

Case Report

# Maintenance with Trabectedin in the Treatment of Platinum-Sensitive Recurrent Ovarian Cancer

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## Keywords

Trabectedin · Ovarian cancer · Recurrent · Platinum

## Abstract

Ovarian cancer is the seventh most common type of cancer and the fifth leading cause of cancer death among women worldwide. The current usual therapeutic approach in this disease includes optimal cytoreductive therapy followed by platinum-based adjuvant chemotherapy, along with neoadjuvant chemotherapy prior to surgery in selected cases. The platinum-free interval (PFI) continues to be the most useful tool to assist in the selection of the subsequent therapy and to predict response to treatment. The combination of trabectedin and pegylated liposomal doxorubicin (PLD) is useful in patients with partially platinum-sensitive recurrent ovarian cancer, in patients who have previously received two or more platinum-based chemotherapy regimens, in patients who have already experienced a platinum-induced hypersensitivity reaction and in patients who have previously failed to respond to a platinum-based treatment. **Case Presentation:** A 64-years-old postmenopausal woman with pain, abdominal distension, and an altered intestinal transit and with partially platinum-sensitive recurrent ovarian cancer, was successfully treated with a second line of trabectedin chemotherapy in com-

bination with PLD, followed by trabectedin in monotherapy. This case proves the effectiveness of the combination of trabectedin and PLD and demonstrates how the administration of trabectedin, even in monotherapy, allows to maintain an adequate clinical response with good tolerance to the treatment during more than two years of drug administration.

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## Introduction

Ovarian cancer is the seventh most common type of cancer and the fifth leading cause of cancer death among women worldwide [1]. Due to the absence of symptomatology in its early stages, the disease is diagnosed at advanced stages in 70% of cases. Therefore, chemotherapy with systemic antineoplastic agents is crucial in the treatment of this disease.

Along these lines, the development in recent years of new therapeutic agents for the treatment of ovarian cancer has resulted in an increase in the progression-free survival (PFS) rates associated with certain lines of treatment; however, overall survival (OS) figures remain practically unchanged [2].

Overall, the current usual therapeutic approach in this disease includes optimal cytoreductive surgery followed by platinum-based adjuvant chemotherapy, along with neoadjuvant chemotherapy prior to surgery in selected cases [3]. However, despite the high proportion of patients who respond satisfactorily to this first line of platinum-based chemotherapy, only 15% reach full resolution and most relapse within two to five years [4]. To classify relapsed patients and establish subgroups for stratification in clinical trials, the Fifth International Ovarian Cancer Consensus Conference of the Gynaecologic Cancer Intergroup on Recurrent Disease held in Tokyo determined that patients should be classified according to the therapy-free interval (TFI). The platinum-free interval (PFI), the non-platinum-free interval (non-PFI), and the biological agent-free interval (TFIb) should also be considered. Thus far, the PFI continues to be the most useful tool to assist in the selection of the subsequent therapy and to predict response to treatment [5]. Its duration allows for differentiating between platinum-sensitive tumours (if relapse occurs 12 months after the last cycle of platinum-based chemotherapy), partially-sensitive tumours (if relapse occurs between six and twelve months after the treatment), and platinum-resistant tumours (if relapse occurs within six months of the last cycle of platinum-based chemotherapy) [3]. In case of relapse, the response to a platinum-based regimen is directly related to the duration of the PFI. Thus, if the relapse occurs in a patient with platinum-sensitive (PFI >12 months) or partially-sensitive (PFI >6 and <12 months) ovarian cancer, a second line of platinum-based combination chemotherapy is recommended. However, a non-platinum-based combination of pegylated liposomal doxorubicin (PLD) and trabectedin has also proven to be effective in patients with platinum-sensitive recurrent ovarian cancer [6].

In 2009, trabectedin – a marine-derived antineoplastic agent initially isolated from the tunicate *Ecteinascidia turbinata* which is currently being produced synthetically – in combination with PLD was approved for the treatment of patients with recurrent platinum-sensitive ovarian cancer [2]. The combination of trabectedin and PLD is a non-platinum-based chemotherapy presenting as an alternative in the treatment of recurrent ovarian cancer. It is especially useful in patients with partially platinum-sensitive recurrent ovarian cancer [2], in patients who have previously received two or more platinum-based chemotherapy regimens (in which case the risk of developing a hypersensitivity reaction increases to 27% after the seventh cycle or during the second line of treatment) [7], in patients who have already

experienced a platinum-induced hypersensitivity reaction (15–20% of all patients receiving platinum) [8], and in patients who have previously failed to respond to a platinum-based treatment.

Below we describe the clinical case of a patient with partially platinum-sensitive recurrent ovarian cancer who was successfully treated with a second line of trabectedin chemotherapy in combination with PLD, followed by trabectedin in monotherapy. The patient maintained a clinical response and a good tolerance to the treatment more than two years after its completion.

### Case Presentation

The case in question concerns a 64-year-old Caucasian postmenopausal woman presenting with pain, abdominal distension, and an altered intestinal transit.

Thoracic and abdominopelvic computed tomography (CT) scans revealed massive peritoneal carcinomatosis, extensive ascites, involvement of the major omentum, extensive involvement small intestine mesentery, diffuse involvement of the parietal peritoneum, implants at the bottom of the Douglas pouch, and probable implants on the ovarian surface, although of normal size (Fig. 1). Her plasma CA-125 tumour marker levels were 1,110.9 U/mL, and those of the remaining tumour markers fell within a normal range. An omentum biopsy was compatible with high-grade serous carcinoma, with positive expression for WT-1, p53, CK-7 and negative expression for CK20 and TTF-1, with tube-ovarian-peritoneal origin.

Given the confirmed diagnosis of a primary peritoneal carcinoma of gynaecological origin stage IIIC and after assessment by a multidisciplinary committee that considers unresectable disease due to mesenteric involvement, neoadjuvant chemotherapy with intravenous (i.v.) paclitaxel 175 mg/m<sup>2</sup> and i.v. carboplatin AUC 6 at three-week intervals was prescribed. The patient received three cycles of this treatment, showing a significant partial response on the follow-up CT scans, and plasma CA-125 tumour marker levels of 65 U/mL (levels at diagnosis: 1110.9 U/mL).

Surgery was subsequently performed, achieving optimal cytoreduction, and the patient had a catheter placed for the administration of the intraperitoneal chemotherapy. The pathological study of all samples obtained during the procedure revealed a high-grade serous carcinoma.

Following the intervention, a total of four cycles of adjuvant intraperitoneal (i.p.) chemotherapy consisting of i.v. paclitaxel 175 mg/m<sup>2</sup> (day 1), i.p. cisplatin 75 mg/m<sup>2</sup> (day 2), and i.p. paclitaxel 60 mg/m<sup>2</sup> (day 8) were administered. The patient achieved a complete response, although she developed grade-2 asthenia and grade-3 neutropenia due to treatment-related toxicity that mandated a delay in the dosing and support with granulocyte-colony stimulating factors (G-CSFs).

Seven months after receiving the last cycle of platinum-based chemotherapy, her CA-125 tumour marker levels were 104 U/mL, and mediastinal lymph node and peritoneal recurrence were identified in the follow-up CT scans. At this time, a germline mutation study was carried out in BRCA, being negative. Given that these findings were considered to be indicative of progression after a PFI of seven months, second-line chemotherapy was started with i.v. trabectedin 1.1 mg/m<sup>2</sup> (day 1) in combination with i.v. PLD 30 mg/m<sup>2</sup> (day 1) at 21-day cycles. The patient achieved a partial response after the third cycle (CA-125: 11.8 U/mL) (Fig. 2, 3).

Chemotherapy with trabectedin and PLD was continued; however, given that the patient experienced haematological toxicity (grade-4 neutropenia), the dose of PLD had to be reduced

to 25 mg/m<sup>2</sup> and that of trabectedin to 0.9 mg/m<sup>2</sup> during the sixth cycle. PLD was subsequently discontinued altogether due to the onset of toxicity associated with this drug (grade-2 mucositis and grade-3 asthenia). From then on, she received i.v. trabectedin 0.9 mg/m<sup>2</sup> in monotherapy at 21-day cycles, with good tolerance and referring only grade-1 asthenia that resolved within two to three days and did not limit her during her basic activities of daily living.

After ten cycles of treatment, and specifically four cycles of trabectedin in monotherapy, the dose of trabectedin had to be reduced to 0.75 mg/m<sup>2</sup> every 21 days due to the onset of grade-3 neutropenia and grade-2 thrombopenia, which mandated frequent delays in the dosing and even G-CSF support. Nevertheless, the subsequent follow-up CT scans performed periodically continued to show evidence of complete response. The patient received a total of 35 cycles of trabectedin (six in combination with PLD and then 29 in monotherapy). During this time, she maintained an excellent quality of life, experiencing no late or cumulative toxicity, and being able to perform her usual activities.

Because peritoneal progression was subsequently detected after a PFI of three years, a third line of treatment with i.v. carboplatin (area under the curve [AUC] = 4) (day 1), i.v. gemcitabine 1,000 mg/m<sup>2</sup> (days 1 and 8 of every 21-day cycle), and i.v. bevacizumab 15 mg/kg (day 1) was started. A subsequent follow-up CT scan carried out after the third cycle of this therapy showed signs of partial response. Given that the response persisted after six treatment cycles, chemotherapy was suspended and treatment with bevacizumab in monotherapy was started. The patient has received a total of 12 cycles of maintenance treatment with bevacizumab in monotherapy to date, having tolerated the treatment well and maintained a partial response.

## Discussion

Trabectedin binds to the minor groove of deoxyribonucleic acid (DNA), bending the helix towards the major groove. This binding triggers a cascade of events that affect several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in alterations in the cell cycle [9]. In addition, trabectedin has also been proven to act in the tumoral microenvironment, decreasing the production of pro-inflammatory factors such as CCL2 and IL-6 [10].

The approval of trabectedin in combination with PLD for the treatment of platinum-sensitive recurrent ovarian cancer was based on the findings of a phase-III clinical trial (OVA-301 study) in which patients with platinum-sensitive recurrent ovarian cancer (PFI ≥6 months) who received trabectedin and PLD had a higher PFS than those who received PLD in monotherapy ( $p = 0.0170$ ) [4]. The difference between the two treatments was even greater among the subgroup of patients with partially platinum-sensitive ovarian cancer (the PFS was 7.4 months among those treated with trabectedin combined with PLD and of only 5.5 months among those treated with PLD in monotherapy) [11]. The hazards ratio (HR) was 0.65 (95% confidence interval [CI], 0.45–0.92), indicating a 35% reduction in the rate of disease progression (DP) or death. Thus, this result significantly favours the combination of trabectedin and PLD ( $p = 0.0152$ ). In the OVA-301 study, the OS of the patients with platinum-sensitive recurrent ovarian cancer (after 47.4 months of follow-up) was higher among those who had received a combination of trabectedin and PLD (median OS = 22.2 months) in comparison with those who had received PLD in monotherapy (median OS = 18.9 months) ( $p = 0.0835$ ). Once more, the most significant difference was observed among the subgroup of patients with ovarian cancer partially sensitive to platinum, as the median OS was 22.4 months among the

patients treated with trabectedin and PLD, and of 16.4 months among those treated with PLD in monotherapy ( $p = 0.0027$ ).

It should be noted that an unanticipated exploratory analysis performed during this study revealed that the median OS was greater when the duration of the PFI was longer, in such a way that the median OS was 32.5 months with a PFI >12 months (95% CI: 28.4–38.5), 13.6 months with a PFI <6 months (95% CI: 11.7–14.8), and 20.3 months with a PFI of six to twelve months (95% CI: 17.7–21.7), respectively. The results of this study indicate that the duration of the PFI is a continuous parameter and a highly important prognostic factor of survival in patients with recurrent ovarian cancer [12]. In the case of the combination of trabectedin and PLD, the OS that characterized patients with a PFI equal to or greater than 12 months (32.5 months) in our study fell within the range of the results obtained with other platinum-based therapies [8].

Thus, the results of the published studies suggest the existence of a clear relationship between the duration of the PFI and overall survival (i.e., the greater the PFI, the longer the survival). As a result, the combination of trabectedin and PLD may be an effective and safe therapeutic option that could allow for lengthening the duration of the PFI and increasing the survival of these patients [2, 13].

The OVA-301 study also analysed what happened when patients with a PFI of six to twelve months were treated with a combination of trabectedin and PLD together with an additional line of subsequent platinum-based chemotherapy. In this case, the addition of a subsequent platinum-based treatment appeared to be more effective, as patients who had received the combined treatment rather than the monotherapy lived almost nine months longer after receiving the platinum-based treatment (18.6 months for the combined treatment and only 9.9 months for the PLD treatment in monotherapy;  $p = 0.0513$ ) [14]. This clinical observation could be explained by *in vitro* and *in vivo* studies that support the treatment sequence-effect hypothesis, given that repeated exposure to trabectedin would select cell populations in the tumour with a deficient nucleotide excision repair (NER) system that are consequently more sensitive to platinum compounds.

The INOVATYON study (NCT013679989), in which patients with platinum-sensitive recurrent ovarian cancer are randomized to receive a platinum-based combination therapy (carboplatin and PLD) or a non-platinum-based combination therapy (PLD and trabectedin), is currently underway with a view to support this hypothesis of the sequence effect [15].

In the clinical case described in this paper, the patient achieved a partial response with a combination of trabectedin and PLD (six cycles), which she maintained for two years after continuing treatment with trabectedin in monotherapy until progression of her disease was detected. The patient tolerated the treatment well, and the duration of her PFI consequently increased. After a PFI of three years, the patient was treated with another platinum-based treatment, achieving a response and maintaining the disease under control for almost a year after finishing this second treatment. These findings pave the way towards new therapeutic options for future disease progression.

The summary of product characteristics (SmPC) of trabectedin recommends administering treatment until progression of the disease is detected provided that the patient's tolerability is acceptable and that there are no pre-defined limits with respect to the number of cycles that can be administered.

## Conclusions

This case proves the effectiveness of the combination of trabectedin and PLD in a patient with platinum-sensitive recurrent ovarian cancer. In addition, it demonstrates how the administration of trabectedin, even in monotherapy, allows to maintain an adequate clinical response with good tolerance to the treatment during more than two years of drug administration. Based on the findings of this clinical case, it appears that trabectedin combined with PLD is an effective and safe alternative in patients with platinum-sensitive recurrent ovarian cancer. Furthermore, this combination could improve clinical outcomes in terms of survival if used properly within the treatment sequence. Further trials comparing different treatment sequences are needed to corroborate this hypothesis.

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## Statement of Ethics

All authors state that subjects (or their parents or guardians) have given their written informed consent to publish their case, including publication of images.

Procedures were in accordance with guidelines established in the Declaration of Helsinki and with the principles of Good Clinical Practices.

## Disclosure Statement

The authors declare that there is no conflict of interest.

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None.

## Author Contributions

All authors participated in the study design, data acquisition, data analysis and the manuscript drafting and revision.

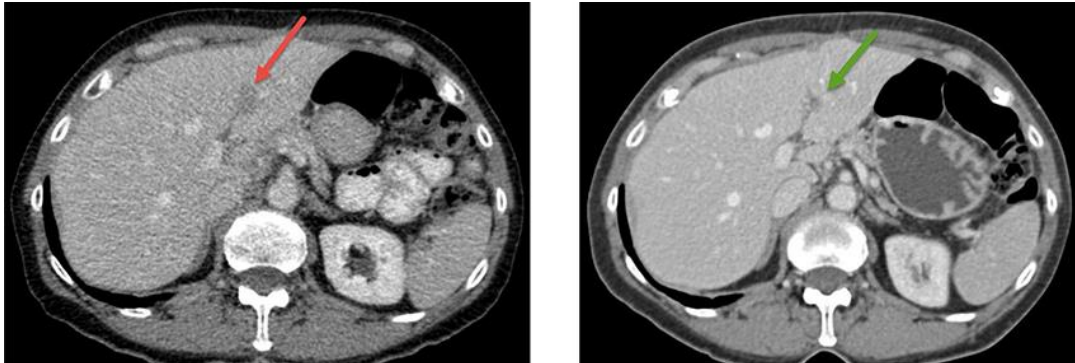
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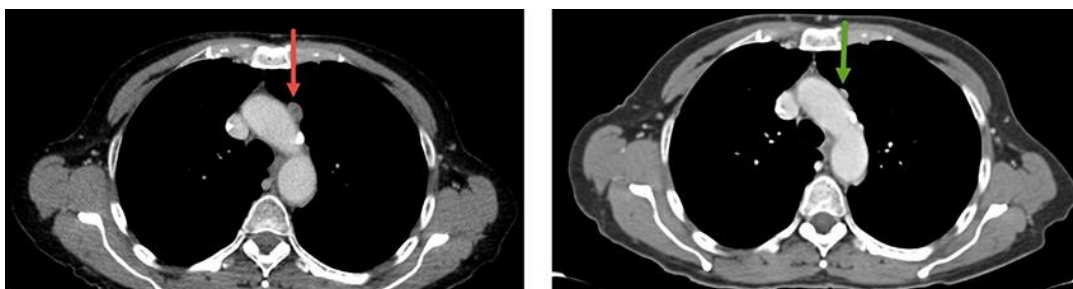


**Fig. 1.** Reformatted contrast-enhanced coronal CT image showing massive ascites and omental carcinomatosis (green arrows) at diagnosis.



**Fig. 2.** Contrast-enhanced axial CT image showing a new tumoral lesion in the falciform ligament of the liver (red arrow) after seven months of first-line platinum-based therapy and downsizing of the tumoral lesion after three cycles of trabectedin + PLD (green arrow).





**Fig. 3.** Enhanced axial CT image showing an enlarged mediastinal lymph node at a prevascular level (red arrow) after seven months of first-line platinum-based therapy and downsizing of the mediastinal lymph node after three cycles of trabectedin + PLD (green arrow).