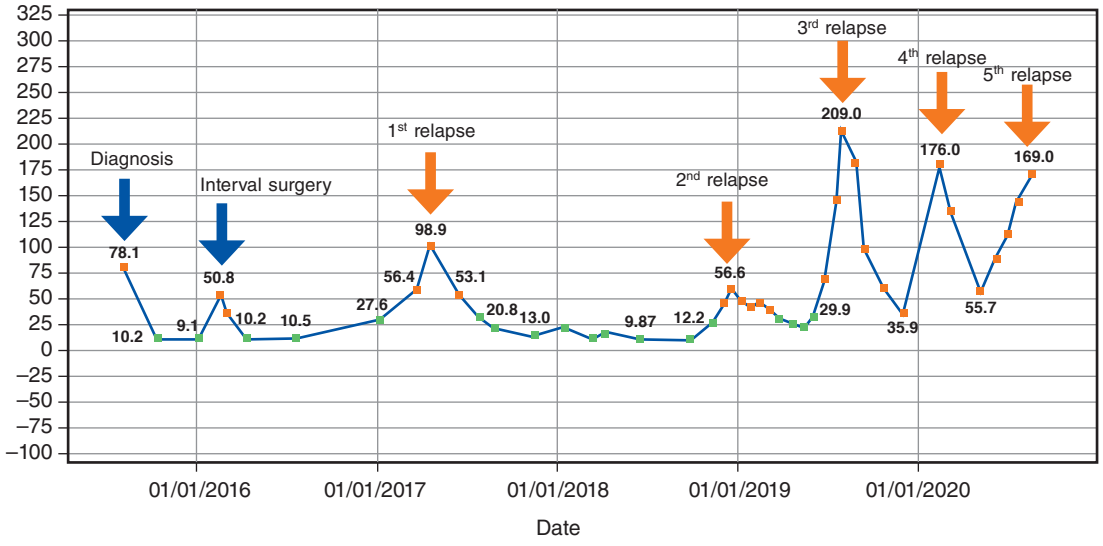

Figure 3. *Evolution of CA125 following diagnosis of the disease.*

Table 1. *Lines of treatment administered to the patient*

Line of treatment	Schedule	Start date	Number of cycles
First	Carboplatin + paclitaxel + bevacizumab	September 2015	6
Second	Carboplatin + gemcitabine + olaparib	April 2017	5
Third	Cisplatin + gemcitabine + bevacizumab + atezolizumab/placebo (Atalante clinical trial)	November 2018	6
Fourth	Trabectedin + PLD	September 2019	9
Fifth	Paclitaxel	April 2020	5

PLD alone, the combination was associated with an increase in neutropenia, together with an increase in growth factor use (42% compared with 17%), but neutropenic fever and sepsis were 8% and < 1%, respectively. Grade 3/4 transaminase elevations were also more common with trabectedin + PLD but were transient, non-cumulative, and did not yield any major clinical consequence. Hand-foot syndrome and mucositis paralleled the dose intensity of PLD and were lower with trabectedin + PLD[5]. Importantly, patient-reported outcomes from the OVA-301 trial showed that the addition of trabectedin to PLD results in no detriment in patients' quality of life[6]. In general, the combination has a manageable safety profile, not associated with disturbing side effects such as alopecia or hypersensitivity reactions often allowing patients to resume normal daily life activities[7].

As illustrated by this clinical case, the combination of trabectedin + PLD is a clinically meaningful treatment for ovarian cancer patients with sensitive relapses, showing remarkable efficacy with adequate safety also when subsequently administered after PARPi.

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Case study 3

Prolonged Response to Trabectedin and Pegylated Liposomal Doxorubicin in an Ovarian Cancer Patient BRCA-Mutated

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Personal background

- A 68-year-old patient.
- High blood pressure and type 2 diabetes.
- Surgical interventions for herniated disk and fractured ankle.

Clinical history

- G2/A0/P2. Menarche: aged 12.
- Menopause: aged 47.

Family background

Mother died of ovarian carcinoma. Sister diagnosed with ovarian carcinoma and carrier of a mutation in exon 11 of the BRCA1 gene.

Signs and symptoms

Asymptomatic patient. After her sister was diagnosed with ovarian carcinoma with a BRCA1 mutation, the patient was referred in March 2016 to the Genetics Guidance Clinic in our department.

Diagnosis

A genetic test was carried out and the patient was also found to be a carrier of a pathogenic mutation of exon 11 in the BRCA1 gene.

On October 14, 2016, the patient underwent a prophylactic bilateral salpingo-oophorectomy laparoscopy procedure. The result of the pathological anatomy was consistent with ovarian and Fallopian tube bilateral high-grade serous carcinoma.

The study was completed with:

- CT scan on the thorax, abdomen, and pelvis (December 2016): multiple irregular pseudonodule formations in the mesenteric fat behind the front abdominal wall, in the mesogastric region, more abundant on the right-hand side. Together, they form a mass that was 11.6 cm at its longest point and 2.4 cm thick. These lesions suggested multiple peritoneal implants. Presence of free fluid in both paracolic gutters, the minor pelvis, and the rectouterine pouch. Anteflexion of the uterus with an increase in volume and heterogeneous density in the endometrial cavity.
- Tumor markers: CA125: 309 IU/mL; HE4: 524 pmol/L.

On December 9, 2016, the patient underwent a total hysterectomy, omentectomy, and appendectomy by laparoscopy. During surgery, little ascitic fluid, subcentimeter implants in the peritoneum, mesocolon, diaphragmatic cupula, and liver surface were found; omentum with shingled appearance, with hepatic flexure attached to the colon serosa. A resected 5 cm tumor implant in the splenic flexure was also observed. A rectum and sigmoid colon adhesion on the left-hand side of the uterus and infiltrated rectouterine pouch were also detected. It was, therefore, suboptimal surgery since subcentimeter implants and a 3-4 cm nodule was left in the right mesocolon.

The anatomopathological report of the total hysterectomy, with cecal appendix and omentum, was a

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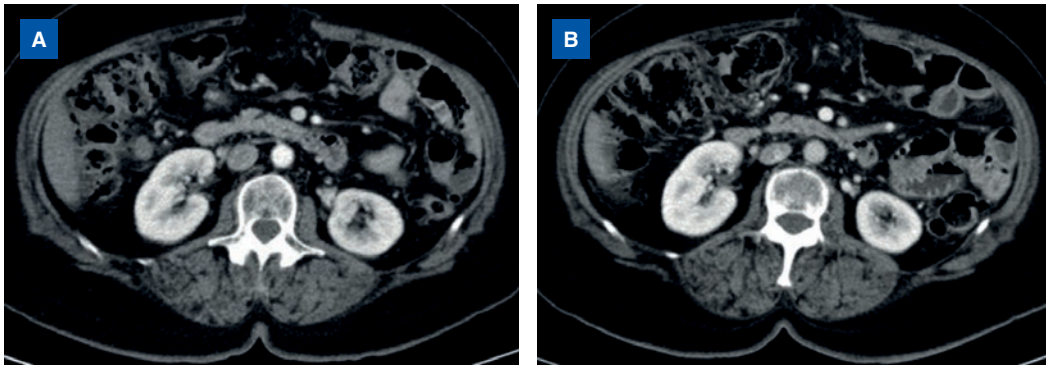

Figure 1. *CT scan of the thorax, abdomen, and pelvis.* ***A:*** *October 2019: progression with olaparib.* ***B:*** *March 2020: following four cycles of trabectedin + PLD.*

high-grade serous carcinoma diagnosis, with a papillary and solid pattern, with implants in the isthmus serosa on the front and rear sides of the uterine corpus serosa and in the left parametrial region. There are also invasive implants in excess of 2 cm in the omentum (the largest measured 9 cm at the largest point across the diameter). Cytologically malignant in peritoneal fluid.

Treatment

With an International Federation of Gynaecology and Obstetrics (FIGO) Stage IIIC ovarian bilateral serous carcinoma diagnosis (suboptimal surgery), the patient was once again referred to our clinic. The post-surgery CA125 was 276 IU/mL.

First line

On January 16, 2017, chemotherapy was initiated with carboplatin AUC 5 and 175 mg/m^2 of paclitaxel every 21 days, combined with 15 mg/kg of bevacizumab from the second cycle until completing five cycles (last cycle: April 18, 2017). The patient had Grade 2 anemia and Grade 3 thrombocytopenia and so the sixth cycle of chemotherapy was suspended. Following five cycles, the CA125 was 5.9 IU/mL and the CT scan of the thorax, abdomen, and pelvis (29/05/2017) did not show signs of disease. Later, the patient continued with the same dosage of bevacizumab for 18 cycles (from June 28, 2017, to June 28, 2018). A maintained full response was observed in the thorax, abdomen, and pelvis CT scan performed on April 16, 2016, and the CA125 was normal (18 IU/mL).

In July 2018, the patient reported abdominal pain. A CT scan of the thorax, abdomen, and pelvis (July 06, 2018) showed conclusive nodular formations in the middle abdomen mesenteric fat. Together, they were approximately 80 x 20 mm in size and had not been detected in the previous evaluation. Suspected peritoneal/conglomerate lymph node mass implants. Other similar small images were observed in the mesenteric fat of the right hemiabdomen. No intraperitoneal free fluid. The CA125 was 5.3 IU/mL.

Second line

Based on the peritoneal relapse diagnosis, six cycles of carboplatin AUC5 and paclitaxel 175 mg/m^2 were administered (from August 8, 2018, to December 20, 2018). Grade 1 sensitive peripheral neuropathy and Grade 1 thrombocytopenia emerged. In January 2019, after treatment completion, CT scan of thorax, abdomen, and pelvis showed partial response with a clear decrease in the size of the lesions observed in the mesentery. The CA125 was 5.8 IU/mL.

Maintenance treatment with olaparib 400 mg/12 h was administered from January 23, 2019, to October 10, 2019. The treatment was interrupted in April 2019 due to Grade 3 anemia that required supportive treatment. In May 2019, treatment started again with a reduced dose (200 mg/12 h of olaparib) after improving the anemia to Grade 1. During treatment with olaparib, the disease remained stable.

In October 2019, after 9 months of olaparib treatment, the CT scan showed disease progression with increased size of the mesenteric irregular thickening, consistent with peritoneal implants. The largest was before the third duodenal portion at the mesenteric root and was 25 × 20 mm in size compared with 15 × 12 mm in the previous evaluation. A peritoneal implant in the pelvis between the bladder and sigma was also observed. In this case, the size had increased from 15 × 12 mm to 25 × 15 mm. (Fig. 1A).

The patient indicated that she had abdominal discomfort. The CA125 was 15.6 IU/mL.

Table 1. *Long-term benefit with trabectedin + PLD in platinum-sensitive ROC patients reported in prospective studies (Phase III OVA-301 trial and observational NIMES-ROC and OVAYOND studies) and in an Italian retrospective study*[4,7-9]

	Trabectedin + PLD line	Median cycles	Maximum cycles	Median PFS (months)	Median OS (months)
OVA-301[4] (n = 218)	2nd line in 100% of patients	6	21	9.2	27.0
NIMES-ROC[7] (n = 218)	≥3rd line in 72.5% of patients	6	24	9.5	23.6
OVAYOND[8] (n = 77)	≥3er line in 66.2% of patients	6	21	6.3	16.4
Italian study[9] (n = 34)	≥3rd line in 100% of patients	5 (9 in 3rd line)	16	6.1	16.3

Third line

In November 2019, treatment with 1.1 mg/m^2 of trabectedin and 30 mg/m^2 of PLD every 21 days begun. The patient received eight cycles from November 25, 2019, to May 21, 2020. In terms of safety, nausea, neutropenia, asthenia, and mucositis were noteworthy (all Grade 2). Following the third cycle, treatment continued with colony stimulating factors support (6 mg of pegfilgrastim, 1 subcutaneous vial on day 2 of the cycle) and a dose decrease to 0.9 mg/m^2 of trabectedin + 25 mg/m^2 of PLD. Following four cycles, a CT scan of the thorax, abdomen, and pelvis (March 17, 2020) showed stabilization of the disease and/or partial response: mesenteric irregular thickening consistent with peritoneal implants persisted with one dominant implant (20 × 14 mm) before the third duodenal portion at the mesenteric root (previously 25 × 20 mm) and subcentimeter implants before the right kidney (less evident with partial radiological regression) and in the minor pelvis between the bladder and the sigma (similar appearance). No intraperitoneal free fluid (Fig. 1B). In the CT scan in June 2020, following eight cycles of trabectedin + PLD, the patient's condition remained stable.

Discussion

Between 10 and 15% of women with ovarian cancer are carriers of a pathogenic germline mutation in BRCA1/2. The prognosis for these patients is better since they are more sensitive to platinum-based chemotherapy.

Both in the GOG 218[1] study and in the ICON 7[2] study, it was proven that adding bevacizumab to chemotherapy with carboplatin + paclitaxel increased PFS. In Stage III and residual disease > 1 cm, an increase in OS was also observed.

In the case presented here, relapse was observed following a treatment-free interval of 15 months following the last platinum and 1 month after the last dose of bevacizumab. For this reason, rechallenge with carboplatin + paclitaxel was advised with the intention of adding olaparib in maintenance if there was a response. Treatment selection was based on the results of the SOLO2[3] study that indicates a benefit of 13.6 months in PFS compared with placebo (19.6 vs. 5.5 months; hazard ratio [HR]: 0.30; p < 0.0001). The OS data with an increase of 12.9 months were presented at the American Society of Clinical Oncology (ASCO) congress in 2020. Although it did not reach statistical significance (HR: 0.74; p = 0.0537), it was clinically relevant.

In our patient, the progression-free interval was shorter, progressing 9 months after starting the maintenance therapy with olaparib. At that time, beginning treatment with trabectedin + PLD was considered. Approval of this combination is based on the OVA-301[4] study comparing trabectedin + PLD with PLD monotherapy in patients who relapse after having received a previous platinum-based therapy. The combination was superior to PLD, showing a median PFS of 9.2 versus 7.5 months (HR 0.73 [95% CI, 0.56-0.95]; p = 0.0170) when used in platinum-sensitive patients. This benefit was more evident in patients who relapse between 6 and 12 months to platinum (median PFS: 7.4 months vs. 5.5 months; p = 0.0015)[5], as the case of our patient. In this subgroup of patients, the combination significantly increased the median OS, entailing a 6-month survival advantage over PLD alone (22.4 months compared with 16.4 months; HR: 0.64 (0.47-0.86); p = 0.0027)[5].

At the time of reporting this clinical case, the patient had received eight cycles of trabectedin + PLD and remained with stable disease. It is important to highlight that trabectedin + PLD combination is

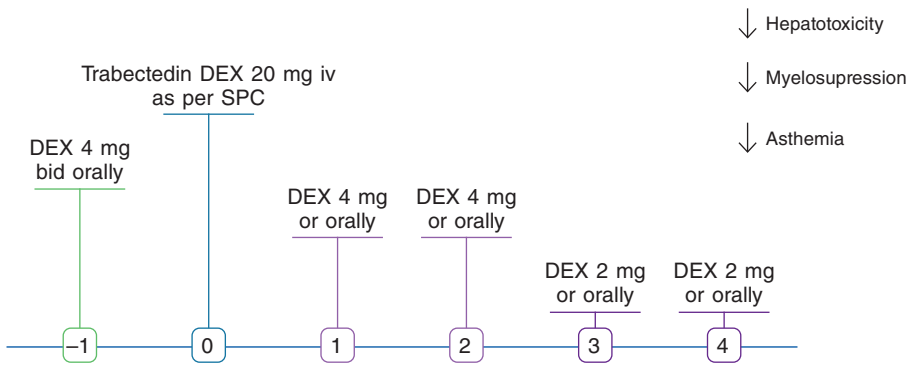

Figure 2. *Long-term dexamethasone regimen including the day before trabectedin + PLD, mandatory administration 30 min earlier on the same day, and a decreasing dose cycle over the next 4 days* (Scandurra et al., 2019)[14].

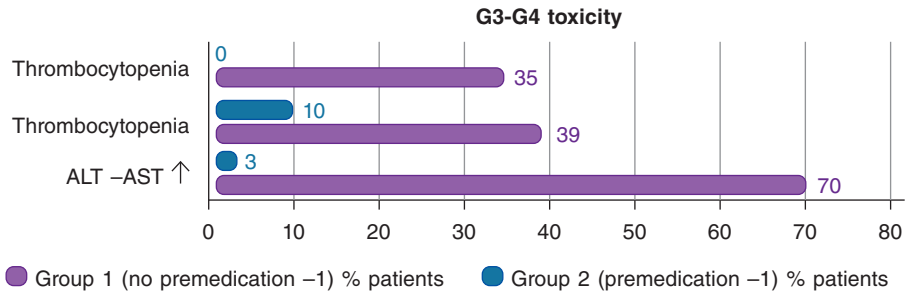

Figure 3. *Main toxicities split according to whether steroid premedication with dexamethasone on the day-1 was given or not* (Scandurra et al., 2019)[14].

compatible with long-term exposure[6], with nearly 60% of patients receiving ≥ 6 cycles and having shown to provide clinical benefit for up to 24 cycles[7].

In general, in trabectedin + PLD clinical studies, there are no predefined limits for the number of cycles and treatment is continued as long as clinical benefit is observed. In fact, several clinical trials and real-life studies have consistently reported a clinically meaningful long-term benefit with trabectedin + PLD in platinum-sensitive ROC patients (Table 1)[8].

The safety profile of trabectedin + PLD, not associated with cumulative end-organ toxicities, allows its prolonged administration[6]. An analysis from the OVA-301 study specifically evaluated the safety profile of trabectedin + PLD when administered for prolonged periods. Interestingly, hematological toxicity and transaminase elevations were considerably less frequent with ≥ 6 cycles of trabectedin + PLD compared with shorter administrations showing a reasonable long-term tolerability (uncommon severe clinical consequences such as febrile neutropenia or hepatic events, no cumulative organ toxicities, 9% of discontinuations due to AEs, and rare severe AEs such as mucositis, stomatitis, cardiac events, alopecia, or neurotoxicity)[10].

Despite its manageable safety profile, there are some cases where it is desirable to improve the safety profile of the combination, such as this patient that presented nausea, neutropenia, asthenia, and mucositis (all grade 2). Several studies[11-13] have suggested that a longer administration of dexamethasone (in addition to the mandatory dexamethasone 20 mg 30 min before) may significantly contribute to optimize trabectedin safety profile. Dexamethasone can be administered orally the day before starting trabectedin and for the subsequent 4 days, reducing the dose of corticosteroid to avoid possible rebound effects. This prophylactic regimen has the positive effect of reducing persistent fatigue without compromising the efficacy of trabectedin (Fig. 2)[14].

Furthermore, a considerable decrease in Grade 3/4 toxicities was observed when the premedication was started the day before the beginning of trabectedin treatment: there was no thrombocytopenia, neutropenia dropped by 75%, and ALT and AST levels decreased by 95% (Fig. 3)[11,14].

In summary, this case is of special relevance since the patient is a BRCA1 carrier who, after a shorter-than-expected time to progression in treatment with a PARPi, showed an enduring response to trabectedin + PLD with adequate tolerance.

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Case study 4

Third-Line Treatment with Trabectedin + Pegylated Liposomal Doxorubicin in a Platinum-Sensitive Ovarian Cancer Patient with BRCA1 Mutation

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Personal background

- A 47-year-old patient
- Hepatitis B at 12 years of age
- No known allergies to medicines
- Former smoker
- No cardiovascular risk factors
- Psoriasis
- Left side spontaneous pneumothorax in 2006
- Herniated disk in L5-S1 with motor complications and denervation data in 2009 diskectomy and hemilaminectomy performed
- Not on treatment of any kind.

Gynecological background

- Menarche: aged 11. Date of last menstrual period 5/14
- E2A0P2
- Has not breastfed
- Does not take oral contraceptives.

Family background

Mother died of breast cancer at 38 years of age. Brother diagnosed with testicular cancer at 27 years of age.

Signs and symptoms

The patient went to her primary healthcare clinic in July 2014 complaining of abdominal distension, dyspepsia, and metrorrhagia.

Diagnosis

A blood analysis was within normal limits except for the CA125 tumor marker which was high: 9,180 IU/mL. The patient was referred to the gynecology clinic and, following a CT scan on the thorax, abdomen, and pelvis, and a gynecological ultrasound scan was diagnosed with suspected ovarian neoplasia. The clinical case was presented at the Gynecological Tumor Committee and the decision to perform scheduled maximal-effort surgery was taken.

On September 11, the patient underwent a hysterectomy, double adnexectomy, omentectomy, excision of peritoneal implants and subdiaphragmatic and subphrenic implants, iliac and para-aortic lymphadenectomy, bowel resection, and Hartmann's procedure.

Optimal debulking surgery was performed with minimal residual disease (small bowel mesentery serosa < 1 mm) with no signs of tumor disease in the post-surgery CT scan.

A high-grade ovarian papillary serous adenocarcinoma was diagnosed, pT3 pN1 M0, and FIGO Stage IIIC.

Treatment

First line

The patient had an ECOG 0 score, no comorbidity, and displayed good post-surgical recovery following optimal surgery with minimal residual disease.

Carboplatin (AUC5) + paclitaxel (175 mg/m^2) + bevacizumab (7.5 mg/kg) every 21 days was selected from among the possible therapeutic options. The

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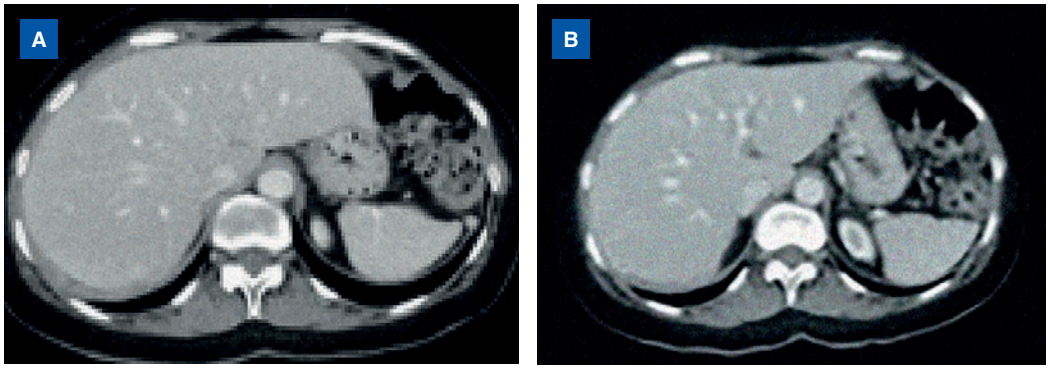

Figure 1. *CT Scan.* ***A:*** *August 2016: perihepatic peritoneal implants + ascites. Perisplenic implant.* ***B:*** *January 2017: partial response. Perihepatic implants + ascites.*

patient received six cycles between October 2104 and late January 2015. In the CT scan in February 2015, there continued to be no radiological evidence of the disease.

From February 2015, the patient continued with the maintenance treatment with bevacizumab (7.5 mg/kg every 21 days) until February 2016, completing 12 months. In the follow-up CT scan image that month, there was no evidence of disease and the CA125 tumor marker was normal.

The patient tolerated the treatment well and there was no relevant toxicity.

In April 2015, a germline BRCA1/2 mutational analysis was performed, revealing a BRCA1 pathogenic mutation (c.211A > G [p.Arg71Gly]).

Second line

The patient had an ECOG 0 score, was asymptomatic, and had no residual toxicity from the previous chemotherapy. The follow-up CT scan in August 2016 showed progression disease with peritoneal carcinomatosis (Fig. 1A) and an increase in the CA125 tumor marker: 900 IU/mL.

The patient had a TFIp of 19 months, a biological treatment-free interval of 6 months, and a BRCA1 mutation.

Treatment with six cycles of carboplatin (AUC5) + paclitaxel (175 mg/m^2) every 21 days was selected and, should there be a response, maintenance with PARPi. The patient was given six cycles of chemotherapy between August and December 2016 and a partial response was observed in the CT scan performed in November 2016. This response was maintained in the CT scan in January 2017 (Fig. 1B). The CA125 also normalized.

Adverse effects were grade 1 neurotoxicity in hands and feet, grade 1 asthenia and anaemia and grade 1 nausea and vomiting.

On December 26, 2016, maintenance treatment with olaparib (400 mg/12 h by mouth) was initiated and stopped 3 months later due to rapid clinical progression observed in imaging (Fig. 2A) together with CA125 increase.

Third line

The following factors were key for the selection of the next treatment line: a 50-year-old BRCA-mutated patient with an ECOG score of 1, abdominal discomfort and early satiety, relapse with no residual toxicity to the last chemotherapy regimen, and just 6-month TFIp.

In April 2017, treatment with trabectedin (1.1 mg/m^2) + PLD (30 mg/m^2) every 21 days was initiated. After four cycles (July 2017), a partial response was observed (Fig. 2B), along with correction of abdominal discomfort. The response remained the same in subsequent CT scans.

From the sixth cycle, the dose was decreased to 0.9 mg/m^2 + PLD 25 mg/m^2 due to Grade 3 thrombopenia and Grade 3 anemia. The patient was given 10 cycles up to October 2017.

In the CT scan performed in November 2017, stable disease was observed. However, the patient reported starting to have discomfort in the right hypochondrium at the same time that an elevation in CA125 was detected (2.538 IU/mL). In December 2107, a PET-CT scan confirmed the clinical suspicion of disease progression with perihepatic and perisplenic peritoneal tumor implants, in addition to metastatic para-aortic and retroperitoneal lymphadenopathies.

Fourth line

The patient had a third relapse with a 13-month TFIp. A moderate pericardial effusion with no functional repercussion was observed in the echocardiogram, with a left ventricular ejection fraction (LVEF) > 55%. After consulting with the Cardiology department, monitoring was prescribed.

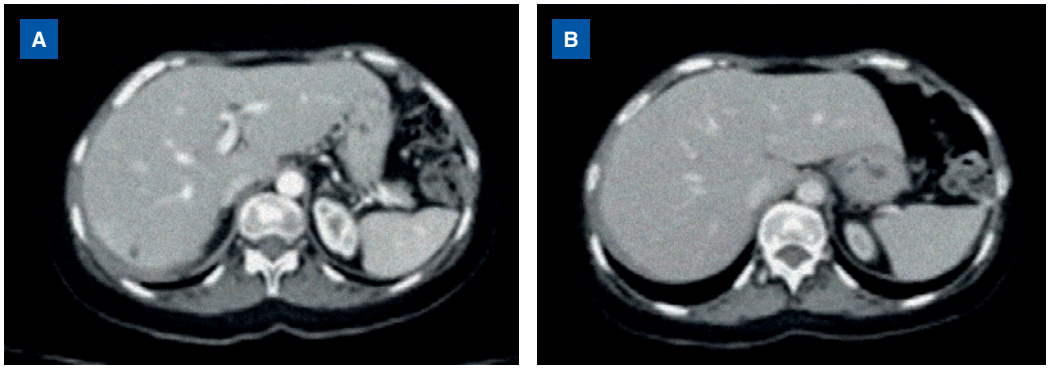

Figure 2. *CT Scan.* ***A:*** *March 2017: progression of the disease. Perihepatic implants + ascites.* ***B:*** *July 2017: partial response. Perihepatic implants.*

We opted for a new platinum doublet with carboplatin (AUC5) + paclitaxel (175 mg/m^2) every 21 days which begun in January 2018. The patient received five cycles until April 2018. In the fifth cycle, the patient had a reaction to carboplatin that was later confirmed with cutaneous allergy tests. Adverse effects, all Grade 1: anemia, vomiting, asthenia, anorexia, and intermittent neurotoxicity.

A week after the fifth cycle (administered on April 9, 2018), the patient started having partial intestinal occlusion-like symptoms and was admitted to hospital. It was resolved with conservative treatment. The treatment was suspended due to clinical disease progression as confirmed by CT scan imaging on April 26, 2018, in which peritoneal carcinomatosis was observed: omental infiltration and left hypochondrial implants and ascites.

Fifth and posterior lines

The patient was considered platinum refractory due to progression during the platinum-based chemotherapy. ECOG 1 level was maintained and a new line of treatment was prescribed: gemcitabine (1000 mg/m^2, days 1 and 8) + bevacizumab (15 mg/m^2, day 1) every 21 days. She received a total of 26 cycles, from May 2018 to December 2019, when the treatment was suspended due to disease progression with peritoneal carcinomatosis and ascites. Tolerance was good with Grade 1 anemia and Grade 1 asthenia. The best response achieved was stable disease and there was a decrease in tumor markers.

In January 2020, the sixth line of treatment with PLD (40 mg/m^2 every 28 days) was initiated. The patient received three cycles up to March 2020 when it was suspended due to clinical progression and partial intestinal occlusion. Based on the patient's own preferences, her clinical condition, and the risk/benefit of the therapeutic options, we opted for symptomatic treatment; the patient died in May 2020.

Discussion

The main objective when treating recurrent ovarian cancer is to extend survival across multiple lines of therapy, using sequential treatment to delay disease progression after each new relapse, while preserving quality of life. Although most treatment regimens for platinum-sensitive patients involve platinum, a loss of efficacy and increasing toxicity after each platinum exposure are well-known phenomena and underlie the importance of using chemotherapeutic agents with differing mechanisms of action[1].

After having received two consecutive platinum-based lines and maintenance with both bevacizumab and olaparib, it was the perfect time to add a new mechanism of action to the treatment plan of this ovarian cancer patient who probably was primary resistant to PARPi despite having a BRCA1 mutation. Trabectedin + PLD is currently the only non-platinum combination approved to treat platinum-sensitive recurrences[1]. The totally different mechanism of action and safety profile of trabectedin expands the treatment opportunities for recurrent ovarian cancer, and provides patients time to recover from the impact of prior platinum-based therapies[2]. Trabectedin has a unique mechanism of action based on interaction with the minor groove of deoxyribonucleic acid (DNA), bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA-binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle. In addition to direct growth inhibition, trabectedin also affects the tumor microenvironment by inducing depletion of monocytes and tumor-associated macrophages and reducing the production of key inflammatory mediators that promote tumor progression[3,4].

In recent years, several agents used to treat recurrent ovarian cancer have been escalated to front-line therapy, necessitating modifications to treatment algorithms used to guide daily practice decisions. The newer approach to ovarian cancer involves selecting

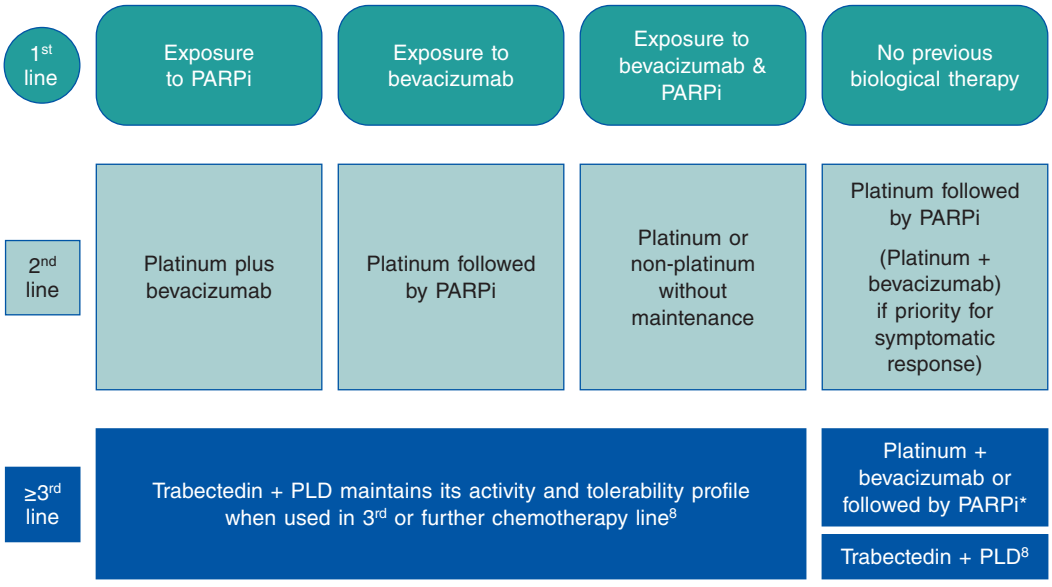

Figure 3. *Different treatment recommendations in platinum-sensitive ovarian cancer based on patients' previous exposure to biological therapy* (adapted from Pignata et al., 2021[1], and Nicoletto et al., 2021[8]).

the most appropriate first-line treatment and then designing an optimal treatment sequence to manage recurrent disease[1].

In the first-line setting, the use of maintenance treatments is already well established. Recent expert recommendations point to the valuable use of PARPi for patients with BRCA mutation status[5] and of bevacizumab in patients with an urgent need for symptom relief (e.g., pleural effusion and ascites) and non BRCA-mutated patients[6].

In the second-line setting, key factors to be considered are the prior therapy, the BRCA status, and the need of urgent symptomatic relief[6]. In patients potentially responsive to platinum with no previous exposure to biological therapy, ESMO-ESGO guidelines[7] recommend platinum-based rechallenge plus bevacizumab for those with a high disease burden and priority for asymptomatic response. The preferred option for remaining patients is platinum-based rechallenge followed by PARPi[1]. In the case of previous exposure to PARPi, platinum-based rechallenge plus bevacizumab is recommended and platinum followed by PARPi in the case of prior exposure to bevacizumab. Finally, options for patients who relapse after first-line exposure to bevacizumab and PARPi are likely to be limited to platinum- or non-platinum-based regimens without maintenance therapy[1,7].

Trabectedin + PLD can be considered as the second-line treatment of non-BRCA-mutated patients with allergy to platinum or other contraindications and represents an effective alternative to treat sensitive recurrences ≥ third line, when a decrease in efficacy and worsening toxicity are expected from platinum[3,6].

Our patient was treated according to the treatment plan exposed in figure 3. Specifically, she underwent first-line maintenance therapy with bevacizumab, followed by maintenance with olaparib in second line, trabectedin + PLD as third-line therapy and three more additional lines with platinum doublet, gemcitabine plus bevacizumab, and PLD monotherapy. This treatment plan led to a probable increased survival of 70 months in a BRCA-mutated patient but resistant to PARPi, initially diagnosed with ovarian cancer Stage IIIC.

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