



Original Article

Effective Dosing of Topotecan with Carboplatin in Relapsed Ovarian Cancer

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Abstract

Patients and Methods: Topotecan was given as a 30-minute infusion daily for 5 days, with carboplatin given immediately after topotecan on day 5. Treatment was repeated every 21 days. Carboplatin and then topotecan were escalated in sequential cohorts of three to six patients. Four dosage combinations of topotecan days 1 to 5 and carboplatin (day 5) were tested: 0.5 mg/m²/d and carboplatin area under the curve (AUC) of 4, topotecan 0.5 mg/m²/d and carboplatin AUC of 5, topotecan 0.75 mg/m²/d and carboplatin AUC of 5, and topotecan 1.0 mg/m²/d and carboplatin AUC of 5.

Results: Grade 3 and 4 neutropenia was common at doses of 0.75 mg/m²/d and above, but dose-limiting hematologic toxicity occurred in only one patient. The most common reason for dose reduction or delay was failure of myelosuppression to resolve by day 21. Nonhematologic toxicity was generally mild. The maximum-tolerated dose as defined in the protocol was not reached, but topotecan dose escalation was stopped at 1.0 mg/m²/d, because delayed neutrophil recovery precluded re-treatment on a 21-day schedule.

Conclusion: Hematologic toxicity was common but rarely serious, and the combination of topotecan with carboplatin on this schedule was safe and well tolerated. Giving carboplatin to patients after topotecan on day 5, rather than on day 1, allowed dose escalation beyond the levels reported in other studies. The recommended doses for previously treated patients are topotecan 0.75 mg/m²/d, days 1 to 5, with carboplatin at an area under the curve (AUC) of 5 following topotecan on day 5. The combination of topotecan 1 mg/m²/d, days 1 to 5, followed on day 5 by carboplatin at an AUC of 5, merits further examination in untreated patients.

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Introduction

Epithelial ovarian cancer is the most frequently fatal gynecologic malignancy. Treatment depends on surgical resection and the use of cytotoxic drugs, and although there have been significant advances in recent years, particularly with the use

of chemotherapy, to improve the quality and duration of survival, there has been little impact on the death rate from this disease. The majority of women with advanced disease initially treated with surgery and chemotherapy experience relapse. There is therefore great interest in

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developing effective second-line treatments for ovarian cancer.

Topotecan is a water-soluble semi-synthetic analog of the alkaloid camptothecin. As a specific inhibitor of topoisomerase I, topotecan causes lethal DNA damage during replication. Topotecan is active in recurrent ovarian cancer, both in platinum-sensitive and platinum-refractory patients.¹⁻⁸ Used as a single agent, doses of 1.5 mg/m² given intravenously on 5 consecutive days gave results at least equivalent to those of paclitaxel at 175 mg/m² over 3 hours, both in terms of a higher response rate (20.5% v 14%) and longer time to progression ($P = .72$).⁵ The major dose-limiting toxicity of topotecan is myelosuppression, which may be severe in some patients, but neutropenic infections are uncommon. Given the single-agent activity of topotecan in cancers such as ovarian, head and neck, and small-cell lung cancer, it has been logical to examine the combination of topotecan with platinum drugs that have a similar spectrum of disease sensitivity and differing principle toxicities.

Patients and methods

Patients

Patients with advanced ovarian cancer who had experienced relapse after platinum-based therapy were eligible for the study. Patients were required to have a creatinine clearance (measured by isotope scan) of at least 50 mL/min, adequate bone marrow reserve, and good liver function. Written informed consent was obtained from each patient. Standard exclusion criteria applied, including extensive prior radiotherapy and concurrent treatment with anticancer therapy or any recent treatment with investigational drugs.

Methods

The primary objective of the study was to establish the maximum-tolerated dose of the combination of topotecan with carboplatin. Secondary objectives were to evaluate the response rate, time to progression, and toxicities of the combination. Simpson's maximum-tolerated doses were taken as the starting doses for topotecan and carboplatin.¹¹ Topotecan was administered as a 30-

minute IV infusion on days 1 to 5, with carboplatin given as a 30-minute infusion immediately after topotecan on day 5. Treatment was repeated three-weekly for up to six cycles. Patients were re-treated on day 21 if nonhematologic toxicities had resolved and neutrophil count was greater than 1,000/mm³, with platelets greater than 100,000/mm³ and hemoglobin greater than 9.0 g/dL. The first cohort of three to six patients was to receive topotecan at a dose of 0.5 mg/m² for 5 days, with carboplatin given at an AUC of 4 (estimated by isotope clearance and the Calvert formula) on day 5.¹² If tolerated, the second cohort would receive the same dose of topotecan with carboplatin at an AUC of 5, and subsequent cohorts were planned with a fixed dose of carboplatin at an AUC of 5 and dose increments of topotecan of 0.25 mg/m²/d. Patients received standard antiemetic prophylaxis of domperidone on days 1 to 4 and dexamethasone with granisetron before treatment on day 5, with dexamethasone and domperidone for a further 3 days. Full blood counts were performed weekly throughout the study, and patients were assessed using clinical examination and CA-125 at each cycle. Tumor assessment by computed tomography scan was performed after cycles 3 and 6 in those patients with measurable disease.

Toxicities were graded according to the National Cancer Institute common toxicity criteria (1994). Dose-limiting toxicity was defined as grade 4 neutropenia or thrombocytopenia lasting for 7 days or complicated by infection or bleeding. Escalation to the next dose level was undertaken if the incidence of dose-limiting toxicity was less than 33% in the previous cohort of three to six patients. Topotecan doses were reduced by 0.25 mg/m²/d in any patient who had experienced grade 4 thrombocytopenia, prolonged or complicated grade 4 neutropenia, or grade 3 neutropenia lasting until day 21 of the previous treatment course.

Results

Patient Characteristics and Dose Escalation

Ten patients entered the study. All had received prior platinum treatment, and 5 had received paclitaxel. The median number of previous

regimens was two, and the time from the last treatment to starting topotecan was a median of 6.5 months (range, 1 to 43 months). Three patients were thought to have platinum-sensitive disease, but 7 had experienced relapse during or within 6 months of platinum.

Two patients were treated at the initial dose level of topotecan 0.5 mg/m²/d on days 1 to 5 with carboplatin at an AUC of 4 on day 5. The carboplatin dose was escalated to an AUC of 5 and the topotecan dose remained the same in the second cohort of two patients. Three patients received treatment at the third dose level of topotecan 0.75 mg/m²/d on days 1 to 5, with carboplatin at an AUC of 5, and the final cohort of three patients was treated with topotecan 1.0 mg/m²/d on days 1 to 5, and carboplatin at an AUC of 5 on day 5.

Ten patients received a total of 41 cycles (median, 4.5; range, one to six cycles per patient), and all cycles were assessable for toxicity. Four patients completed six cycles of therapy, two of them at the highest dose level. Six stopped prematurely because of disease progression (two patients), hematologic toxicity (two at the third dose level), intercurrent illnesses (one), or surgery (one).

These delays and dose modifications resulted in treatment being delivered at a dose-intensity that was considerably less than planned at all dose levels (Table 1). Although the maximum-tolerated dose as defined in the protocol had not been reached, dose escalation was stopped after cohort 4, when it was apparent that the majority of cycles could not be given at the planned doses on a 21-day schedule.

Table 1. Planned and Actual Dose-Intensity Per Dose Level

Dose Level	No. of Cycles at Planned Dose-Intensity/Total No.	Planned/Actual Topo Dose (mg/m ² /d)	Planned/Actual Carbo Dose (AUC)
Carbo AUC4	12 /19	0.50 /0.41	4.0 /3.3
Topo 0.50			
Carbo AUC5	13 /19	0.50 /0.42	5.0 /4.7
Topo 0.50			
Carbo AUC5	12 /18	0.75 /0.56	5.0 /4.0
Topo 0.75			
Carbo AUC5	9 /27	1.00 /0.72	5.0 /4.3
Topo 1.00			

NOTE. Actual dose-intensity is administered dose-corrected for weeks on therapy.

Abbreviations: Carbo AUC, carboplatin dose described by target AUC; Topo, topotecan dose in mg/m² days 1-5.

Hematologic Toxicity

Hematologic toxicity was common and increased with topotecan dose (Table 2). Grade 4 neutropenia did not occur at topotecan doses less than 0.75 mg/m²/d but was experienced by three patients treated at the highest dose level. The proportion of cycles with grade 3 or 4 neutropenia was three (33%) of 9, eight (53%) of 15, and three (75%) of four, when topotecan doses of 0.5, 0.75, and 1.0 mg/m²/d, respectively, were administered with carboplatin at an AUC of 5 on day 5. Grade 3 or 4 thrombocytopenia was less common, occurring

in one (10%) of 10 cycles at dose level 2 and three (20%) of 15 at dose level 3. There was no serious thrombocytopenia at the highest dose administered. Anemia was common, but the incidence of grade 3 anemia was only 7% (three of 41 cycles). The median neutrophil and platelet count nadirs ($\times 10^9/L$) for cycles administered at topotecan doses of 0.5, 0.75, and 1.0 mg/m²/d with carboplatin at an AUC of 5 were 1.1 and 104, 0.9 and 96, and 0.4 and 80, respectively.

Although myelosuppression was common, dose-limiting hematologic toxicity was not. Two

episodes of grade 4 thrombocytopenia were documented at topotecan doses of 0.5 mg/m²/d (one of 21 cycles) and 0.75 mg/m²/d (three of 30 cycles) both with carboplatin at an AUC of 5. One patient required platelet support; this patient also experienced febrile neutropenia during the

same cycle requiring GCSF, and withdrew from treatment. There were no toxic deaths and no other episodes of prolonged or complicated neutropenia. None of the other patients required GCSF or platelets.

Table 2. Hematologic Toxicity: Worst CTC Grade Per Patient

Dose Level	Toxicity	CTC Grade				
		0	1	2	3	4
Carbo AUC4	Neutropenia	—	1	1	—	—
Topo 0.50	Thrombopenia	—	1	1	—	—
	Anemia	—	—	2	—	—
Carbo AUC5	Neutropenia	1	—	—	2	—
Topo 0.50	Thrombopenia	—	2	1	—	—
	Anemia	—	—	2	1	—
Carbo AUC5	Neutropenia	—	—	1	2	1
Topo 0.75	Thrombopenia	—	1	1	1	2
	Anemia	—	1	1	2	—
Carbo AUC5	Neutropenia	—	—	—	1	2
Topo 1.00	Thrombopenia	—	—	2	1	—
	Anemia	—	—	3	1	—

Abbreviations: Carbo AUC, carboplatin dose described by target AUC; Topo, topotecan dose in mg/m² days 1-5; CTC grade, NCI common toxicity criteria grades, 1994.

The duration of myelosuppression seemed to be related to topotecan dose. Recovery by day 21 was the rule at the first dose level, but delays beyond day 21 were necessary in one of two patients and two of three patients entering the second and third dose levels, respectively, often after three or four cycles. At the highest dose, two of three patients had grade 3 neutropenia lasting beyond day 21 of the first cycle, necessitating a dose reduction.

The dose of topotecan was reduced in four patients. Three of these reductions were for patients with grade 3 neutropenia who did not recover to grade 2 by day 21, and one other was because of grade 4 thrombocytopenia. A total of 13 cycles were given at a reduced dose of topotecan: zero of 10 cycles at the first dose level, two of 10 at the second, three of 9 at the third, and 9 of 14 cycles administered to patients who entered at the highest dose level.

Nonhematologic Toxicity

Toxicity was generally mild, and there were no dose-limiting nonhematologic toxicities. Alopecia occurred in 5 of 10 patients, and was as high as grade 2 in only one of these. Mild to moderate fatigue was reported by most patients and was graded as severe in one. Grade 3 emesis occurred in two patients despite prophylactic antiemetics. No serious adverse events occurred that were thought to be related to the combination.

Efficacy

Partial responses were documented in three of 10 patients (30%; 95% confidence interval, 6% to 44%). Two patients had stable disease for at least 8 weeks, and the disease was progressive in two others. Three patients were not assessable for objective response; one had no measurable disease on scan, one withdrew after one cycle, and one patient was taken off the study without repeat abdominal scans, having suffered a cerebrovascular accident. Two of the responses

occurred at the highest topotecan dose level, at which point two patients were assessable for response. Marker reductions of more than 50% were seen in 5 of 9 (55%; 95% confidence interval, 33% to 79%) patients whose CA-125 levels were significantly elevated at study entry, including four who had a complete marker response. Two of the patients who were not assessable for objective response had a marker response.

No patient had prior topotecan, but all had received at least one platinum-based regimen before. Two of 5 patients who had received prior paclitaxel responded, including one who had experienced disease progression with paclitaxel treatment. There were no responses among patients who had had three prior regimens, but two of 20 patients who had received two prior regimens responded. There was no clear relationship between the probability of response and time from previous therapy.

Four patients were alive at the time of the analysis, with a median follow-up of 63 weeks (range, 24 to 96 weeks). The disease progressed in 9 patients, and the median time to progression was 24 weeks (range, 7 to 46 weeks); two others had not progressed at 24 and 25 weeks of follow-up. Four patients died of ovarian cancer, and one died of other illnesses. Median survival was 37 weeks (range, 8 to 82+ weeks).

Discussion

In this study we examined the combination of 5 days of IV topotecan with carboplatin administered on day 5 given on a 21-day cycle to try to achieve higher doses of both drugs than in previously reported schedules.¹¹ Our patient population included those with platinum-sensitive and platinum-resistant tumors. The highest dose level that we achieved was 1 mg/m²/d of topotecan, days 1 to 5, followed by carboplatin at an AUC of 5 given on day 5. These patients were not treated with prophylactic GCSF. Do the actual doses matter? By investigating cell lines under laboratory conditions, it is possible to demonstrate positive synergy, additive effects, and less-than-

additive effects with different sequences of exposure to these two drugs using different cell lines.⁹ Although some would argue that doses approximate to the single-agent maximum-tolerated doses would be preferable, the converse argument could be made that if there is synergy with regard to toxicity (myelosuppression), there may similarly be a positive antitumor synergy in schedules where lower doses have been achieved. Rowinsky et al⁹ suggested that the more marked myelosuppression occurring when cisplatin precedes topotecan could be due to lower renal clearance of the topoisomerase inhibitor, consequent on renal toxicity from cisplatin. Interestingly, in the de Jonge study¹⁰ with oral topotecan, no pharmacokinetic sequence-dependent effects were demonstrated.

Although no direct comparison can be made with the trial reported by Simpson et al,¹¹ our results may support the existence of a sequence effect when carboplatin is given with topotecan. We were able to escalate both the carboplatin and the topotecan dose beyond Simpson's maximum-tolerated doses of 0.5 mg/m²/d and AUC 4, when we gave the carboplatin on day 5 rather than day 1. It seems unlikely that this effect is accounted for by changes in the systemic exposure to topotecan. In a study in which carboplatin was given on day 1 or day 5 with topotecan and etoposide, Faucette et al¹³ reported that the AUC of topotecan was lower in the more myelotoxic schedule of carboplatin given on day 1. Whatever the mechanism of any possible interaction, the schedule we have used in this study is clearly active, with sustained responses in platinum- and paclitaxel-resistant as well as platinum-sensitive tumors. The CA-125 data suggest that half of the patients had some benefit from treatment.

Severe hematologic toxicity was less than has been reported for many other combinations of topotecan with platinum drugs. The incidence of dose-limiting myelosuppression was acceptable, occurring in 5% of cycles, and only one patient in 10 experienced neutropenic infection. Nadir counts were modest, with no recorded neutrophil

count below $200/\text{mm}^3$ and only one platelet count below $15,000/\text{mm}^3$. We had not reached the maximum-tolerated dose as defined in the protocol when dose escalation was discontinued, because it was apparent that the majority of patients could not tolerate the highest dose level when it was given on a 21-day cycle. At a topotecan dose of $1 \text{ mg}/\text{m}^2/\text{d}$, neutropenia failed to resolve to grade 2 by day 21 in two of three patients. Perhaps this slow recovery was not surprising; because carboplatin was given on day 5 of the schedule, we were attempting to re-treat with topotecan on day 16 after the previous carboplatin dose in a population of patients who had received two or three prior regimes. The protocol did not allow us to explore the feasibility of further topotecan escalation given on a 28-day cycle, and we did not wish to use prophylactic GCSF to maintain the dosing interval, but both of these approaches may be worth further examination. Although we cannot extrapolate our results to an untreated population, it may be that patients without prior platinum exposure would tolerate our highest dose level or even a further dose escalation.

Despite the inconvenience of a 5-day dosing schedule, compliance was good, and the regimen was acceptable to patients. Alopecia was mild in the majority, and there was a low incidence of significant nonhematologic toxicity. The recommended doses for previously treated patients are topotecan $0.75 \text{ mg}/\text{m}^2/\text{d}$, days 1 to 5, with carboplatin at an AUC of 5 (estimated by isotope clearance and the Calvert formula) after topotecan on day 5. We believe that, in view of the excellent patient tolerability of the combination of topotecan and carboplatin given in the schedule reported in this study, doses of $1 \text{ mg}/\text{m}^2/\text{d}$ of topotecan and carboplatin at an AUC of 5 on day 5 should be explored as first-line therapy for patients who have not received any previous myelotoxic treatment.

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