

## Topotecan as a Continuous Infusion Over 14 Days in Recurrent Ovarian Cancer Patients

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**Abstract.** *Objective:* In recurrent ovarian cancer the topoisomerase-1 inhibitor topotecan shows activity after prior treatment with platinum and taxanes. Overall response rates of up to 38% in combination with an acceptable toxicity profile have been reported. We performed a pilot study to evaluate the therapeutic efficacy and toxicity profile of a low-dose continuous infusion protocol of topotecan. *Patients and Methods:* Twelve patients with recurrent ovarian cancer and a measurable lesion received a continuous infusion of topotecan (0.4mg/m<sup>2</sup>/d) over 14 days, repeated every 28 days. All patients had at least one prior platinum-containing regimen of chemotherapy (range 1-7). Responses were evaluated by ultrasound, computed tomography (CT) scans and/or magnetic resonance imaging (MRI). *Results:* A total of 57 (median 5, range 1-12) topotecan treatment cycles were administered. The overall response rate was 2/12 (17%). Four patients had stable disease (33%), among them two patients with platinum-refractory tumors. The median time to progression was 26 (range 20-100) weeks. No grade 3 or 4 hematological toxicities were observed. However, one patient developed a grade 2 allergy leading to discontinuation of topotecan. *Conclusion:* Treatment of recurrent ovarian cancer with low-dose continuous infusion of topotecan over 14 days demonstrated response rates comparable to other dosing schedules with minimal toxicity in a preliminary series of 12 patients.

Epithelial ovarian cancer, the second most common malignancy of the female genital tract, has a lifetime risk for women living in western industrial countries of about 1.4% (*i.e.*, one woman in 70 will develop the disease) (1,2). Due to the absence of symptoms in early stages (FIGO I and II), about two-thirds of patients present with advanced disease (FIGO III or IV). Currently, first-line palliative as well as adjuvant chemotherapy for ovarian cancer consists of a

combination of a platinum compound and a taxane (3,4). Despite initial responses to this regimen of 60%-75% (3,5), the majority of the patients will relapse and may be treated with second-line chemotherapy under palliative auspices.

Topotecan (S-9-dimethylaminomethyl-10-hydroxycamptothecin) was the first camptothecin analogue to be approved for clinical use by the US Food and Drug Administration (FDA) (6). Due to its inhibiting activity against topoisomerase I, this drug has a proven anti-neoplastic effect as a second-line agent in recurrent ovarian cancer (7). The usually recommended dosage schedule is a 30-minute infusion of 1.5mg/m<sup>2</sup> daily for 5 days every 21 days (7). The published response rates are between 13% and 29% depending on the platinum-sensitivity of the tumor, with a median time to progression of 23 weeks.

One of the disadvantages associated with the recommended application schedule of topotecan is the high rate of hematological toxicity. In the published trials the incidence rates of grade 3 and 4 neutropenia are between 47% and 92%, of grade 3 and 4 thrombocytopenia between 34% and 67%, and of anemia between 13% and 28% (8-11). Therefore a number of different application schedules have been evaluated recently with the intent of decreasing myelosuppression rates while maintaining equivalent efficacy (12-15). Two Phase II trials have been published utilising continuous infusion of topotecan in patients with recurrent ovarian cancer (13,15). The response rates in these 2 studies varied between 8% and 38%, with a median time to progression between 16 and 26 weeks and a favourable hematological toxicity profile with an incidence of grade 3 and 4 neutropenia between 38% and 33%. To add to the existing literature on new topotecan regimens in recurrent ovarian cancer, we prospectively evaluated a continuous 14-day application schedule of topotecan in 12 patients with recurrent ovarian cancer.

### Patients and Methods

Twelve patients were enrolled in this study. All of them had a histopathological diagnosis of epithelial ovarian cancer and all had been previously treated with one or more different regimens of platinum-containing cytotoxic chemotherapy. Furthermore, all

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Table I. Demographic data.

Characteristics	No. of Patients
Total number of patients	12
Age (years)	
Median: 65	
Range: 45-80	
Primary tumor	
Ovarian	12
Histology	
Papillary serous	12
Number of prior chemotherapy regimens / patient	
Median	2
Range	1-7
Response to prior platinum-based therapy	
Platinum-refractory	4
Platinum-resistant	2
Platinum-sensitive	6

patients were grouped by their prior response to platinum as platinum-refractory (four patients with progressive disease while on initial platinum), platinum-resistant (relapse within 6 months after discontinuing platinum therapy in two patients), or platinum-sensitive (relapse after more than 6 months after the end of initial chemotherapy in six patients). Pre-treatment demographics are listed in Table I. A total of 57 14-day cycles of topotecan were administered, with a median of 5 (range 1-12) cycles per patient. A time period of at least 4 weeks since the date of prior surgery or last chemotherapy regimen was required for inclusion in the study. For the continuous application of chemotherapy we used a semi-permanent venous access device. All patients had a measurable lesion of at least 2 cm in diameter on ultrasound, computed tomography (CT) scan, or magnetic resonance imaging (MRI).

All patients were treated with a continuous intravenous infusion of topotecan (Hycamptin®, SmithKline Beecham Pharmaceuticals) at a dose of 0.4mg/m<sup>2</sup>/d over 14 days using a INFUSOR® (Baxter) ambulatory infusion pump. This pump utilises elastomeric technology to provide a reliable infusion schedule with the advantage of not needing a power source and completely silent operating conditions. Administration was repeated every 28 days and treatment duration depended on tumor response.

Patients were assessed by weekly blood cell counts, serum CA-125 testing every cycle and abdominal-pelvic CT scans every two cycles of treatment. Complete response (CR) was defined as complete resolution of all evidence of disease on imaging studies. Partial response (PR) was defined as a decrease  $\geq 50\%$  of the lesion on imaging studies. Progressive disease (PD) was defined as a  $\geq 50\%$  increase of the lesion on imaging studies, or as the occurrence of any new lesion during therapy. Stable disease (SD) was defined as less than 50% increase or decrease of the lesion on imaging studies. Furthermore, time to progression was defined as the period from the first administration of topotecan until PD or death due to cancer-related death.

Table II. Response by prior platinum-based therapy results.

Platinum	No. of patients	CR / PR	SD	PD
Refractory	4	0	2	2
Resistant	2	1	0	1
Sensitive	6	1	2	3
Total	12			

Table III. Hematological toxicities.

Toxicity	Grade 1	Grade 2	Grades 3 and 4
Leukopenia	2	0	0
Anaemia	1	2	0
Thrombocytopenia	0	0	0

## Results

The response rates to topotecan broken down by the response to the initial platinum-containing chemotherapy are shown in Table II. The overall response rate (CR and PR) was 2/12 patients (17%), which included 1 patient with platinum-resistant disease and 1 patient with platinum-sensitive disease. Four patients had stable disease (33%). The median time to progression was 26 (range 20-100) weeks.

We observed only minor hematological toxicities; none of the patients developed grade 3 or 4 hematological toxicity (Table III). One patient experienced grade 2 anemia and grade 1 leukopenia, another patient developed grade 1 anemia and leukopenia, and one patient experienced anemia grade 2 alone. Overall, 3 of the 12 patients (25%) developed grade 1 and 2 hematological toxicity. The non-hematological toxicities, *e.g.* diarrhoea, nausea and vomiting, were generally mild and therefore not dose-limiting. One patient suffered grade 2 allergic toxicity, which resulted in the discontinuation of topotecan.

## Discussion

The efficacy of topotecan in recurrent ovarian cancer using a regimen of 1.5 mg/m<sup>2</sup>/d for 5 days every 21 days has been demonstrated in randomised controlled studies (7). Pre-clinical experimental evidence suggests that the anti-tumor activity of topoisomerase-I inhibitors is schedule-dependent. Therefore, alternate schedules have been and are being currently evaluated. However, depending on the used

schedule, different outcomes have been reported. Whereas a 24-hour infusion weekly for 4 weeks repeated every 6 weeks was significantly inferior regarding the response rate compared to a standard regimen (16), the prolonged continuous low-dose infusion of topotecan up to 3 weeks showed comparable activity (12,13).

In our prospective series of 12 patients, the overall response rate was 17%. Furthermore 50% of the patients achieved at least stable disease. Median time to progression was 26 weeks. These data indicate the efficacy of topotecan administered as a prolonged continuous low-dose and are comparable to previously published data using the usually recommended dosage schedule (bolus infusion of 1.5mg/m<sup>2</sup>/d given on days 1 to 5 in a 21-day regimen) (7).

The major advantage of the regimen used in our study was the low incidence of hematological and non-hematological toxicities. In contrast to the usually recommended regimen with hematological toxicities grade 3 or 4 up to 50% and even higher (9), we only observed minimal myelosuppression with no grade 3 or 4 toxicity. Therefore, the exposure to lower steady-state levels of topotecan for longer time periods seems to have a favourable safety profile as well as comparable efficacy. Our data suggest that topotecan administered in this continuous schedule is an attractive treatment option and might be more easily combined with other cytotoxic agents with the intention to further increase its anti-tumor activity in future trials.

It is of note that, despite the small inconvenience of being connected to an infusion pump for 14 days, the patients were allowed to continue therapy in a comfortable setting due to the portable handling and the silent operation of the pump.

Finally, we conclude that the treatment of recurrent ovarian cancer with a low-dose continuous infusion of topotecan over 14 days demonstrates response rates comparable to other established regimens with a lower incidence of hematological toxicities. However, due to the preliminary nature of this study, our observations warrant further investigation in a larger trial.

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