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A phase I study of paclitaxel, topotecan, cisplatin and Filgrastim in patients with newly diagnosed advanced ovarian epithelial malignancies: A Gynecologic Oncology group study

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Abstract

Objectives—To determine a recommended dose level (RDL) of paclitaxel, cisplatin and topotecan in women with previously untreated epithelial ovarian or peritoneal cancer as a possible experimental arm in a future Gynecologic Oncology Group phase III study.

Methods—Patients with newly diagnosed stage III or IV disease were treated with paclitaxel 175 mg/m²/3h, followed two hours later by cisplatin 50 mg/m² on day 1. Topotecan was administered on consecutive days as a 30 minute infusion, beginning after cisplatin on day 1, receiving either 5 days beginning at 0.3 mg/m² (cohort 1), or 3 days beginning at 0.5 mg/m² (cohort 2). Treatment was given every 21 days for a maximum of 8 cycles.

Results—Forty-five evaluable patients were enrolled in the two cohorts. Thrombocytopenia and prolonged neutropenia were the major dose-limiting toxicities. Dose limiting neutropenia was seen at the first dose level, thus all subsequent dose escalations included Filgrastim. The RDL of cohort 1 was paclitaxel 175 mg/m²/3h, cisplatin 50 mg/m² and topotecan 0.5 mg/m² daily × 5 with Filgrastim. The RDL of cohort 2 was paclitaxel 175 mg/m²/3h, cisplatin 50 mg/m² and topotecan 0.75 mg/m² daily × 3 with Filgrastim.

Conclusion—In women with previously untreated epithelial ovarian or peritoneal cancer the combination of paclitaxel, cisplatin and topotecan is feasible. However, this treatment requires the use of Filgrastim and attenuated dosing of topotecan in both a 5-day and 3-day topotecan infusion schedule.

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Introduction

Advanced ovarian cancer is characterized by high rates of response to initial chemotherapy. The combination of paclitaxel and a platinum agent is considered the standard of care in the treatment of newly diagnosed patients.¹⁻³ However, most patients recur and eventually develop treatment refractory disease. Chemotherapeutic agents with activity in platinum-resistant disease hold promise not only for treating patients in relapse but also for incorporation into initial therapy.

Topotecan, a semi-synthetic water-soluble analog of camptothecin, inhibits activity of the nuclear enzyme topoisomerase I through stabilization of the cleavable DNA complex.⁴⁻⁶ Topotecan has documented activity in recurrent ovarian cancer⁷⁻⁹ and has been approved by the FDA for this indication. The main toxicities of topotecan are myelosuppression, alopecia and fatigue.^{9,10} Myelosuppression is not cumulative but is related to dose, schedule, and extent of prior therapy¹¹, suggesting that the therapeutic index of topotecan may favor less heavily pretreated patients.

Targeting topoisomerase I may enhance the toxicity of DNA-damaging drugs such as the platinum agents¹²⁻¹⁴, possibly through interactions between the cleavable complexes formed by topoisomerase I-targeting agents and the DNA replication fork that is formed during repair of DNA damage.¹⁵ An analysis of therapeutic interactions between paclitaxel, topotecan, and cisplatin showed synergism and suggested that lower doses could be utilized to achieve optimal anti-tumor effects in combination.¹²

Phase I trials of the combination of topotecan (days 1-5) and cisplatin (day 1) have shown more myelosuppression than expected from either agent alone.¹⁶ In one study, grade 4 neutropenia was dose-limiting, with a recommended topotecan dose of 1.0mg/m²/day for 5 days and cisplatin 50mg/m² on day 1 without Filgrastim. When Filgrastim was added, the dose of cisplatin could be increased to 75mg/m². When the sequence of drug administration was evaluated, there was significantly more myelosuppression when cisplatin was given on day 1 before topotecan, compared to administration of cisplatin on day 5, after topotecan.¹⁵ One explanation for this difference is that topotecan increases the toxicity of cisplatin by inhibiting the repair of cisplatin-induced DNA damage. An alternate explanation for the increased toxicity is that topotecan renal and/or hepatic clearance is lower when it is given after cisplatin due to subclinical platinum-related renal tubular toxicity or cisplatin effects on hepatic cytochrome activity.

Phase I trials of the combination of paclitaxel and topotecan demonstrated that these drugs can be safely given together with the use of colony stimulating factors (CSF). The combination of increasing doses of paclitaxel (3 hour infusion, day 1), followed by a fixed dose of topotecan at 1.0mg/m²/day for 5 days was evaluated by the Cancer and Leukemia Group B (CALGB).¹⁷ Again, neutropenia was the principal toxicity, defining a maximal tolerated dose (MTD) with paclitaxel at 80 mg/m², which could be escalated to 230 mg/m² with incorporation of Filgrastim. Sequence dependant effects were evaluated by GOG, with paclitaxel as a 24-hour infusion either before topotecan on day 1 or after topotecan on day 5. Dose-limiting myelosuppression occurred at the first dose level (topotecan 0.75 mg/m² and paclitaxel 135 mg/m²/24h). Although topotecan could be escalated to 1.5mg/m²/day with the addition of Filgrastim, 2 of 4 patients at this dose level developed fatal neutropenic sepsis. The high frequency and degree of hematologic toxicity made the analysis of sequence dependant effects non-informative.

The current study was designed to determine the feasibility of incorporating topotecan into a triplet with platinum and paclitaxel in patients with newly diagnosed previously untreated Stage III or IV ovarian cancer. A randomized trial comparing paclitaxel and carboplatin with

paclitaxel and cisplatin showed that the regimens were equally effective however the arm with carboplatin had significantly more thrombocytopenia than the arm with cisplatin³. Cisplatin may thus be better suited for combination therapy with other myelosuppressive agents, particularly agents like topotecan that are associated with significant platelet toxicity. Since myelosuppression was expected to be dose-limiting in this trial, paclitaxel as a three hour infusion was selected as it is less myelosuppressive than paclitaxel given as a 24 hour infusion.¹⁹ Our specific goals were to determine the RDL and to describe and quantitate the clinical toxicities of the three drug combination of paclitaxel, topotecan and cisplatin.

Materials and Methods

Eligibility

Patients were required to have newly diagnosed, stage III or IV, epithelial ovarian cancer or primary peritoneal carcinoma without prior chemotherapy. Patients could have either optimal or suboptimal residual disease. Patients were required to have adequate performance status (GOG 0 or 1) and organ function with absolute neutrophil count $\geq 1500/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$ and creatinine clearance ≥ 60 ml/min. Patients were excluded if they had any of the following: borderline ovarian tumor, previous treatment with chemotherapy or radiotherapy, a significant cardiac history, active infection, sensory neuropathy, known hypersensitivity to E. Coli derived drug preparations, another invasive malignancy (excepting non-melanoma skin cancer) within the last 5 years. All participants provided written informed consent in accordance with GOG, local institutional and federal guidelines.

Dosage and Administration

The starting dose for this phase I study was paclitaxel $175 \text{ mg}/\text{m}^2$ over 3h on day 1, cisplatin $50 \text{ mg}/\text{m}^2$ beginning 2h after completion of paclitaxel on day 1 at a rate of $1 \text{ mg}/\text{min}$, and topotecan over 30 min beginning on day 1 after cisplatin. The first cohort used a starting dose of topotecan $0.3 \text{ mg}/\text{m}^2/\text{day}$ for 5 consecutive days. Due to observed hematologic toxicity, a second cohort was added using a starting dose of topotecan of $0.5 \text{ mg}/\text{m}^2/\text{day}$ for 3 consecutive days. Treatment was to be given every 3 weeks for a maximum of 8 cycles. Filgrastim therapy was to be incorporated after definition of MTD without growth factor support. When used, Filgrastim was given subcutaneously at a dose of $5 \mu\text{g}/\text{kg}/\text{day}$ starting no sooner than 24h after the last dose of topotecan and was discontinued at least 72 hours before the subsequent cycle.

Paclitaxel was to be given with routine prophylaxis to reduce the risk of hypersensitivity reactions. Hydration and antiemetics were given before cisplatin administration. A comprehensive metabolic panel was obtained prior to each cycle of therapy. Electrolytes, magnesium, BUN and creatinine were obtained weekly. Complete blood counts were obtained on days 3, 5 and 8, and three times weekly until the post-nadir ANC was $>1500/\mu\text{L}$ on 2 consecutive determinations, or was $> 10,000/\mu\text{L}$ when Filgrastim was used.

Dose de-escalation by one dose level was allowed for patients who experienced a dose limiting toxicity but were responding to treatment.

Statistical Considerations

Hematologic toxicity and neurotoxicity were predicted to be dose limiting toxicities (DLTs). Because neurotoxicity is cumulative with delayed onset, cisplatin and paclitaxel doses were held constant, while the dose of topotecan was escalated. In the absence of DLT, four patients were to be treated at each dose level. All patients at an assigned dose level were required to have completed one 21 day course before subsequent patients were entered at the next highest dose level. If DLT was observed in 1 new patient, then two additional patients (total 6 patients) were treated at that same dose level. If less than 2 of the 6 patients treated at a dose level

experienced DLT, dose escalation continued. If DLTs occurred in 2 or more patients at a dose level, then further entry at that dose level was terminated. The recommended phase II dose was then defined as the previous dose level and at least 8 patients were to be treated at that dose level.

DLTs were defined during the first cycle of therapy based on the following events: Grade 3 or 4 unexpected nonhematologic toxicity; unresolved nonhematologic toxicity resulting in delay of the subsequent course of chemotherapy by more than 7 days; platelet count $<25,000/\mu\text{L}$; and delay of initiation of a subsequent course of chemotherapy by more than 14 days. Absolute neutrophil count (ANC) of $<500/\mu\text{L}$ for more than 3 days, even if asymptomatic, was also a DLT. This relatively conservative definition of DLT was used because of reports of treatment-related fatal sepsis from topotecan/cisplatin and topotecan/paclitaxel combinations.²⁰

Results

Patients

A total of 48 previously untreated patients from 8 institutions were enrolled in two cohorts; 25 patients in the first cohort received topotecan daily for 5 consecutive days, 23 in the second cohort received topotecan for 3 consecutive days. Patient characteristics are summarized in Table 1. Three of 48 patients were not evaluable, two due to paclitaxel reactions with the first course of therapy, preventing full dosing, and one due to an error in dosing.

Non-Hematologic Toxicity

Non-hematologic adverse events were uncommon and usually low grade. One patient in Cohort I had a gastrointestinal DLT consisting of hyperbilirubinemia. This patient was receiving total parenteral nutrition, which likely explained the elevated bilirubin, however, a contribution from treatment could not be excluded. There were no other non-hematologic DLTs. There was one case of grade three bone pain attributed to Filgrastim. Because this occurred in the fourth cycle of therapy, it was not considered dose limiting. There were no reports of grade 3 or greater neuropathy or renal toxicity, even after multiple cycles.

Hematologic Toxicity and Determination of the Recommended Dose Level

The first cohort of this study received topotecan daily for five consecutive days (Table 2). DLT, consisting of uncomplicated prolonged neutropenia, was observed in 2 of 6 patients treated at the first dose level and further escalation without Filgrastim was abandoned. Dose level 1 was repeated with incorporation of Filgrastim and all subsequent cycles of therapy at all dose levels in both cohorts used Filgrastim. None of the four evaluable patients in dose level 1 with Filgrastim experienced a DLT. Four patients were then enrolled at dose level 2 with no DLT, however, three of four patients at dose level 3 had a DLT. One was a gastrointestinal DLT (described above), one was grade 4 thrombocytopenia, and one was asymptomatic, uncomplicated but prolonged neutropenia. Four more patients were subsequently enrolled at dose level two (total 8 patients) with no further DLT observed.

The RDL from the first cohort (5-day topotecan with Filgrastim) was paclitaxel $175\text{ mg}/\text{m}^2/3\text{h}$ (day 1), cisplatin $50\text{ mg}/\text{m}^2$ (day 1) and topotecan $0.5\text{ mg}/\text{m}^2$ daily (days 1-5).

In the second cohort of the study, we used shorter duration topotecan in an effort to ameliorate the dose-limiting myelotoxicity that was seen in cohort 1. The second cohort continued with the same doses of paclitaxel, cisplatin, and Filgrastim, beginning with topotecan at $0.5\text{ mg}/\text{m}^2$ daily for 3 consecutive days (Table 3). At this first dose level one patient experienced neutropenic fever with the first cycle of therapy. A total of 6 patients were treated at this level

with no further DLT identified. Four patients were treated at the second and third dose levels using topotecan doses of 0.6 mg/m² and 0.75 mg/m² respectively, without DLT. Dose escalation proceeded until five patients were treated at the 4th dose level using topotecan 1.0 mg/m² daily × 3. Two patients at that dose level experienced dose limiting toxicities, one grade 4 thrombocytopenia, and one prolonged grade 4 neutropenia. Therefore, no further patients were treated at dose level 4. Four more patients were subsequently entered at the prior dose level (dose level 3), for a total of 8 patients, and none of these patients experienced a DLT, thus level 3 was determined to be the RDL for the administration schedule using three consecutive days of topotecan.

The RDL from the second phase of this study (3-day topotecan with Filgrastim), was a paclitaxel 175 mg/m²/3h (day 1), cisplatin 50 mg/m² (day 1) and topotecan 0.75 mg/m² daily (days 1- 3). Hematologic adverse events for both cohorts of patients are summarized in Table 4.

Cumulative Toxicity over Multiple Cycles

In this study DLT was defined by toxicity during the first cycle of therapy. After the first cycle, modifications in dose and/or schedule could be made at the discretion of treating physician. Thirty of the 45 patients completed 6 cycles of therapy and 3 completed 8 cycles. In the 45 evaluable patients there were 4 reports of grade 2 neurotoxicity and one of grade 2 ototoxicity. The remaining 41 patients reported grade 1 (20 patients) or no (21 patients) neurotoxicity or ototoxicity. There was no evidence of cumulative thrombocytopenia or severe non-hematologic toxicities as noted above.

Discussion

In this study, we found that the three-drug combination of paclitaxel, cisplatin and topotecan was feasible, but required the use of Filgrastim and attenuated dosing of topotecan in two cohorts using three days and five days of topotecan, respectively. Based on the known contribution of topotecan to hematologic toxicity, we felt that modification of the daily × 5 administration schedule of topotecan might ameliorate the myelotoxicity seen with this regimen. Although data with single-agent topotecan suggests that more prolonged administration schedules may be preferable, the therapeutic synergism reported for topotecan in combination with cisplatin suggests that maximizing the early, post-cisplatin topotecan exposure by concentrating topotecan administration over a shorter period of time may be preferable. For this reason, we treated a second cohort of patients using topotecan on a daily × 3 administration schedule. Although a higher daily dose of topotecan is tolerable using the contracted three-day schedule, the total dose of topotecan that can be administered per cycle at the RDL is almost identical in the two cohorts; 2.5 mg/m² for cohort 1 (0.5 mg/m²/d × 5 days) and 2.25 mg/m² for cohort 2 (0.75 mg/m²/d × 3 days).

Interestingly, a computerized model to quantify therapeutic interactions between these three drugs suggests that the synergistic antitumor activity is sufficiently potent that the doses of these agents required for antitumor effect may be twofold to eightfold less when the three drugs are given in combination.¹² If this model is relevant in the clinical setting, the doses of topotecan achievable in our study may be sufficient, and the daily × 3 topotecan schedule may be preferable.

The GOG has evaluated the sequence-dependent toxicity of carboplatin and topotecan in an extended-cohort phase I trial conducted in previously untreated patients.²¹ A “forward sequence” of carboplatin day 1 followed by topotecan on days 1-3 had unacceptable hematologic toxicity. The “reverse sequence” using topotecan on days 1-3 and carboplatin on day 3 was feasible with only one of 15 patients experiencing a DLT. The “extended reverse

sequence” using topotecan on days 1-5 and carboplatin on day 5 was associated with excessive DLTs. A potential drawback of sequential topotecan followed by carboplatin is that some preclinical data support a sequence-dependent antitumor activity favoring the platinum-topotecan sequence.¹²⁻¹⁵

A goal of this study was to develop this regimen as a possible experimental arm for a future GOG phase III study. Recently, the results of GOG 182, comparing paclitaxel and carboplatin with experimental regimens incorporating topotecan, gemcitabine or liposomal doxorubicin as a third agent were presented.²² The topotecan containing arm of GOG 182 was a sequential doublet with four cycles of topotecan and carboplatin given in the “reverse sequence” of topotecan daily $\times$ 3 and carboplatin on day 3, followed by four cycles of paclitaxel and carboplatin. The study failed to show an improvement in outcome for any of the experimental arms. These results have tempered enthusiasm for the addition of a third chemotherapeutic agent to a backbone of paclitaxel and platinum for treatment of ovarian cancer. Instead, a major focus of ongoing studies is the incorporation of targeted biologic agents to standard chemotherapy regimens.

The EORTC is currently comparing an arm of sequential doublet therapy of cisplatin plus topotecan using the “forward sequence” followed by paclitaxel plus carboplatin with an arm of paclitaxel and carboplatin alone as first line chemotherapy in newly diagnosed ovarian cancer. If that study demonstrates a benefit for the sequential doublet arm, it would support the hypothesis that there is sequence-dependent antitumor activity favoring the forward sequence of platinum-topotecan. Such a finding would reinvigorate interest in a topotecan-platinum combination for initial therapy of ovarian cancer.

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TABLE 1

Patient Characteristics

[[Median Age]]	[[53 (range 39-69)]]	[[[]]]
[[Median Performance Status]]	[[1 (range 0-1)]]	[[[]]]
[[[]]]	Number (48)	Percent
[[Stage III]]	[[40]]	[[83%]]
[[Stage IV]]	[[8]]	[[17%]]
[[Ovarian]]	[[43]]	[[90%]]
[[Peritoneal]]	[[5]]	[[10%]]
[[Grade 1]]	[[2]]	[[4%]]
[[2]]	[[2]]	[[4%]]
[[3]]	[[40]]	[[83%]]
[[Not specified]]	[[4]]	[[8%]]
[[Serous]]	[[39]]	[[81%]]
[[Endometrioid]]	[[4]]	[[8%]]
[[Clear Cell]]	[[2]]	[[4%]]
[[Adenocarcinoma NOS]] *	[[3]]	[[6%]]

* Not otherwise specified

TABLE 2

Cohort 1, Topotecan Daily × 5

[[Dose Level]]	[[Filgrastim]]	Topotecan (mg/m ² /day)	Paclitaxel (mg/m ²)	Cisplatin (mg/m ²)	[[Evaluable/Total Pts]]	[[DLT/Eval Pts]]
[[1]]	[[No]]	[[0.3]]	[[175]]	[[50]]	[[6/6]]	[[2/6]]
[[1]]	[[Yes]]	[[0.3]]	[[175]]	[[50]]	[[4/5]]	[[0/4]]
[[2]]	[[Yes]]	[[0.5]]	[[175]]	[[50]]	[[8/10]]	[[0/8]]
[[3]]	[[Yes]]	[[0.6]]	[[175]]	[[50]]	[[4/4]]	[[3/4]]

TABLE 3

Cohort 2, Topotecan Daily × 3

[[Dose Level]]	[[Filgrastim]]	Topotecan (mg/m ² /day)	Paclitaxel (mg/m ²)	Cisplatin (mg/m ²)	[[Evaluable/Total Pts]]	[[DLT/Eval Pts]]
[[1]]	[[Yes]]	[[0.5]]	[[175]]	[[50]]	[[6/6]]	[[1/6]]
[[2]]	[[Yes]]	[[0.6]]	[[175]]	[[50]]	[[4/4]]	[[0/4]]
[[3]]	[[Yes]]	[[0.75]]	[[175]]	[[50]]	[[8/8]]	[[0/8]]
[[4]]	[[Yes]]	[[1.0]]	[[175]]	[[50]]	[[5/5]]	[[2/4]]

Table 4

Adverse Events*

	[[0]]	[[1]]	[[Cohort 1]]			[[Cohort 2]]		
			[[1]]	[[2]]	[[3]]	[[1]]	[[2]]	[[3]]
[[0]]	[[0]]	[[0]]	[[1]]	[[1]]	[[3]]	[[1]]	[[2]]	[[4]]
[[0]]	[[0]]	[[0]]	[[1]]	[[1]]	[[3]]	[[1]]	[[2]]	[[4]]
Toxicity	Grade	[[0]]	[[1]]	[[2]]	[[3]]	[[1]]	[[2]]	[[4]]
[[Neutropenia]]	[[3]]	[[2]]	[[0]]	[[1]]	[[2]]	[[1]]	[[0]]	[[0]]
[[0]]	[[4]]	[[3]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[2]]
[[Platelets]]	[[3]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]
[[0]]	[[4]]	[[0]]	[[0]]	[[0]]	[[1]]	[[0]]	[[0]]	[[1]]
[[Infection]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]
[[Febrile Neutropenia]]	[[3]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]
[[Metabolic]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]	[[0]]
[[Bilirubin]]	[[2]]	[[0]]	[[0]]	[[0]]	[[1]]	[[0]]	[[0]]	[[0]]

* Adverse events are reported for the first course of therapy only. All toxicities are graded based on CTC version 3 criteria.

† Treatment given without Filgrastim, all other dose levels include Filgrastim