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Tolerance and Activity of Oxaliplatin with Protracted Topotecan Infusion In Patients With Previously Treated Ovarian Cancer. A phase I study

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Abstract

Background—Topotecan 14-day infusion combined with cisplatin was highly active in ovarian cancer, but too myelosuppressive. We therefore sought to evaluate the feasibility of substituting oxaliplatin for cisplatin to improve safety.

Methods—Ovarian and primary peritoneal cancer patients, pre-treated with at least one prior platinum-containing regimen, performance status (PS) 0–1, without prior pelvic radiation were eligible. Topotecan was continuously infused days 1–15; oxaliplatin was given days 1 and 15; cycles repeated every 28 days. Five dose levels were explored: topotecan (mg/m²/day)/oxaliplatin (mg/m²) doses 1) 0.2/65; 2) 0.2/75; 3) 0.2/85; 4) 0.3, 85; 5) 0.4/85.

Results—Twenty-three patients (20 ovarian, 1 tubal, and 2 peritoneal) were entered: median age 56 yrs (range, 37–77); PS: 0 = 12 and 1 = 11; histology: papillary serous 7, serous 4, adenocarcinoma 8, poorly differentiated 2. Median of 4 cycles (1–9) were delivered. Grade 3 neutropenia occurred in 3 of 7 patients at level 5 (with fever at levels 4 and 5), without grade 4 neutropenia or thrombocytopenia. Other toxicities were mild and reversible (mainly gastrointestinal), except one grade 3 neuropathy and one oxaliplatin-related grade 3 hypersensitivity reaction. Six objective responses (five of them complete) were documented among 22 patients spanning several dose levels.

Conclusion—Topotecan continuous infusion, combined with oxaliplatin was associated with no grade 4 hematologic toxicity, and evidence of activity. The recommended phase II dose is topotecan 0.4 mg/m²/day continuous infusion d1–15 with oxaliplatin 85 mg/m² on days 1, 15. A phase II evaluation as 2nd-line treatment for both platinum-sensitive and resistant ovarian cancer recurrences is ongoing.

BACKGROUND

Ovarian cancer most often presents at advanced stages and, in spite of very active platinum-based induction regimens, the majority of women relapse within 3 years of diagnosis. At recurrence, if occurring beyond 6 months, carboplatin or cisplatin retreatment has been considered standard until recent randomized studies showing superiority of carboplatin in

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combination with gemcitabine or paclitaxel over single-agent carboplatin. However, early (<6 months from cessation of initial chemotherapy) relapses are usually not responsive to reintroduction of these platinum while other 2nd line drugs including topotecan have shown modest efficacy under these circumstances. Based on preclinical findings (1) we sought to explore clinically the feasibility of a combination of topotecan with a platinum with potentially less myelosuppression, such as oxaliplatin..

Topotecan (Hycamtin®, topotecan hydrochloride) became established as a treatment of patients with metastatic carcinoma of the ovary after failure of initial or subsequent chemotherapy, based on a Phase III clinical trial of topotecan as a 5 day bolus versus paclitaxel (2). Another Phase III trial of topotecan compared to pegylated liposomal doxorubicin also confirmed activity against both platinum-sensitive and platinum resistant patients (3). In addition, an open-labeled, non-comparative trial of 111 platinum resistant patients reported an overall response rate (ORR) of 16.3% (3). In the cisplatin-refractory, cisplatin-resistant, and cisplatin-sensitive strata, the response rates were 5.9%, 17.8%, and 26.7% respectively. The median duration of documented response was 21.7 weeks.

Continuous infusion topotecan may be advantageous in terms of prolonging inhibition of topoisomerase -1, intranuclear target of this class of agents. Our studies have shown increased enzyme depletion using this schedule, and the ability to deliver more drug with less dose-limiting myelosuppression compared with the five-day bolus schedule. We initially examined continuous intravenous infusion (CIVI) topotecan in heavily pretreated ovarian cancer patients, suggesting that the frequency and duration of administration may determine in part the toxicity and efficacy of the drug. An ORR of 38% (CR 24%) with a favorable toxicity profile was achieved with a 21 day infusion compared to standard bolus regimens (4, 5). This led to studies exploring these protracted infusion schedule in combination with cisplatin as first line therapy by the NYGOG and ECOG (6), and in combination with pegylated liposomal doxorubicin in pretreated patients (7)). In both these studies the dose-limiting toxicities were mostly related to myelosuppression of all three blood elements. Moreover, prior studies had shown these toxicities to be schedule dependent – more severe if the other DNA-damaging drug precedes topotecan (8).

Activity of oxaliplatin, a DACH (diaminocyclohexane) substituted platinum, in ovarian cancer is quite promising and is supported by a number of preclinical and clinical observations: 1) Although the mechanism of action for oxaliplatin is similar to cisplatin, DNA-oxaliplatin adducts have been shown to be bulkier and more hydrophobic, potentially leading to more effective inhibition of DNA synthesis and greater cytotoxicity (9), 2) DNA mismatch repair complexes cannot readily excise DNA-oxaliplatin adducts (10), 3) oxaliplatin was found to be active against various cisplatin resistant cell lines, including human ovarian cancer (11), and 4) in limited clinical data, oxaliplatin alone or when combined with cyclophosphamide was as active as cisplatin in untreated and previously treated patients (12–16). We therefore postulated that the better hematologic tolerance of oxaliplatin would allow a combination with nearly full doses of topotecan by protracted infusion, and that it might prove synergistic.

Our current study was started to identify the maximally tolerated dose (MTD) and the dose-limiting toxicities (DLTs) of an oxaliplatin with CIVI topotecan combination in patients with ovarian cancer and other cancers of mullerian origin. The protracted infusion schedule of topotecan was chosen since it provides greater margin of safety when used with potentially myelosuppressive agents and we had previously shown infusional topotecan could be successfully combined with the more toxic cisplatin as first-line therapy (6). Moreover, it allowed for comparison with our extensive, prior experience with infusional topotecan regimens.

PATIENTS AND METHODS

Patients

Patients with measurable or evaluable, histologically or cytologically proven epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer were eligible. All had prior platinum-based treatment, without limit on the number of other regimens, as long as patients met the following requirements: an absolute neutrophil count $> 1.5 \times 10^9/L$, and a platelet count $> 100 \times 10^9/L$; total bilirubin $\leq 1.5 \times$ the institutional upper limit of normal (IULN), and (AST (SGOT) $\leq 2.5 \times$ IULN unless liver metastases were present and documented at baseline by radiographic image. Karnofsky performance status more than 70, with life expectancy of at least 4 months, was required. All patients gave written informed consent to participate in this study. The recommended phase II dose (RPTD) was defined at an expanded dose level in which only 1 or no episodes of DLT occurred in a cohort of 6 patients (or no DLTs in a cohort of 5 patients). Expansion was to take place when the maximal tolerated dose (MTD) became manifest at the highest level reached and at least 2 patients experienced DLT. DLT was defined as grade 3 non-hematologic toxicity (except for nausea/vomiting or diarrhea reversible with medication) or any grade 4 toxicity based on the first 2 cycles. Neutropenic fever or dose delays of > 2 weeks due to toxicity during the first 2 cycles were also considered DLTs.

Treatment

On days 1 and 15 of each 28-day treatment cycle, the patients received oxaliplatin as a 2 hour IV infusion. Topotecan was reconstituted in 50 ml of 5% dextrose to deliver the appropriate daily dose in 7 ml, to be infused over 1 week. Following oxaliplatin on day 1, topotecan was administered as a 14-day continuous infusion (7 ml/day) via a central venous catheter (e.g., PICC line or mediport) and ambulatory chemotherapy pump (e.g., CADD pump or disposable Baxter infusor) with weekly reservoir change as previously described (5). Dosing was interrupted for low blood counts or other significant toxicity. Topotecan infusion was discontinued on day 15 and followed by the second two-hour administration of oxaliplatin.

Pharmacokinetics

Plasma specimens were processed according to our modifications of a previously described method using methanol dilution (18). To allow for better sensitivity, given the low doses administered, we used a solid-phase extraction (SPE) technique that concentrated rather than diluted the specimens in the protein-removal step. Specimens were processed using C-18 SPE columns as previously described, with acidification of the extracted plasma to allow for conversion of all of the topotecan to the lactone form, followed by high-performance liquid chromatography (HPLC) reverse-phase chromatographic analysis as detailed below. Three to 5 mL of plasma from clinical samples were centrifuged at $1000 \times g$ for 10 minutes; buffers and an internal standard (SKF 105107; SmithKline Beecham, King of Prussia, PA) were then added. The reference internal standard was camptothecin, kindly provided by Dr. Monroe Wall (Research Triangle Park, NC). PK methods were as described previously (4). Standard topotecan curves were run daily with samples. All samples were run in duplicate and modeled using WinNonlin version 4.5 (Scientific Consulting Inc, Apex, NC).

Statistical Methods

The primary endpoint of this study was to identify the maximum tolerated dose (MTD), dose-limiting toxicities (DLT) and recommended phase II dose (RPTD) of oxaliplatin and topotecan when administered in combination.

Efficacy endpoints included objective disease response by RECIST criteria, duration of response, and time to progression.

RESULTS

Twenty-three patients were entered into this study and were evaluated for toxicity, response and topotecan blood level (table 1). The median age of all patients was 56 years (range, 37 to 77 years). All patients had an ECOG performance status of 0–1. The type of histology is listed as follows: papillary serous 9, serous 4, adenocarcinoma 8, poorly differentiated 2. All patients were previously treated with platinum-based chemotherapy prior to study enrollment. Overall, 4 patients received one prior regimen, 7 received two regimens, 5 received three regimens, 4 received four regimens, 1 received five regimens and 2 patients received six prior regimens. A median of 4 cycles of chemotherapy (range 1–9 cycles) was delivered in the study. Two patients with small bowel obstruction and receiving total parenteral nature were otherwise qualified for the protocol based on their performance status and organ function and were included.

As expected, the predominant toxicities were hematologic, as shown in table 2: During the first 2 cycles, grade 3 neutropenia was seen in 7 (two each at dose level 3 and 4; three at dose level 5 including one with fever on day 11 of the second course). Grade 3 thrombocytopenia was also noted in 4 (two each at dose level 4 and 5), necessitating 9 dose delays (two at dose level 3, four at dose level 4, three at dose level 5) followed by dose reduction in three patients (one each at dose levels 3, 4 and 5). No grade 4 neutropenia or thrombocytopenia was observed. Overall, two DLT's were observed, one each at dose levels 4 (dose delay >2 weeks) and 5 (neutropenic fever noted above). Subsequent dose delays (after cycle 2) were seen at the higher dose levels (2 at dose level 3; 2 at dose level 4, 3 at dose level 5) due to prolonged bone marrow recovery (2 grade 2 occurrences at level 3: 1 grade 1 and grade 3 at level 4; 1 grade 2, 3, and 4 at level 5) though none led to treatment discontinuation. Anemia related to therapy was treatable with growth factors with only 2 occurrences higher than grade 2 (both at level 5). No blood transfusions were required during the first two cycles.

Non-hematologic toxicity included one patient with grade 3 neuropathy after 6 cycles at dose level 3. Mild gastrointestinal complaints (nausea, vomiting, diarrhea) were common among all dose levels but were transient or reversible with antiemetics and loperamide in more severe cases (five grade 3 occurrences among levels 2 thru 5). A case of oxaliplatin induced hypersensitivity was seen halfway through the 5th dose (at level 5). She was successfully rechallenged following pre-medication with steroids and antihistamines and successfully completed a 6th cycle.

Responses to therapy are shown in table 3: Five patients with complete responses were observed (1 at dose level 3, and 2 each at levels 4 and 5); two remain disease free with long-term follow-up. All responders were considered platinum resistant except for the 2 at dose level 5; Other responses include 1 partial response, 8 stable disease, 7 progressions, and 2 unevaluable for response. Decrease of CA125 ranged from 0–95% with complete and partial responders having the largest declines. Median PFS among responders was 45.5 weeks (range 18–144 weeks). Topotecan steady-state levels were 1.04 ± 0.5 ng/ml (mean $\pm$ SD) at 0.2 mg/m^2 , 1.29 ± 0.88 ng/ml at mg/m^2 and 2.69 ± 1.66 ng/ml at 0.4 mg/m^2 .

DISCUSSION

Topotecan is a difficult drug to use in combination because of substantial need for dose-attenuation when used with other drugs active in advanced ovarian cancer. Rowinsky et al

(8) reported in detail on the toxicity profile for the combination of cisplatin with topotecan in the daily $\times$ 5 schedule, in a phase I study. Doses of topotecan and cisplatin greater than 0.75 mg/m² (d1-5) and 50 mg/m² (d1), respectively led to dose-limiting neutropenia and thrombocytopenia, despite hematologic support with growth factors. Though toxicity was decreased when cisplatin was given on day 5, better efficacy was suggested with the former schedule. We subsequently showed that topotecan 0.3–0.4 mg/m² CIVI for 14 days with cisplatin 75mg/m² on day 1 was very active with an overall response rate of 93% in 60 previously untreated advanced ovarian cancer patients but associated with a high degree of myelosuppression (i.e., 90% grade 3 and 4 changes) (6).

Clinical studies performed in Europe suggest that the DACH platinum, oxaliplatin, is tolerable and has efficacy in patients with advanced ovarian cancer comparable to other platinum. Overall response rates of 25% (11) to 29% (12) were recorded at doses ranging from 60 to 130 mg/m² every three weeks. In platinum-resistant patients, ORR was 17% while platinum-sensitive patients, according to Markman's criteria (13), had an ORR 46%. A phase II study attempting to increase total platinum delivery, oxaliplatin 90 to 150 mg/m² combined with cisplatin 60–110 mg/m², yielded an ORR of 58% and 23% for platinum sensitive or resistant disease, respectively (15). Comparisons of oxaliplatin with other active ovarian cancer agents have also been reported: A phase II/III study of 182 patients (16) compared the association of cyclophosphamide (1000 mg/m²) with either oxaliplatin (130 mg/m²) or cisplatin (100 mg/m²) every three weeks for six courses as first-line chemotherapy for advanced ovarian cancer patients. No significant difference in terms of ORR (51.5 vs. 65%), progression-free survival, nor overall survival were noted in this underpowered study. Noteworthy were the significantly lower incidence of myelosuppression in the oxaliplatin arm. Subsequent results of a randomized phase II study from the European Organization for Research on Treatment for Cancer (EORTC) showed comparable efficacy and toxicity with oxaliplatin (130mg/m²) vs paclitaxel (175 mg/m²) among 86 cis- or carboplatin pretreated advanced ovarian cancer patients (24). However, activity was mostly confined to platinum-sensitive patients.

Preclinical data have suggested that the combination of oxaliplatin and topotecan would be synergistic (17), confirming the extensive pre-clinical data on synergistic activity of platinum compounds with topoisomerase-I inhibitors (1). However, a phase I study of oxaliplatin 85 mg/m² D1 followed by topotecan D1-5 bolus every 3 weeks reported excessive DLTs (20) even at the lowest dose level (topotecan 0.5 mg/m²).

A striking finding in our studies emerged when we compared the myelosuppressive effects of oxaliplatin versus cisplatin, when these drugs were combined with continuous infusion topotecan. In these sequential studies, our oxaliplatin treated patients had been exposed to prior drug regimens and yet had milder effects on platelets and neutrophils. In this study, we observed a favorable toxicity profile with oxaliplatin in combination with topotecan CIV. Specifically, neutropenia and thrombocytopenia were the most significant toxicities at the highest dose levels, though not reaching grade 4. Despite heavy pretreatment, myelotoxicity was considerably milder than observed in the aforementioned studies of bolus topotecan combined with either cisplatin or oxaliplatin. Oxaliplatin induced neuropathy was generally mild, allowing for extended use in a population heavily pretreated with platinum and taxanes. Nausea, vomiting and diarrhea were relatively more common, though manageable with antiemetics and loperamide as needed. Oxaliplatin induced hypersensitivity reaction was rare in our study (1 case) and similar to what has been described (21).

Having demonstrated the feasibility of an oxaliplatin with CIV topotecan combination, we must consider its possible future role in the treatment of ovarian cancer. In the recurrent setting, topotecan is an attractive partner to a platinum in the presence of residual

neuropathy from taxane-platinum combinations. However, the myelosuppressive effects of carboplatin make it difficult to combine with topotecan without marked attenuation in dose. In fact, when such combinations formed part of front-line phase III studies (24,25), not only was it necessary to drastically reduce the topotecan dose, but carboplatin had to be given last (i.e., the reverse of the optimal sequence).

The topotecan schedule to be used in a combination with oxaliplatin requires further comment. Our positive experience with continuous infusion topotecan alone (26) or in combination (27), is shown to be suitable for use in combination with oxaliplatin. While we consider this topotecan schedule to be optimal because it allows nearly full doses of either agent in the doublet, oxaliplatin and topotecan in other schedules have also been published (28). Weekly topotecan has gained advocates for retaining activity with lower toxicity; and recently it has been combined with oxaliplatin in a small phase I trial showing promising activity (29).

In conclusion, the combination of topotecan 14 day CIV with oxaliplatin in patients with previously-treated ovarian cancer has shown a favorable toxicity profile and can be given in nearly full doses of either agent. The activity noted encourages further development of this doublet in platinum-sensitive recurrences. However, it also holds some interest as a potential way to overcoming platinum resistance and exploiting platinum-topotecan synergistic interactions. This combination may be an effective option for patients pretreated and perhaps resistant to other conventional platinum drugs. A phase II study of the combination is currently being conducted by the NYGOG phase II consortium.

Confirmation of safety and efficacy at this recommended phase II dose is being pursued in a phase II study, and, if encouraging, should be pursued in a superiority design in phase III trials over other approaches currently favored after the initial carboplatin/taxane combinations.

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Table 1

Patient characteristics

Number entered	23
Age (y)	56 (range 37–77)
Ethnicity	
White	19
Hispanic	2
Asian	2
Performance Status	
0	12
1	11
Primary site	
Epithelial ovarian	20
Tubal	1
Primary peritoneal	2
Prior chemotherapy regimens	Median 3 (range 1–6) *

* All cis- or carboplatin pretreated

Table 2

Number of patients with hematologic toxicity (First 2 cycles)

Dose Level	# Pts	Topotecan (mg/m ² /day)	Oxaliplatin (mg/m ²)	Grade 3 ANC	Grade 4 ANC	Grade 3 PLT	Grade 4 PLT	DLT*
I	3	0.2	65	0	0	0	0	0
II	3	0.2	75	0	0	0	0	0
III	4	0.3	75	2	0	0	0	0
IV	6	0.3	85	2	0	2	0	1
V	7	0.4	85	3	0	2	0	1

* Dose limiting toxicity at level IV (dose delay>2 weeks) and V (febrile neutropenia)

Table 3

Treatment Results

Dose level	Best Response	PFS(wks)	# cycles	CA125 (% of baseline)
1	Stable disease	30	6	31% decrease
	Stable disease	24	6	47% decrease
	Progressive disease	--	3	16% decrease
2	Stable disease	23	6	23% increase
	Stable disease	22	5	56% increase
	N/E	N/E	2	N/E
3	Complete response	+144	6	N/E
	Progressive disease	--	2	10% increase
	N/E	N/E	2	83% increase
	Stable disease	+119	6	57% decrease
4	Complete response	+111	4	90% decrease
	Progressive disease	--	2	N/E
	Complete response	+94	6	90% decrease
	Stable disease	+90	9	61% decrease
	Progressive disease	--	2	34% decrease
	Stable disease	21	4	42% decrease
5	Progressive disease	--	2	N/E
	Progressive disease	--	2	12% decrease
	Complete response	+63	6	N/E
	Stable disease	+61	4	89% decrease
	Complete response	+30	6	N/E
	Progressive disease	--	2	93% decrease
	Partial response	18	4	95% decrease

(N/E) not evaluable