Trabectedin for reversing platinum resistance and resensitization to platinum in patients with recurrent ovarian cancer

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Aims: We evaluated trabectedin in patients with platinum-resistant/refractory and partially platinum-sensitive recurrent ovarian cancer and the outcomes after reintroduction of platinum. **Methods:** Twenty-seven patients (platinum-resistant/refractory $n = 24$ /PPS; $n = 3$) treated with trabectedin were retrospectively analyzed. **Results:** Trabectedin resulted in an objective response rate (ORR) of 18.2% with a 59.1% of disease control rate (ORR plus stable disease). The median progression-free and overall survival were 3.0 and 21.3 months, respectively. Subsequently, 17 patients were retreated with platinum and yield an ORR of 41.2% and DCR of 47.0%. The median progression-free and overall survival after platinum rechallenge were 5.0 and 14.7 months, respectively. **Conclusion:** Our results suggest that trabectedin may contribute to resensitize tumor cells to platinum rechallenge.

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Keywords: ovarian cancer • platinum rechallenge • platinum-resistant/refractory • resensitization • trabectedin

Ovarian cancer is the leading cause of death from gynecological malignancies and the seventh leading cause of cancer-related death among women in the EU in the period 1970–2003 [1]. Early stage ovarian carcinoma is generally asymptomatic, thus often resulting in a late diagnosis with approximately 75% of all the cases presenting with an advanced stage associated with poor outcome [2]. Despite of high response rates to front-line treatment for advanced disease with cytoreductive surgical debulking followed by platinum/taxane-based chemotherapy (up to 80%), most patients with advanced disease relapse within 2 years from diagnosis [3].

Recurrent ovarian cancer (ROC) is not a curable disease; thus, the principal objective of salvage treatments is to prolong survival, alleviate cancer-related symptoms and improve quality of life [4,5]. The usual treatment approach in relapsed patients is determined by their response to the first-line platinum-based chemotherapy, as measured by the platinum-free interval (PFI) [6]. Patients with platinum-sensitive disease, defined as a PFI ≥ 6 months, are usually re-treated with platinum-containing regimens, yielding response rates ranging from 30–60% [7]. Among platinum-sensitive patients, patients with partially platinum-sensitive disease (PPS), who experience disease relapse from 6–12 months after front-line platinum-based therapy, typically obtain substantially lower response rate to platinum re-challenge [8–10]. On the other side, no best postprogression treatment at relapse is agreed on for chemoresistant women whose disease progresses while receiving initial platinum-based treatment or within 4 weeks of last platinum dose (platinum-refractory) and those experiencing progressive disease (PD) within 6 months (PFI < 6 months) of platinum-based therapy in the primary setting (i.e., platinum-resistant) and thus, represents a therapeutic challenge [6]. Taking into consideration that the likelihood of response to re-treatment with platinum-based treatment in patients with platinum-resistant/refractory (PRR) ROC is low, nonplatinum monotherapy is the preferred treatment for those patients. A variety of single agents, including paclitaxel, etoposide, gemcitabine, topotecan, pemetrexed and pegylated liposomal doxorubicin (PLD) have shown limited activity in patients with

PRR disease with an objective response rate (ORR) usually between 6–25%, median progression-free survival (PFS) ranging from 3–5 months and median survival time from 11–13 months [11–17].

Trabectedin (Yondelis®) is the first anticancer marine drug to be approved by the EU and many other countries worldwide. Results from a Phase III randomized study conducted in 672 patients with platinum-sensitive and platinum-resistant ROC (OVA-301; NCT00113607) showed a clinically relevant benefit for the combination of trabectedin plus PLD as compared with PLD alone [18,19]. Trabectedin has a unique multifaceted mechanism of action that involves transcription regulation and DNA repair systems, including transcription-coupled nucleotide excision repair and homologous recombination as the main hallmarks of its antiproliferative activity [20]. In addition to direct growth inhibition, trabectedin at therapeutic concentrations has selective anti-inflammatory and immunomodulatory properties due to the inhibition of production of factors that promote tumor growth, angiogenesis and metastasis [21–23]. Recently, it has been reported that cancer cells that have become less sensitive or resistant to trabectedin, following repeated exposures to trabectedin, become much more sensitized to next platinum-based chemotherapy [24]. In addition, two analyses of overall survival (OS) carried out in all platinum-sensitivity subsets of patients treated in the OVA-301 study showed that the treatment with trabectedin plus PLD prior to subsequent platinum retreatment results in at least 6-month favorable trend toward longer OS compared with PLD alone [25,26]. Those results have provided further supportive clinical evidence for the sequential combination of trabectedin and platinum. Based on these observations, we retrospectively analyzed data from heavily pretreated patients with PRR and PPS ROC who had been treated with trabectedin and subsequent platinum at our institution to evaluate, if trabectedin may play a role in reverting platinum resistance and resensitization to further platinum.

Methods

Study design

For this retrospective analysis, patient attendance records and the institutional chemotherapy database were searched for all patients commencing chemotherapy with trabectedin for advanced ROC, between January 2003 and March 2013 at the University Hospital San Carlos in Madrid, Spain. Eligible patients were patients ≥ 18 years old with unresectable advanced or metastatic, histologically proven recurrent epithelial ovarian carcinoma who had experienced either relapse or disease progression. All patients were duly informed about treatment and signed informed consents were obtained from all study participants before any treatment. In addition, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Treatments

Trabectedin was administered as a 3-h intravenous infusion every 3 weeks. The initial dose of trabectedin ranged between 1.1 mg/m² body surface area, which is the recommended dose for trabectedin when combined with PLD [18] and 1.5 mg/m². Antiemetic and hepatoprotective prophylaxis with dexamethasone 20 mg intravenously 30 min prior to trabectedin and serotonin antagonists were considered mandatory for all patients. In addition, antiemesis prophylaxis included corticosteroid medication with dexamethasone or prednisone pre- and postchemotherapy. Treatment with trabectedin was discontinued at progression or for other reasons such as unacceptable toxicity, investigator decision or consent withdrawal.

Study evaluations

Tumor response was assessed at screening and every 12 weeks thereafter, according to the standard response evaluation criteria in solid tumors v.1.0 and v.1.1 [27,28]. Radiological efficacy assessments of trabectedin and post-trabectedin treatments were conducted in an all-evaluable patient population. The disease control rate (DCR) was defined as the percentage of patients with a complete response (CR) plus partial response (PR) plus stable disease (SD). Duration of response was defined as the time from the start of treatment until documentation of PD. For the time-to-event analyses, as time-to-progression (TTP), PFS and OS, the Kaplan–Meier method was used to estimate fixed time points. The TTP, PFS and OS analyses following trabectedin and post-trabectedin platinum-based treatment were defined as the time interval from the first administration of trabectedin or subsequent platinum treatment to disease progression for TTP or until disease progression, death or lost to follow-up for PFS, whereas OS was defined as the time between the start of trabectedin or subsequent platinum administration and patient death from any cause or last follow-up. Moreover, PFI was defined as the interval from the last date

Table 1. Patient and disease characteristics at baseline.

Patients	(n = 27) n (%)
Age at treatment with trabectedin (years):	
– Median (range)	63 (45–81)
Platinum sensitivity:	
– PRR	24 (88.9)
– PPS	3 (11.1)
Number of prior chemotherapy lines:	
– Median (range)	5 (1–9)
– 1	3 (11.1)
– 4	5 (18.5)
– ≥ 5	19 (70.4)
ECOG PS:	
– 0	11 (40.7)
– 1	12 (44.4)
– ≥ 2	4 (14.8)
Histology:	
– Serous-papillary	18 (66.6)
– Clear-cell	3 (11.1)
– Endometrioid	2 (7.4)
– Undifferentiated	2 (7.4)
– Mucinous	2 (7.4)

Data shown are numbers and percentage of patients or median and range values with available data.
ECOG PS: Eastern Cooperative Oncology Group performance status; PPS: Partially platinum-sensitive; PRR: Platinum resistant/refractory.

of platinum-based therapy until documented disease progression. For subsequent platinum-based chemotherapy, administered after disease progression and discontinuation of trabectedin, the tumor response and the outcomes of time-to-event assessments were also recorded.

Results

Patient characteristics

This analysis included a total of 27 patients with PD at the time of trabectedin initiation. Overall, 24 patients were considered resistant/refractory to platinum (88.9%), whereas three patients had PPS disease (11%) following the initial treatment with carboplatin and paclitaxel. Patients and tumor characteristics are summarized in Table 1. At the time of treatment with trabectedin patients had a median age of 63 years (range: 45–81 years) and most had serous-papillary carcinoma (n = 18; 66.6%) and a good Eastern Cooperative Oncology Group performance status score of 0/1 was recorded in 23 (85.2%) patients. Patients were pretreated with a median of five lines of chemotherapy (range: 1–9 lines) prior to trabectedin administration with 19 of them (70.4%) who were exposed to more than five lines of prior chemotherapy. Several nonplatinum-based chemotherapies were intercalated between front-line treatment with platinum and before the treatment with trabectedin. Most patients received weekly topotecan (n = 17), bevacizumab (n = 13) or PLD (n = 11), whereas oral chronic etoposide, gemcitabine and paclitaxel were given to four, three and one patient, respectively.

Response to trabectedin treatment

Patients received a median of 3.5 trabectedin cycles per patient (range: 1–14 cycles) with no signs of cumulative toxicities. Overall, 14 patients received < four cycles (51.8%), four patients received 4–5 cycles (14.8%) and nine patients > six cycles (33.3%) of trabectedin. The most commonly used trabectedin dose was 1.3 mg/m² (n = 20; 74.1%), followed by 1.1 and 1.5 mg/m² administered to six (22.2%) and one (3.7%) patients, respectively. The median interval between the last platinum treatment and the first trabectedin dose was 5 months (range: 1.0–18.0 months) with an interquartile range of 1.3–9.0 months.

At time of analysis, 22 of 27 patients (81.5%) were assessable for response as two patients early progressed and died and three patients were considered not evaluable due to clinical deterioration. Regarding the overall

Figure 1. Responses to trabectedin and subsequent platinum-based treatment.
DCR: Disease control rate; ORR: Objective response rate; SD: Stable disease.

trabectedin activity, one patient (4.5%) had a CR and three patients (13.6%) obtained PR reaching the ORR of 18.2% with a median duration of 16.5 weeks (range: 5.9–44.4 weeks). Moreover, nine (40.9%) patients had SD as a best result with a median duration of 5.8 months (range: 4.1–9 months) for a DCR of 59.1% (Figure 1). Nine (40.9%) patients experienced disease progression during the treatment with trabectedin. Treatment with trabectedin resulted in a median PFS of 3.0 months (95% CI: 2.2–3.7) and median OS of 21.3 months (95% CI: 15.1–27.5) (Figure 2).

Response to platinum rechallenge

Seventeen patients who progressed after a median of six cycles of trabectedin and with no contraindications or morbidities to be rechallenged with platinum salts, were eligible to be retreated with subsequent platinum-based chemotherapy. Five patients were not rechallenged with platinum after trabectedin owing to a rapid deterioration and death, two patients had bowel obstruction, one patient refused further treatment with platinum, one had renal insufficiency and another patient had a severe hypersensitivity reaction to carboplatin that hindered her subsequent treatments with platinum.

After the median duration of time between the last trabectedin administration and the first subsequent platinum dose of 2.5 months (range: 1–5 months), eligible patients were rechallenged with a median of six cycles (range: 1–10 cycles) of platinum-based chemotherapy. The most frequently used combination was carboplatin plus paclitaxel in eight patients (pretreated with a median of four prior chemotherapy lines; range: 1–8) followed by carboplatin plus paclitaxel and bevacizumab in four, carboplatin plus gemcitabine in two patients and carboplatin monotherapy, carboplatin plus PLD and oxaliplatin with paclitaxel and bevacizumab in one patient each. Seven patients had confirmed a PR according to response evaluation criteria in solid tumors giving an ORR of 41.2%. Of note, the ORR was retained in patients pretreated with ≥ 5 prior platinum-based lines. Additionally, one patient (5.9%) had SD for a DCR of 47.0% (Figure 1). Analysis of time-to-event end points following platinum rechallenge resulted in a median PFS of 5.0 months (95% CI: 4.0–5.9 months) and a median OS of 14.7 months (95% CI: 5.7–23.6 months) in this heavily pretreated-patient population (Figure 3).

An analysis of the patients who were treated with trabectedin and achieved an ORR, SD or disease progression showed that the patient who had a CR with trabectedin did not respond to subsequent carboplatin treatment, whereas among the three patients who achieved PR with trabectedin one had PR to subsequent carboplatin, one patient progressed and another was not rechallenged with platinum. Among those who obtained SD with

Figure 2. Median progression-free survival and overall survival following the treatment with trabectedin.

Figure 3. Median progression-free survival and overall survival after trabectedin treatment and platinum rechallenge.

trabectedin, five patients attained PR after subsequent platinum, two patients progressed and another patient had SD (one of those patients did not receive subsequent platinum). Finally, among patients who progressed with trabectedin, one had a PR, two obtained SD and three patients also progressed after the treatment with subsequent platinum.

Discussion

Patients with PRR ROC have a dismal prognosis with a mean life expectancy of approximately 12 months despite treatment with salvage chemotherapy. For this group of patients, therapeutic options are limited and usually consist in nonplatinum agents. This retrospective analysis aimed to evaluate the efficacy of trabectedin monotherapy and the outcomes after reintroduction of a platinum-based treatment. To date, three Phase II studies evaluating the efficacy of single agent trabectedin in the treatment of ROC demonstrated response rates of 39–43% [29–32]. The results of an integrated pooled analysis of Phase II studies have confirmed that trabectedin as single agent is an active treatment in ROC as reported an ORR for the whole pooled population of 26% and a median OS of 17.1 months [32]. In addition, one prospective study in patients with *BRCA* patients and another retrospective multicenter study showed similar response rates (27.5–40%) [33,34]. The results of this single institution series suggest that trabectedin is an effective treatment that provides clinically meaningful benefits to heavily pretreated patients with PRR/PPS ROC (e.g., ORR: 18.2%; median OS: 21.3 months) and favorably compare with those observed in patients with platinum-resistant ROC and treated with trabectedin as the second/third-line monotherapy in Phase II studies [29–32] and are comparable with those seen with other nonplatinum agents [11–17]. We should point out that due to a worldwide shortage of PLD, caused by an 18-month halt in production from 2011 to 2013, single agent trabectedin was proposed as an alternative to our patients with ROC. The outcomes from our analysis were achieved in a population that had been heavily treated with a median of five lines of chemotherapy (range: 1–9 lines) and with 70% patients pretreated with ≥ 5 prior regimens before trabectedin administration. Arguably, advances in supportive care could explain, at least partly, the improved outcomes in our series. Although, due to its retrospective nature, this study was not designed to evaluate the safety of trabectedin, the patients received a median of 3.5 cycles of trabectedin, suggesting an acceptable safety profile that allowed prolonged treatment (i.e., up to 14 cycles), being consistent with previous reports of trabectedin safety [35].

Studies in human ovarian cancer cells and patients with platinum-resistant ovarian cancer have reported that primary or secondary (acquired) resistance to platinum could be a variable phenotype over time, which could be considered as an unstable, inducible, multifactorial and reversible phenomenon after a drug-free interval and/or sequential treatment with nonplatinum drugs [36–38]. Up to date trabectedin is the only compound for which convincing experimental evidence of the platinum-restoration mechanism is available [39]. Noteworthy, the results of the analysis among patients who obtained disease progression as a best response with trabectedin and were rechallenged with platinum suggest that a response to trabectedin is not requested to potentially obtain a benefit from the next rechallenge with platinum-based therapies. In contrast with what has been reported for other DNA-interacting drugs like platinum salts, which are more effective against cells with defects in nucleotide excision repair mechanism (NER) [40,41], trabectedin efficacy is linked to an efficient transcription-coupled NER and deficient homologous recombination repair activity in the targeted tumor cells [20,33,42–44]. Several preclinical data have indicated that trabectedin treatment enhances the collateral sensitivity to subsequent treatments with platinum drugs. Recent *in vitro* and *in vivo* studies evaluating trabectedin-resistant cell lines from ovarian carcinoma and myxoid liposarcoma have confirmed that resistance to trabectedin is associated with the loss of NER function, with a consequent increased sensitivity to platinum drugs [24]. Thus, these data suggested that cancer cells that have become less sensitive or resistant to trabectedin after repeated exposures to trabectedin become much more sensitized to next platinum-based chemotherapy. Those data have provided a clear molecular rationale for the efficacy of the sequential use of trabectedin and platinum drugs. Importantly, those results seem to translate well into clinically useful approaches considering the results from two post hoc, exploratory analyses of OS performed in patients according to platinum-sensitivity categories [25] and separately in patients with platinum-resistant disease [26], who were subsequently retreated with platinum-based chemotherapy after completing either trabectedin plus PLD or PLD treatment in OVA-301 trial. In all subsets of patients, the treatment with trabectedin plus PLD prior to subsequent third-line platinum retreatment resulted in an at least 6-month favorable trend toward longer OS compared with PLD alone. Significantly longer OS was recorded in patients with PPS disease with a notable improvement of 9 months in median OS (median OS: 27.7 vs 18.7 months; $p < 0.0153$) [25], whereas a 6.7-month improvement in median OS and a 38% decrease in the risk of death was observed in patients with platinum-resistant disease (22.2 vs 15.5 months; hazard ratio: 0.62, 95% CI: 0.36–1.06; $p = 0.078$). Of note, the median OS reported in the cohort of patients with platinum-resistant ROC treated with trabectedin plus PLD in the OVA-301 trial (22.2 months) is very similar to that observed in this analysis (21.3 months) [26].

Apart from the limited number of patients and the retrospective nature of this study, the principal limitation of this study was the lack of the control platinum-based arm in order to demonstrate that trabectedin increases the likelihood of response to subsequent platinum over immediate platinum-based re-treatment. Although speculative, it could be also argued the hypothesis that in a less heavily pretreated patient population, the efficacy of trabectedin and the results of platinum rechallenging could have led to a more extensive benefit. Taking into account that no prospective data are available comparing trabectedin or trabectedin plus PLD with a platinum-based postprogression regimens, two prospective clinical trials are ongoing aiming to shed some more light on this issue. The results of this retrospective study provided the rationale for designing a Phase II clinical trial to prospectively evaluate the effect of reintroduction of platinum salts after trabectedin treatment in women with platinum-resistant ROC who have been pretreated with a maximum of four chemotherapy lines (No EudraCT: 2014-004020-21). Moreover, the ongoing academic Phase III INOVATYON (refers to: INternational OVarian cancer patients Treated with YONdelis) trial is aimed to demonstrate that the combination of trabectedin plus PLD prolongs OS over carboplatin plus PLD in patients with PPS ROC (ClinicalTrials.gov identifier: NCT01379989). Indeed, in both the trials, the expected improvement in survival could be not only related to intercalation of the combination of trabectedin plus PLD or trabectedin alone before subsequent platinum rechallenge but also due to a peculiar aspect of the mechanism of action of trabectedin that could enhance the efficacy of subsequent platinum-based therapies.

Conclusion

In conclusion, the results of this retrospective, real-life analysis suggest that sequential treatment with trabectedin might resensitize the tumor cells of patients with PRR and PPS ROC and improve the efficacy of subsequent platinum-based chemotherapy.

Future perspective

Although platinum-based drugs are regularly used in patients with platinum-sensitive disease, uncertainties abound in the treatment of women with PPS relapse and women unsuited for platinum rechallenge. Particularly the results from the Phase III OVA-301 study have called into question the paradigm of platinum as mainstay treatment for patients with platinum-sensitive relapse. The results of further prospective Phase II–III clinical studies and expanded access programs will probably definitely confirm the role of the non-platinum combination of trabectedin plus PLD (and/or trabectedin monotherapy) in relapsed ovarian cancer patients with a platinum-free interval (PFI) beyond 6 months. It will be particularly the case in patients who experience residual toxicities to platinum, have limited sensitivity to platinum (i.e., for patients with PPS disease with a PFI of 6–12 months), or have developed hypersensitivity reactions to platinum. Nevertheless, to date in the absence of randomized trials it is impossible to demonstrate the superiority of trabectedin plus PLD over standard platinum-based chemotherapy in the setting of platinum-sensitive recurrent disease. Notably, a Phase II clinical trial will prospectively evaluate the effect of re-introduction of platinum salts after trabectedin treatment in women with platinum-resistant ROC, whereas the ongoing academic Phase III INOVATYON trial is aimed to demonstrate that the combination of trabectedin plus PLD prolongs overall survival over carboplatin plus PLD in patients with PPS disease.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Executive summary

- We retrospectively analyzed 27 heavily pretreated patients (24 with platinum-resistant/refractory [PRR]/three with partially platinum-sensitive [PPS] recurrent ovarian cancer [ROC]). Tumor response was assessed every 12 weeks according to Response Evaluation Criteria in Solid Tumors.
- This retrospective analysis was performed to better understand, if the treatment with trabectedin may increase the likelihood of response to subsequent platinum in patients with PRR and PPS ROC.
- Principal molecular rationale for the efficacy of such a sequential use lays in the fact that cancer cells, which have become less sensitive or resistant to trabectedin after repeated exposures to trabectedin, become much more sensitized to next platinum-based chemotherapy.
- Preclinical data have suggested that trabectedin enhances the collateral sensitivity to subsequent treatments with platinum salts by reverting platinum resistance and resensitization to platinum.

Main results

- Patients received a median of 3.5 trabectedin cycles per patient (range: 1–14 cycles) with no signs of cumulative toxicities.
- Among 22 patients (81.5%) assessable for response with trabectedin one (4.5%) had a complete response and three patients (13.6%) obtained partial response reaching the objective response rate of 18.2%. Nine other (40.9%) patients achieved stable disease for a disease control rate of 59.1%. Treatment with trabectedin resulted in a median progression-free survival of 3.0 months and median overall survival of 21.3 months.
- After a median time between the last trabectedin and the subsequent platinum dose of 2.5 months, 17 patients were retreated with platinum, seven of whom had a partial response giving an objective response rate of 41.2%. Additionally, one patient (5.9%) had stable disease for a disease control rate of 47.0%. The median progression-free survival and overall survival after platinum rechallenge were 5.0 months and 14.7 months, respectively.

Conclusion

- The results of this retrospective, real-life analysis suggest that sequential treatment with trabectedin followed by subsequent platinum rechallenge might re-sensitize the tumor cells of heavily pretreated patients with PRR and PPS ROC.
- Prospective studies are ongoing to definitely establish the role of trabectedin and sequential treatments in women with platinum-resistant and PPS ROC.

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