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Trabectedin as single agent in the salvage treatment of heavily treated ovarian cancer patients: A retrospective, multicenter study

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HIGHLIGHTS

- Trabectedin provided 27.5% objective response, and 61.2% clinical benefit in recurrent ovarian cancer patients.
- Trabectedin was more effective in platinum sensitive recurrent ovarian cancer patients.
- Trabectedin shows acceptable toxicity in heavily treated recurrent ovarian cancer patients.

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ABSTRACT

Objective. The aim of this multicenter, retrospective study was to evaluate the efficacy and the safety of single agent Trabectedin (ET-743, Yondelis®) in very heavily treated, relapsed ovarian cancer (ROC) patients.

Patients and methods. Response to treatment was classified according to RECIST criteria. Progression-free (PFS), and overall survival (OS) were also assessed.

Results. 98 patients were analyzed (originally 67 platinum sensitive, and 31 platinum refractory/resistant). Median number of previous regimens was 4 (range: 1–6). In the whole population, overall response rate (ORR) was 27.5%; stable disease (SD) was observed in 33 patients (33.6%), and clinical benefit was achieved in 60 cases (61.2%). ORR was 38.6% in fully platinum sensitive population, and 26.1% in partially platinum sensitive patients. In platinum refractory/resistant disease, ORR was 12.9%. Overall, median PFS and OS were 5, and 13 months, respectively. Patients responding to Trabectedin showed a more favorable PFS (median = 9 months) than patients with SD (median = 6 months), or progression (median = 2 months). Median OS of responding patients was 18 months compared to 14 months in SD patients, and 9 months in progressing patients. Grade 3–4 neutropenia was observed in 17 (17.3%) patients. Transient and non-cumulative Grade 3–4 AST and ALT level elevation was found in 7 (7.1%), and 13 (13.3%) cases, respectively. There was 1 case of Grade 3, and 1 case of Grade 4 cardiac toxicity.

Conclusions. Trabectedin, as a single agent, retains its efficacy in terms of rate of ORR and clinical benefit in heavily treated ROC patients, especially in the group of platinum sensitive disease.

Introduction

Despite the efforts of surgery and efficacy of platinum–paclitaxel containing chemotherapy [1,2], prognosis of advanced ovarian cancer patients remains unfavorable, with the majority of cases eventually recurring within 12–24 months since diagnosis [1,2].

Responsiveness to first line treatment remains one of the most important determinants of clinical outcome: in particular, patients recurring within 6 months from initial therapy exhibit low rates of response (4–23%) to salvage treatment [3]. On the other side, cases who recur >12 months after initial therapy are defined as fully platinum sensitive, and are usually re-challenged to platinum based combinations [4]. More recently, patients recurring within 6–12 months

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from primary treatment have been acknowledged as partially platinum sensitive since the rate of response to platinum re-challenge (25–30%) is similar to what can be achieved with non-platinum agents [5]. Until the date, in the crucial scenario of novel chemotherapeutics to be employed for management of recurrent ovarian cancer (ROC) patients, great enthusiasm has been fuelled into drugs endowed with different structures, and unique mechanism of action. Trabectedin (ET-743, Yondelis®) is a marine derived tetrahydroisoquinoline alkaloid with antitumor activity, originally isolated from the tunicate *Ecteinaiscidia turbinate* and currently synthetically produced; its covalent binding to N2 guanine at the minor DNA groove induces a bend to the major DNA groove: Trabectedin-induced DNA damage is recognized by the nucleotide excision repair (NER) system, thus leading to the accumulation of ternary DNA-Trabectedin–protein repair complexes which, upon collision with the replication fork, result in formation of double strand DNA breaks (DSB) [6,7]. These findings support the demonstration that, contrary to what is shown for other DNA binding agents, a functional NER system seems required for efficient Trabectedin cytotoxicity [6,8]. On the other hand, Trabectedin is expected to be more effective in cells lacking functional homologous recombinant repair mechanisms, such as those endowed with BRCA gene mutation or BRCAness phenotype [9]. Besides blocking cell cycle and inducing p53-independent apoptosis, and interfering with transcription regulatory pathways, Trabectedin has been shown to selectively deplete blood monocytes and tumor-associated macrophages in tumor bearing mice as well as in soft tissue sarcoma and ovarian cancer patients, suggesting that part of the antitumor activity of the drug could be ascribed to its ability to act as a tumor microenviroment modifier [10–13].

Trabectedin has been first approved in Europe in 2007 for treatment of soft tissue sarcoma patients failing anthracyclines or ifosfamide or unsuited to receive them, and in 2009 for recurrent platinum sensitive ovarian cancer patients in combination with pegylated liposomal doxorubicin [14–17].

Trabectedin, as single agent, has been analyzed in relapsed ovarian cancer patients in three phase II studies which reported a response rate ranging between 29% and 43.5% in platinum sensitive versus 6.5–7.0% in platinum resistant disease [18–20]. It has to be considered that in these series very recently evaluated in a pooled analysis [21], the vast majority of patients had received Trabectedin as second line treatment: in particular, only 29% up to 36% of cases had been administered ≥2 previous chemotherapy lines before Trabectedin [18–20].

These observations prompted us to retrospectively evaluate in a multicenter study the efficacy and the safety of single agent Trabectedin in a population of very heavily treated, relapsed ovarian cancer patients.

Patients and methods

Study design

This was a multicentric, retrospective uncontrolled study aimed at evaluating the activity and safety of Trabectedin, as a single agent, in heavily treated ROC patients. Written informed consent to treatment and to the use of clinical data for scientific purposes had been provided by all patients at time of chemotherapy administration. Given the retrospective design of the study, approval of local Ethical Committee to retrieve data from clinical charts was not required.

Clinical data were collected from six Italian Institutions which had employed Trabectedin as single agent in ROC patients since January 2010 to September 2012. Consecutive patients with histologically confirmed epithelial ovarian carcinoma, previously treated with at least one platinum/paclitaxel chemotherapy regimen, and with radiological evidence of measurable recurrence/progression of disease were included in the study. Further selection criteria were: age over 18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, life expectancy >3 months, absolute neutrophil count (ANC) >1500/mm^3; platelet count >150,000/mm^3; bilirubin and creatinine levels less than 1.5 times the upper limit of normal; normal cardiac function defined as LVEF ≥50%. Pre-treatment evaluation included pelvic examination, abdomino-pelvic CT, Ca125 assay. Trabectedin (Yondelis®, PharmaMar, Madrid, Spain) was supplied as a lyophilized powder in glass vials of 0.25 or 1 mg; the total amount of drug was diluted in 500 ml of 0.9% normal saline and administered as a 3-hour infusion through a separate line, preferably through a central venous access. Antiemetic prophylaxis was mandatory and included intravenous 5-hydroxytryptamine-3 antagonists with dexamethasone 10 mg intravenously, 1 h before starting chemotherapy; oral metoclopramide 10 mg thrice a day was given during the infusion and afterward. Premedication with corticosteroids as prophylaxis against hepatic toxicity consisted of oral dexamethasone 4 mg bid starting 24 h before treatment and up to 72 h after treatment.

Cycles were administered every 21 days as long as re-treatment criteria were met (complete recovery of hematological and non-hematological toxicities, or until disease progression or discontinuation for other reasons). Treatment-related toxicity was assessed according to NCI-CTC criteria (version 2.0) [22]. All patients who received any Trabectedin infusion were considered assessable for response to treatment which was classified according to RECIST criteria (version 1.0) [23]. Response was also evaluated according to Ca125 levels (GCIG criteria) [24]. Progression-free (PFS), and overall survival (OS) were also assessed.

Statistical analysis

The $\chi 2$ test or Fisher's exact test for proportion or Mann–Whitney non-parametric test was used to analyze the distribution of categorical or continuous data. Objective response rate (ORR) included complete and partial response. Stable disease was defined as "neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease", according to RECIST criteria [23]. Clinical benefit included complete, partial response, and stabilization of disease. The 95% confidence interval (95% CI), has been provided. PFS and OS were defined as the time elapsed between the start of treatment and documentation of progression, or death of disease or the date last seen. Medians and life tables were computed using the product-limit estimate by the Kaplan and Meier method [25] and the log-rank test was employed to assess the statistical significance [26]. Statistical analysis was carried out using SOLO (BMDP Statistical Software, Los Angeles, CA, USA).

Results

Patient characteristics

A total of 98 patients were analyzed (Table 1): median age at diagnosis of recurrence was 53 years (range: 29–79); most patients (N = 78, 79.6%) had serous carcinoma. In the whole population, 44 patients were considered fully platinum, 23 patients partially platinum sensitive, and 31 patients as platinum refractory/resistant, according to the initial platinum sensitivity.

Median number of previous regimens was 4 (range: 1–6); 93.9% of patients had received ≥2, and 57.1% of patients had received ≥4 prior treatments before starting Trabectedin. The vast majority of patients (N = 72, 73.5%) had already been treated with anthracyclines. The median treatment-free interval was 4 months (range = 1–21) in fully platinum sensitive patients, 2 months (range = 1–7) in partially platinum sensitive patients, and 2 months (range = 1–9) in platinum resistant patients.