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Single agent trabectedin in heavily pretreated patients with recurrent ovarian cancer☆

Jean-Philippe Adam [a,b,*], Feriel Boumedien [c], Nathalie Letarte [a,b,d], Diane Provencher [b,e]

[a] Pharmacy Department, Centre Hospitalier de l'Université de Montréal (CHUM), Montreal, Quebec, Canada
[b] Centre de Recherche du CHUM, Montreal, Quebec, Canada
[c] Faculty of Medicine, Université de Montréal, Montreal, Quebec, Canada
[d] Chaire Famille Sabourin en santé des femmes, Faculty of Pharmacy, Université de Montréal, Montreal, Quebec, Canada
[e] Division of Gynecologic Oncology, CHUM, Quebec, Canada

HIGHLIGHTS

- Trabectedin has an interesting activity in patients with recurrent ovarian cancer.
- ORR was achieved in 48% of our heavily pretreated population.
- First time that trabectedin shows an efficacy in platinum-resistant patient.
- Trabectedin is well tolerated with few severe adverse events.

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ABSTRACT

Purpose. In 2012, due to a shortage of pegylated liposomal doxorubicin, single agent trabectedin was proposed as an alternative of treatment to our patients with recurrent ovarian cancer (ROC) at our center. The aim of this retrospective study was to evaluate efficacy and tolerability of trabectedin in this context.

Patients and methods. This retrospective study included all patients who received intravenous trabectedin 1.3 mg/m^2 over 3 h every 3 weeks for ROC between January 2012 and December 2015 at the Centre hospitalier de l'Université de Montreal. The primary outcome was the progression-free survival (PFS) based on CA-125 levels, clinical exam and/or Response Evaluation Criteria in Solid Tumors criteria. We also evaluated overall survival (OS), response rate and toxicities.

Results. A total of 42 patients with a median age of 59 years received trabectedin in 2nd or 3rd line (12% of patients), 4th or 5th line (43%), and ≥6 lines (45%) and 45% were platinum-resistant. The median number of cycles received was 6 (range 1–19 cycles). Complete response (CR), partial response (PR), stable disease (SD) and progression occurred in 19%, 29%, 33% and 19% of patients, respectively. The median PFS and OS was 4.3 months (95% CI, 3.4–5.1) and 16.2 months (95% CI, 9.0–23.5), respectively. In patients with a clinical benefit (CR, PR, SD), the median PFS was 4.6 months. Trabectedin was well tolerated with few adverse events.

Conclusion. Our results demonstrate that trabectedin has an interesting efficacy as a single agent in heavily treated ROC patients.

1. Introduction

Ovarian cancer is often diagnosed in the advanced stages due to the absence of specific symptoms in earlier stage disease. In this situation, the prognosis is poor and the 5-year survival rate varies from 40 to 55% [1–3]. For the last two decades, a platinum-based combination with a taxane is considered as the standard front-line treatment in ovarian cancer [4,5]. The duration of response is highly variable according to the initial response obtained with the platinum agent and is shorter with subsequent chemotherapies.

Patients recurring <6 months from platinum-based treatment are considered as resistant to platinum and have low response rates (4–23%) to salvage treatment [6]. Patients who are recurring between 6 and 12 months and ≥12 months are considered respectively as partially and fully platinum-sensitive, and have better outcomes because

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* Corresponding author at: Oncology Pharmacist, Centre Hospitalier de l'Université de Montréal (CHUM), 1560 rue Sherbrooke Est, Montréal, Québec H2L 4M1, Canada.
E-mail address: jean-philippe.adam.chum@ssss.gouv.qc.ca (J.-P. Adam).

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platinum regimens can be reused. Eventually, patients with advanced disease will relapse and single-agent chemotherapy is preferred in a third-line treatment or more. In this context, pegylated liposomal doxorubicin (PLD), paclitaxel, topotecan or gemcitabine have shown response rates between 9 and 20% [7–10].

Trabectedin (Yondelis[MD]) is a marine-derived tetrahydroisoquinoline alkaloid with antitumor activity, originally isolated from the tunicate *Ecteinaiscidia turbinate* and currently synthetically produced [11]. By binding the guanine residues in the DNA minor groove, trabectedin initiates a cascade of events that causes a disruption with several transcription factors, DNA binding proteins, and DNA repair pathways, leading to tumor cell arrest and death [9].

In Canada and Europe, trabectedin is approved in combination with PLD for relapsed platinum-sensitive ovarian cancer in patients who are not expected to benefit, are ineligible, or are not willing to receive a retreatment with a platinum-based chemotherapy. Approval was based on a phase III study demonstrating a benefit on progression-free survival (PFS) when using the trabectedin-PLD combination (7.3 months versus 5.8 months, $p = 0.019$) [12]. However, the benefit on overall survival (OS) was significant only in the subgroup of patients with a partial sensitivity to platinum. Two phase II studies evaluating the efficacy of single agent trabectedin every 3 weeks in the treatment of ROC demonstrated response rates of 39–43% [13,14]. One prospective study in patients with BRCA patients and one retrospective multicenter study showed similar response rates (27.5–40%) [15,16].

Due to a world-wide shortage of PLD in 2012, single agent trabectedin was proposed as an alternative to our patients with recurrent ovarian cancer (ROC) after failure to a second-line treatment or more. The aim of this study was to evaluate retrospectively the efficacy and tolerability of trabectedin in a heavily treated population. The primary outcome was PFS. Secondary outcomes included OS, response rate and toxicity.

Table 1
Patient and cancer characteristics.

Characteristics	n = 42 (%)
Median age at diagnosis, years [range]	59 ± 8.5 [46–83]
Median time since diagnosis, years [range]	4 ± 3.3 [1–18]
Previous lines of treatments before trabectedin [range]	4 ± 2.5 [1 − 12]
1 or 2 lines	5 (12%)
3 or 4 lines	18 (43%)
5 or 6 lines	8 (19%)
7 or 8 lines	8 (19%)
≥9 lines	3 (7%)
Ethnicity	
Caucasian	40 (95%)
Other	2 (5%)
Any treatment received 6 months before starting trabectedin	32 (76%)
Mean time between the last line of treatment and the 1st cycle of trabectedin (months)	3.7 months
Ovarian cancer histology	
Serous	37 (88%)
Endometrioid	4 (10%)
Mix (clear cell and serous)	1 (2%)
Histologic grade at diagnosis	
Low grade	3 (7%)
High grade	35 (83%)
Unknown	4 (10%)
FIGO stage at diagnosis	
IC, IIC or IIIB	5 (12%)
IIIC	28 (67%)
IV	9 (21%)
Presence of abdominal carcinomatosis at diagnosis	26 (62%)
Platinum resistance to the last platinum regimen received	
Sensitive	12 (29%)
Partially sensitive	12 (29%)
Resistant	18 (43%)
Estrogen receptor	
Positive	30 (71%)
Negative	1 (2%)
Unknown	11 (26%)
Progesterone receptor	
Positive	7 (17%)
Negative	24 (57%)
Unknown	11 (26%)
BRCA status	
BRCA-1 positive	4 (10%)
BRCA-2 positive	2 (5%)
BRCA-1 and 2 negative	8 (19%)
Unknown	28 (67%)

Figo, Federation Internationale de Gynecologie et d'Obstetrique.

2. Patients and methods

2.1. Study design

This retrospective study is unicentric and aimed to evaluate the efficacy and tolerability of trabectedin in a heavily treated population. Our local independent ethics committee/independent institutional review board approved the study for data retrieval from clinical charts.

Clinical data was collected for all patients who received trabectedin monotherapy between January 1st 2012 and December 31th 2015 at the Centre hospitalier de l'Université de Montréal (CHUM), a university teaching hospital in Montreal, Canada. Patients were included if they had histologically confirmed epithelial ovarian carcinoma (EOC), were previously treated with at least one line of treatment (including at least one platinum/paclitaxel chemotherapy regimen), and had measurable evidence of recurrence/progression of disease before starting trabectedin (based on either radiological, clinical or CA-125 evidence). Other inclusion criteria included age over 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and life expectancy of >3 months. Patients with brain metastasis were also included. Exclusion criteria were contraindications to trabectedin, which included the presence of Child-Pugh B or C liver disease prior to treatment, or transfer to another hospital during or after the administration of trabectedin [17].

2.2. Trabectedin treatment

Trabectedin (Yondelis[MD], Janssen, Toronto, Canada) was supplied as a lyophilized powder in glass vials of 1 mg. Every 3 weeks, trabectedin 1.3 mg/m^2 was diluted in 500 mL of 0.9% Sodium Chloride and administered as a 3-hour infusion through a central venous access line. Antiemetic prophylaxis consisted of intravenous granisetron 1 mg and dexamethasone 20 mg, both administered 30 min before trabectedin. Delayed nausea and vomiting was observed in the first patients treated, thus, oral dexamethasone 4 mg taken twice daily for 48 h starting the day after trabectedin, was added as an antiemetic post-chemotherapy. Premedication with dexamethasone 20 mg also served as a prophylaxis

Table 2
Treatment characteristics.

Treatment characteristics	n = 42 patients (%)
Median number of cycles of trabectedin given per patient [range]	6 ± 3.4 [1–19]
Starting dose of trabectedin	
1.3 mg/m^2	41 (98%)
1.1 mg/m^2	1 (2%)
Patients with dose reduction during treatment	11 (26%)
Number of treatment delays for 7 days	73/242 cycles (30%)
Mean dose intensity received	87% ± 13 (52–100%)
Dose intensity received	
100%	13 (31%)
90–99%	7 (17%)
80–89%	11 (26%)
70–79%	5 (12%)
>70%	6 (14%)

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