Retrospective trial on trabectedin (ET-743) monotherapy in very heavily pretreated advanced ovarian cancer

D. Lorusso[1], M. Marinaccio[2], E. Mele[2], I. Sarno[1], G. Scambia[3], F. Raspagliesi[1]

Abstract

Background: Trabectedin, is a natural product derived from the marine tunicate *Ecteinascidia turbinata* binding the minor groove of DNA. The present phase II prospective trial was designed to address the activity and toxicity profile of trabectedin in a population of very heavily pretreated recurrent ovarian cancer patients.

Patients and methods: Sixty recurrent ovarian cancer patients were treated with trabectedin 1.1–1.3 mg/m^2 i.v. over 3 hours every 3 weeks; 37 (62%) were platinum-sensitive and 23 (38%) platinum-resistant. Median number of previous chemotherapy lines was four. The primary study objective was overall response rate (ORR) according to RECIST version 1.1 criteria.

Results: ORR was 25%; 13 responses were registered among 37 platinum-sensitive patients (35%) and two responses were reported among the 23 platinum-resistant patients (9%). Disease stabilization was registered in 20/60 (33%) patients. The most common trabectedin-related grade 3–4 non-haematological adverse events per patient were asthenia (50%), transaminitis (31%) and nausea (14%). The most common grade 3–4 haematological toxicities per patient were neutropenia (32%), leukopenia (32%), anaemia (18%) and thrombocytopenia (14%).

Conclusions: Trabectedin plays a definite therapeutic role as single agent in the ovarian cancer recurrent setting, with activity maintained even after several previous chemotherapy lines.

Key words: cardiac toxicity, recurrent ovarian cancer, trabectedin

Introduction

Epithelial ovarian cancer is the leading cause of death among gynaecologic cancers in Western countries [1, 2]. Most patients present with advanced disease (FIGO Stage III and IV), and are managed with surgical resection followed by platinum-paclitaxel chemotherapy [3].

Although most patients respond to first-line chemotherapy, more than 70% experience disease recurrence within 2 years after completion of first-line treatment and, in general, 5-year overall survival remains disappointingly low at around 30% [4].

Treatment options for recurrent patients are primarily based on the platinum-free interval, the treatment of choice being the reintroduction of platinum-based combination therapy for recurrence in sensitive patients (patients recurring >6 months after the completion of platinum treatment) while non-platinum cross-resistant single agents (i.e., pegylated liposomal doxorubicin [PLD], topotecan, gemcitabine, and etoposide) are the preferred treatments for resistant patients (patients recurring <6 months after the completion of platinum treatment) [5].

More recently, the subset of partially platinum-sensitive patients (patients with 6–12 months platinum-free interval) was defined: treatment options for these patients include either carboplatin-based doublets (with paclitaxel or gemcitabine or PLD) [6], and PLD-trabectedin (ET-743) combination therapy, which was recently showed to be superior to PLD monotherapy in terms of progression-free and overall survival in recurrent platinum-sensitive patients [7, 8].

Several phase II studies have addressed the activity and toxicity profile of trabectedin in advanced and recurrent ovarian cancer reporting a quite disappointing response rate (RR) of 7% in platinum-resistant patients while a median RR of 36% was registered in the sensitive setting [9, 10].

The present retrospective trial was performed to investigate the activity and toxicity profile of trabectedin mono-

[1]Department of Gynaecologic Oncology, Fondazione IRCCS Istituto Nazionale Tumori, Milano, Italy.
[2]Department of Obstetrics and Gynaecology, University of Bari, Bari, Italy.
[3]Department of Gynaecologic Oncology, Università Cattolica del Sacro Cuore, Roma, Italy.

Correspondence to: Dr. Domenica Lorusso
Fondazione IRCCS Istituto Nazionale Tumori,
Via Venezian 1, 20133 Milano, Italy.
Phone: +39 02 23903697; Fax: +39 02 23902349;
E-mail: domenica.lorusso@istitutotumori.mi.it

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therapy in a population of very heavily pretreated recurrent ovarian cancer patients.

Methods

The study protocol was approved by the Independent Local Ethics Committee. Eligibility criteria included patients >18 and <80 years old with histological confirmation of progressive ovarian carcinoma; previous treatment with platinum, taxanes and anthracyclines; one or more measurable lesions; reference imaging within the prior 4 weeks; Eastern Cooperative Oncology Group (ECOG) performance status (PS) score 0–1; life expectancy >3 months; and adequate haematological (haemoglobin >10 g/dL; absolute neutrophil count >0.5 × 10^9/L; platelets >100 × 10^9/L), renal (serum creatinine <1.25 × upper limit of normal (ULN); creatinine clearance >60 mL/min) and hepatic function [serum bilirubin <ULN; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) <2.5 × ULN; and total alkaline phosphatase (AP) <ULN; creatine kinase <2.5 × ULN and albumin >25 g/L].

Patients were excluded if they had history of congestive heart failure or left ventricular ejection fraction <50%; chronic liver disease; primary central nervous system malignancies, or another serious illness or medical condition.

Treatment regimen

The patients received trabectedin at 1.1–1.3 mg/m^2 over 3 h every 3 weeks by an i.v. infusion with central line.

Prophylactic medication included dexamethasone (4 mg p.o. 24 and 12 h before infusion plus 20 mg i.v. 30 min before infusion plus 4 mg p.o. 24, 36, 48, 60, and 72 h post infusion) and serotonin antagonists. Therapeutic use of hematopoietic colony growth factors [granulocyte colony-stimulating factor (G-CSF)] and use of erythropoietin were permitted. Treatment was continued until disease progression, unmanageable toxicity, patient refusal or administration delay >2 weeks due to toxicity.

A maximum of one dose reduction from 1.3 to 1.1 mg/m^2 was permitted in case of any of febrile neutropenia; grade 4 neutropenia >5 days; platelets <25 × 10^9/L; ≤2-week delay of recovery of grade 3/4 ALT or AST; elevation of alkaline phosphatase (AP) or bilirubin of any grade; grade 3/4 nausea/vomiting (except for that reversible with adequate supportive/symptomatic therapy), or any other grade 3/4 toxicity excluding alopecia or phlebitis.

Assessment of response and toxicity

Patients who received a minimum of two cycles were evaluated for efficacy. The primary endpoint was overall response rate (ORR) according to RECIST 1.1 criteria. Secondary efficacy endpoints included progression-free survival (PFS) and overall survival (OS). All patients who received any trabectedin infusion were assessable for safety. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, v.4.0.

Statistical analysis

Time-to-event variables (PFS and OS) were analysed according to the Kaplan-Meier method. PFS was defined from the date of the first study drug administration to the date of confirmed radiological progression. Platinum sensitivity was defined according to the last platinum-based chemotherapy treatment.

Results

Patient characteristics

From March 2010 to April 2012, a total of 60 patients were treated (Table 1). Patients' median age was 54 years (range 25–78 years), 37 patients (62%) were platinum-sensitive and 23 (38%) platinum-resistant [11]. Median number of previous chemotherapy lines was 4 (48.3% of patients received trabectedin as 4th, 33.3% as 5th and 13.3% as 6th line of treatment).

Table 1. Patient characteristics and treatment parameters

Characteristics	Value
N	60
Previous chemotherapy lines	4 (3-6)
Courses (median, range)	293 (5, 2-9)
Dose reduction, n/N (%)	22/60 (36.6)
Cycle delay*, n/N (%)	36/293 (12.3)

* Median delay 7 days.

A total of 293 cycles were administered with a median of 5 cycles/patient (range 2–9). Median delay of 7 days was necessary in 36 out of 293 cycles (12.3%). Haematological events (mainly transient neutropenia) and mild liver dysfunctions were the most common reasons for cycle delays. Dose reduction to 1.1 mg/m^2 was made in 22 out of 44 patients treated with trabectedin 1.3 mg/m^2.

Efficacy endpoints

All 60 treated patients were evaluable for activity. At a median follow-up of 14 months, PFS was 5.6 months (95% CI 1.4–11.3 months). Median OS in the overall population was 8.1 months (95% CI 1.4–12.8 months).

The partial response (PR) rate was 25% (Table 2). Thirteen partial responses were registered among 37 platinum-

Table 2. Efficacy data

	Patients, n/N (%)		
	Platinum-sensitive	Platinum-resistant	Overall
Patients	37 (62)	23 (38)	60 (100)
CR	–	–	–
PR	13/37 (35)	2/23 (9)	15/60 (25)
SD	13/37 (35)	7/23 (30)	20/60 (33.3)
Overall clinical benefit (PR + SD)	26/37 (70)	9/23 (39)	35/60 (58.3)
PD	11/37 (30)	14/23 (61)	25/60 (41.7)

CR, complete response; PD, progression of disease; PR, partial response; SD, stable disease.

sensitive patients (35%) and two partial responses were reported among the 23 platinum-resistant patients (9%). Stabilization of disease was registered in 20/60 (33.3%) patients with an overall clinical benefit (PR + stable disease [SD]) of 58.3%.

Toxicity

All 60 treated patients were evaluable for safety. The most common trabectedin-related grade 3–4 non-haematological adverse events (AEs) per patient were asthenia (50%), transaminitis (31%) and nausea (14%). Peripheral neuropathy and alopecia occurred in <10% of patients and never exceeded grade 2. Three patients reported drug related cardiac toxicity (5%): two patients presented with myocardial infarction with full recovery and one patient died of acute arrhythmia. All three patients had previously received anthracyclines.

The most common grade 3–4 haematological toxicities per patient were neutropenia (32%) and leukopenia (32%), followed by anaemia (18%) and thrombocytopenia (14%) [Table 3]. No patients presented with febrile neutropenia and no bleeding complications were associated with thrombocytopenia.

Table 3. Haematologic and non-haematologic toxicity (per patient)

Grade 3-4 toxicity	Patients, n/N (%)
Anaemia	8/60 (18)
Leukopenia	19/60 (32)
Neutropenia	19/60 (32)
Thrombocytopenia	10/60 (14)
Nausea	8/60 (14)
Asthenia	30/60 (50)
Transaminase elevation	18/60 (31)
Cardiac toxicity	3/60 (5)

Discussion

The results of this retrospective trial fit with those previously reported [9, 10, 12, 13] and confirm the effectiveness of trabectedin as a single agent in recurrent ovarian cancer in terms of ORR and disease stabilization (DS).

The antitumor activity observed is of note: the 25% overall response rate in this very heavily pretreated recurrent ovarian cancer population is in keeping with the clinical antitumor activity registered by other authors.

In our study, 13 patients achieved a partial response (35%) in platinum-sensitive patients and 9% responses were registered in resistant patients, which is absolutely in line with what previously reported in a less pretreated populations.

The 9% response rate in platinum-resistant patients observed in our study suggests that trabectedin might not be a cost-effective salvage treatment in this setting.

Another interesting finding in a so heavily pretreated population was the duration of PFS of 5.6 months with an OS of 8.1 months.

The study has also the value of providing an in-depth assessment of trabectedin toxicity in a population previously treated with platinum, taxanes and anthracyclines. The most common AEs registered during trabectedin treatment were a self-limiting and reversible liver enzyme elevation and noncumulative myelosuppression.

In our study, the main grade 3–4 non-haematological toxicities were asthenia (50%), asymptomatic AST or ALT elevation (31%) and nausea and vomiting (14%). Severe grade 3–4 neutropenia and leukopenia were observed in 32% of patients, whereas severe anaemia and thrombocytopenia occurred in 18% and 14% of patients, respectively. The reduced incidence of transaminitis, asthenia and nausea reported, compared with what is described in the literature, is possibly related to the corticosteroid premedication that all patients systematically received and to the lower dose we use in our clinics.

In our study, three patients reported drug related cardiac

toxicity (5%): two patients presented with myocardial infarction with full recovery, and one patient died of acute arrhythmia. All three patients had previously received treatments with anthracyclines and taxanes. Lebedisnsky et al. [14] recently reported the results of a cardiac safety analysis of trabectedin in sarcoma, breast and ovarian cancer patients: in 19 phase II trials cardiac AEs (CAEs) were reported in 1.8% of patients and arrhythmias (1.1%) were the most common registered events. Only one death (0.1%) attributable to trabectedin cardiac toxicity was reported [14]. Relevant predisposing risk factors for CAEs identified by the authors were previous anthracycline and taxane exposure and, in this context, our recurrent ovarian cancer population was at high risk given that all the patients had previously received treatment with anthracyclines and taxanes and 76% and 45% of them presented with hypertension and hypercholesterolemia, respectively. In this view, it may be prudent when using trabectedin in high-risk patients, heavily pretreated with anthracyclines and taxanes, to monitor clinical conditions closely for early detection of cardiac dysfunction and, when indicated, perform appropriate instrumental evaluation.

In the present study, 50% of patients receiving trabectedin at the initial dosage of 1.3 mg/m² reduced their dose to 1.1 mg/m², mainly because of a grade 3–4 increase of AP and/or bilirubin, and 12.3% of cycles were delayed by a median of 7 days, mainly because of lack of recovery of AST or ALT elevation and/or absolute neutrophil count. No patients discontinued treatment because of hematologic or non-hematologic toxicities. Overall, tolerability data indicate that trabectedin at 1.1–1.3 mg/m² infused over 3 hours every 3 weeks with corticosteroid premedication is feasible and applicable for multiple cycles in the majority of patients regardless of the number of previous chemotherapy lines.

A limitation of our study is the absence of quality of life data given that the maintenance of quality of life and the prevention or amelioration of cancer-related symptoms is among the principal aims of the treatment in recurrent disease.

Conclusion

When considering our results within the context of available second- or third-line therapies with well-established activity in ovarian carcinoma, trabectedin stands as a drug that may play a definite therapeutic role also as single agent in the recurrent setting with activity maintained after several previous chemotherapy lines.

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