Emerging Role of Topotecan in Front-Line Treatment of Carcinoma of the Ovary

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ABSTRACT

The conventional front-line chemotherapy strategy for advanced epithelial ovarian carcinoma has become adjuvant administration of platinum (carboplatin and cisplatin), either alone or, most often, in combination with a taxane. However, a number of active agents have been identified in phase II/III trials of second-line and salvage ovarian cancer patients that may augment this front-line strategy. One agent, topotecan, has antitumor activity comparable with paclitaxel in patients with recurrent ovarian cancer and is an established treatment in second-line or salvage settings. Additionally, its mechanism of action is different from paclitaxel and is nonoverlapping. These properties, coupled with the in vitro synergy observed in tumor models among topotecan, paclitaxel, and platinum, have provided the rationale for investigators to examine topotecan in front-line ovarian cancer therapy. A number of strategies for incorporating topotecan into front-line therapy are under active investigation, including the replacement of paclitaxel with topotecan, a triplet regimen with cisplatin or carboplatin and paclitaxel, a consolidation regimen consisting of several courses of a platinum agent and paclitaxel followed by several courses of topotecan, and a sequential doublet regimen in which patients receive platinum in every course as part of a doublet with alternating or sequential topotecan and paclitaxel. Preliminary data from ongoing clinical trials of these new regimens show favorable response rates and generally manageable toxicity profiles. This review summarizes the preliminary clinical findings associated with the four strategies and outlines ongoing and future randomized studies of topotecan in front-line ovarian cancer. The Oncologist 2002;7(suppl 5):46-55

INTRODUCTION

The current front-line treatment strategy for advanced epithelial carcinoma of the ovary typically involves exploratory laparotomy and cytoreductive surgery, followed by systemic chemotherapy with platinum-based regimens. Several widely used regimens include cisplatin plus paclitaxel, carboplatin plus paclitaxel, and single-agent carboplatin. Carboplatin or cisplatin in combination with paclitaxel

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Epithelial carcinoma of the ovary is several-fold. First, topotecan was approved in 1996 for the treatment of metastatic carcinoma of the ovary after failure of first- or second-line chemotherapy. Several studies have demonstrated tumor response and survival. One such agent, topotecan, is a potent topoisomerase I inhibitor with broad activity in solid tumors, including ovarian tumors. The U.S. Food and Drug Administration approved the agent in 1996 for the treatment of metastatic carcinoma of the ovary after failure of first- or second-line chemotherapy. Several studies have demonstrated the efficacy of topotecan as a second-line therapy, with tumor response rates ranging from 13%-33% [6-11], (review by Herzog pp 3-10 [12]). The maximum tolerated dose (MTD) of topotecan was 1.5 mg/m²/day using a 5-day regimen every 21 days. Myelosuppression, particularly neutropenia, was its major dose-limiting toxicity (DLT). An 80%-90% decrease in white blood cell count at nadir was observed after the first cycle of therapy; however, bone marrow suppression was short-lived, noncumulative, and reversible and manageable. Nonhematologic toxicities were usually mild to moderate in severity and included alopecia and gastrointestinal toxicities, such as nausea, vomiting, diarrhea, and constipation (review by Dunton pp 11-19 [13]).

Based on the data observed in preclinical and clinical phase I, II, and III studies, a number of clinical trials are ongoing or planned to evaluate the feasibility and efficacy of topotecan in front-line treatment of ovarian cancer. This review summarizes the existing clinical efficacy and tolerability of topotecan in combination with carboplatin and paclitaxel in front-line therapy for ovarian cancer, presents the preliminary response data for patients treated with topotecan-based regimens, and summarizes ongoing or planned randomized studies of topotecan in this setting.

**Rationale for Topotecan in Front-Line Ovarian Cancer**

The rationale for evaluating topotecan in front-line epithelial carcinoma of the ovary is several-fold. First, topotecan has a different, non-overlapping mechanism of action from that of platinum or paclitaxel. Second, data derived from in vitro tumor model studies have demonstrated synergy among topotecan, paclitaxel, and cisplatin. Third, the antitumor activity and tolerability of topotecan have been established in second-line or salvage settings. These clinical settings often serve as a yardstick against which agents targeted for evaluation as front-line therapy are measured. Lastly, there is an absence of cross-resistance between topotecan and paclitaxel, and topotecan has demonstrated activity in platinum- and paclitaxel-resistant tumors. Each element of the rationale is described in more detail below.

**Unique Mechanism of Action and Synergy Potential**

Topotecan targets a different pathway in cell division from those targeted by platinum and taxanes. Topotecan is a semisynthetic derivative of camptothecin, a potent inhibitor of the nuclear enzyme topoisomerase I. This enzyme relieves torsional strain on supercoiled DNA and creates single-strand breaks in DNA during replication. Topotecan prevents topoisomerase I from repairing the cleaved DNA. As a result, the DNA continues to replicate, which leads to double-stranded DNA breaks and apoptosis. In contrast, paclitaxel promotes the formation of microtubules in rapidly dividing cells and inhibits their subsequent breakdown, which results in the cessation of cell division and cell death. Lastly, platinum exerts antitumor activity through the facilitation of DNA cross-linking. The novel mechanism of action of topotecan relative to other antineoplastic agents suggests that topotecan may act synergistically when administered in combination with other active agents.

In vitro tumor models have demonstrated synergy between topotecan and a number of chemotherapeutics used in ovarian cancer management, including cisplatin, carboplatin, oxaloplatin, doxorubicin, etoposide, irinotecan, and the alkylating agents. In particular, synergy has been shown between topotecan and paclitaxel in a colon cancer cell line experiment [14]. In this study, preincubation of cells with paclitaxel resulted in a 10- to 40-fold decrease in the concentration of topotecan required to decrease cell survival by 50%. Synergy has also been demonstrated for topotecan and cisplatin, or for topotecan and paclitaxel, in 54% and 22% of primary human tumor-cell culture samples, respectively [15]. A number of additional studies have shown synergy between topoisomerase I inhibitors and cisplatin [16-18]. Specifically, synergy between cisplatin and topotecan was demonstrated in vitro in a panel of eight solid tumor cell lines [19]. Three dose schedules were investigated: coincubation of cisplatin and topotecan, cisplatin preceding topotecan, and topotecan preceding cisplatin. Among ovarian cancer cell line models, cytotoxicity...
was found to be schedule dependent, with cisplatin followed by topotecan representing the most active sequence.

Similar studies in ovarian and lung cancer cell lines, and in an in vivo tumor xenograft model, have also demonstrated synergy between cisplatin and topotecan [15, 20, 21]. In vitro studies using a teratocarcinoma cell line, 833K, and its cisplatin-resistant subline, 833K/64CP10, were conducted to quantitatively analyze the cytotoxicity of various drug combinations [22]. In particular, these studies demonstrated a strong synergy among the triplet combination of topotecan, cisplatin, and paclitaxel. The two regimens exhibiting greatest synergy were cisplatin plus topotecan and cisplatin plus paclitaxel plus topotecan, whereas paclitaxel plus topotecan was less active in this in vitro model. These observations provide a valid rationale for pursuing these particular combinations in ovarian cancer trials in the front-line setting.

**Antitumor Activity of Topotecan and Potential for Non-Cross-Resistance**

Topotecan has significant activity as a single agent administered either intravenously or orally in patients with recurrent ovarian cancer [6, 10, 11, 23-25]. Several phase II trials have documented its efficacy as a second-line and salvage therapy regimen among patients failing platinum and/or paclitaxel [7-10]. In a phase III trial, single-agent topotecan was at least equivalent to single-agent paclitaxel as a second-line agent in patients with platinum-resistant ovarian cancer [26]. In that study, 110 of 226 originally randomized patients later crossed over from either topotecan to paclitaxel or vice versa in the third-line setting. An ORR (both cohorts) of 12% was observed, including partial responses (PRs) in 2 of 22 patients initially progressing on topotecan and 3 of 35 patients initially progressing on paclitaxel when they received their third-line therapy [27]. The results of these studies suggest that prior treatment with topotecan or paclitaxel may not adversely affect future responses to the crossover treatment [12]. Additionally, albeit limited by patient numbers, these findings suggest that patients could benefit from receiving topotecan in a front-line strategy because topotecan had activity against tumors that were resistant to both platinum and paclitaxel.

**CLINICAL TRIAL STRATEGIES FOR TOPOTECAN AS FRONT-LINE THERAPY**

The optimal approach for incorporating topotecan into front-line therapy of ovarian cancer is currently unknown, and therefore, has been the focus of several ongoing or planned trials. Four approaches are under evaluation, including a replacement strategy involving the substitution of topotecan for paclitaxel; a triplet strategy involving the addition of topotecan to the current standard, a consolidation strategy consisting of several courses of platinum plus paclitaxel followed by several courses of topotecan; and a sequential doublet strategy involving platinum in all courses and alternating courses of topotecan and paclitaxel (Fig. 1). Each of these approaches, along with preliminary clinical data, are summarized below.

**Topotecan Replacement Regimen**

The rationale for replacing paclitaxel with topotecan in a doublet regimen with platinum is based on in vitro synergy between the two agents [15] and clinical trial data in the recurrent setting demonstrating favorable objective response rates with topotecan relative to paclitaxel (20% versus 13%) and significantly improved time to progression (23 weeks versus 14 weeks, $p = 0.002$) [26]. A number of phase I/II studies are investigating the potential clinical

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**Figure 1. Investigative approaches to incorporating topotecan into front-line epithelial carcinoma of the ovary.** i.v. = intravenous; p.o. = oral.
benefit of paclitaxel replacement with topotecan, and these are summarized in Table 1 ([26-28] and Lissoni, personal communication).

Rowinsky et al. [28] reported the results of a phase I dose-escalation study of topotecan and cisplatin administered in two different schedules. Topotecan was administered as a 30-minute i.v. infusion daily for 5 days, and cisplatin was administered either on day 1 before topotecan or on day 5 after topotecan. The primary outcome in the study was regimen tolerability. Doses of topotecan and cisplatin greater than 0.75 mg/m² and 50 mg/m², respectively, led to dose-limiting neutropenia and thrombocytopenia, irrespective of hematologic support with G-CSF (Neupogen®; Amgen Inc.; Thousand Oaks, CA). The schedule of cisplatin administered on day 1 before topotecan produced greater neutropenia and thrombocytopenia than the alternate sequence. Further, pharmacokinetic studies suggested that cisplatin was associated with a decrease in renal clearance of topotecan, which may account for the greater toxicity observed with this dosing schedule. Although more toxic, the investigators recommended the day 1 cisplatin (before topotecan) regimen for further clinical evaluation. It was suggested that adequate patient hydration might prevent cisplatin-induced subclinical renal tubular toxicity.

Studies of topotecan administered over 21 days by continuous i.v. infusion have also shown some promise in the second-line treatment of ovarian cancer [31], and this schedule represents a potential strategy for front-line combinations. Prolonged infusion of topotecan coupled with cisplatin was investigated in 60 treatment-naïve patients with stage II to IV ovarian cancer [29]. Treatment of the initial four patients with topotecan, 0.4 mg/m², for 21 days and cisplatin on day 1 resulted in significant myelosuppression. As a result, the remaining patients were treated with topotecan, 0.3 mg/m², for 14 days, and cisplatin, 75 mg/m², on day 1. The ORR was 93%. Of the 51 patients with stage III/IV disease, 20 (47%) achieved a complete clinical response (CCR) and 20 (47%) a clinical PR. Median time to progression was 14.2 months. Adverse events associated with the 14-day regimen included grade 3/4 neutropenia in 72% of patients, grade 3/4 thrombocytopenia in 73%, grade 2/3 anemia in 89%, and grade 2/3 gastrointestinal toxicity in 29%. The investigators concluded that the antitumor activity of this regimen was at least equivalent to that of other platinum-based regimens.

Topotecan has also been investigated in combination with carboplatin in two recent studies ([30] and Lissoni, personal communication). In these studies, each 21-day course consisted of topotecan administered on days 1 and 3 and carboplatin on day 1. In the study by Estape et al. [30], topotecan was administered at 1 mg/m², and carboplatin was administered on day 3 q 21 days. The ORR was 73%. In the study by Lissoni (personal communication, October 2001), topotecan was administered at 1.5 mg/m², and carboplatin was administered on day 3 q 21 days. The ORR was 40%.

### Table 1. Role of topotecan in front-line ovarian carcinoma: replacement regimen

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose, mg/m²</th>
<th>Schedule</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rowinsky et al.</td>
<td>1) Topotecan 0.75, cisplatin 50; 2) Topotecan 1.0, cisplatin 50; 3) Topotecan 0.75, cisplatin 75</td>
<td>1) Topotecan on days 1-5, cisplatin on day 1; 2) Topotecan on days 1-5, cisplatin on day 5</td>
<td>Cisplatin followed by topotecan produced greater toxicity</td>
</tr>
<tr>
<td>Speyer et al.</td>
<td>Topotecan 0.3, cisplatin 75</td>
<td>Topotecan × 14 days (CI), cisplatin on day 1</td>
<td>ORR = 93%, CR = 47%, PCR = 38%, PR = 47%, SD = 5%, PD = 2%, Median TTP = 14.2 months</td>
</tr>
<tr>
<td>Estape et al.</td>
<td>Topotecan 1.0, carboplatin AUC = 5</td>
<td>Topotecan × 3 days, carboplatin on day 3 q 21 days</td>
<td>CR = 73%</td>
</tr>
<tr>
<td>Lissoni (personal</td>
<td>Topotecan 1.5, carboplatin AUC = 6</td>
<td>Topotecan × 3 days, carboplatin on day 3 q 21 days</td>
<td>CR = 40%</td>
</tr>
</tbody>
</table>

Abbreviations: AUC = area under the curve; CI = continuous infusion; CR = complete response; ORR = overall response rate; q = every; SD = stable disease; PCR = pathologic complete response; PD = progressive disease; TTP = time to progression.
In summary, the topotecan/platinum combination in front-line therapy shows promising activity. The major DLT was schedule-dependent myelosuppression, with greater hematologic toxicity observed when platinum was administered on day 1 of each course. Identifying optimal dosing and a schedule that will maximize the antitumor activity of the topotecan-based combination but limit the severity of myelosuppression requires further investigation.

**Triplet Regimen**

The rationale for integrating topotecan into the existing standard as part of a triplet regimen is based on in vitro synergy among topotecan, platinum, and paclitaxel [15] and on non-cross-resistance between topotecan and paclitaxel in clinical trials [27]. As summarized in Table 2, clinical investigations have recently evaluated the antitumor activity and tolerability of topotecan administered as part of a triplet regimen with paclitaxel and platinum ([32-34] and Engelholm and Scarfone, personal communications).

Frasci and colleagues [32] conducted a phase I study to determine the MTD of topotecan given weekly over 30 minutes in combination with cisplatin and paclitaxel, with G-CSF support. Nineteen ovarian cancer patients, 11 of whom were chemotherapy naïve, received a combination of cisplatin, 40 mg/m², paclitaxel, 85 mg/m² (1-hour infusion), and escalating doses of topotecan (beginning at 0.75 mg/m² over 30 minutes) weekly. Of nine chemotherapy-naïve ovarian cancer patients who were evaluable for tumor response, seven (78%) achieved responses, including three CCRs and four PRs. The most frequent serious toxicity was hematologic. A weekly topotecan dose of 2.25 mg/m² was recommended for phase II studies.

An ongoing study by the Gynecologic Oncology Group is evaluating the triplet regimen in patients with newly diagnosed stage III/IV ovarian cancer to determine the feasibility of adding topotecan to a paclitaxel and cisplatin regimen [33]. Topotecan, 0.3 mg/m², was administered on days 1 to 5 of every 21-day course. Patients received paclitaxel, 175 mg/m² over 3 hours, and cisplatin, 50 mg/m², on day 1. Dose escalations of topotecan (0.5, 0.6, and 0.75 mg/m²) and cisplatin (60, 75 mg/m²) are planned. Topotecan was administered 30 minutes after cisplatin on day 1. Of the initial 10 patients enrolled, there were six responses, including three PCRs. DLTs to date include uncomplicated but prolonged neutropenia in patients without G-CSF support. No DLT was observed in the presence of G-CSF support.

A similar study was conducted by Herben et al. [34] in previously untreated patients with stage III/IV ovarian cancer. Paclitaxel, 110 mg/m², was administered over 24 hours on day 1, followed by cisplatin, 50 mg/m² over 3 hours, on day 2, and topotecan, 0.3 mg/m² over 30 minutes, on days 2 to 6. Escalation was planned for cisplatin first (to 75 mg/m²), and then topotecan (to 0.4 mg/m²) with G-CSF support. Topotecan was administered 30 minutes after cisplatin on day 1. Of the initial 10 patients enrolled, there were six responses, including three PCRs. DLTs to date include uncomplicated but prolonged neutropenia in patients without G-CSF support. No DLT was observed in the presence of G-CSF support.

<table>
<thead>
<tr>
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<th>Schedule</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Frasci et al. [32]</td>
<td>Topotecan 0.75-2.5, cisplatin 40, paclitaxel 85 (1-hour i.v.), G-CSF 5 µg/kg</td>
<td>Topotecan, cisplatin, paclitaxel on day 1 q week, G-CSF on days 3-5 q week</td>
<td>MTD = topotecan 2.25 mg/m²/week, cisplatin 40 mg/m², paclitaxel 85 mg/m², ORR = 78%, CR = 33%, PR = 44%</td>
</tr>
<tr>
<td>Armstrong et al. [33]</td>
<td>Topotecan 0.3-0.75, cisplatin 50, paclitaxel 175 (24 hours), G-CSF 5 µg/kg</td>
<td>Topotecan on days 1-5, cisplatin and paclitaxel on day 1 q 21 days</td>
<td>ORR = 67%, CR = 50%, PR = 17%</td>
</tr>
<tr>
<td>Herben et al. [34]</td>
<td>Topotecan 0.3, cisplatin 50, paclitaxel 110 (24-hour i.v.), G-CSF 5 µg/kg</td>
<td>Paclitaxel on day 1, topotecan on days 2-6, cisplatin on day 2 q 21 days</td>
<td>CR = 60%, PR = 27%, SD = 13%</td>
</tr>
<tr>
<td>Engelholm (personal communication)</td>
<td>Topotecan 1.0-2.0, carboplatin AUC = 5, paclitaxel 135-175 (over 3 hours)</td>
<td>Topotecan on days 1-5, carboplatin and paclitaxel on day 5</td>
<td>All patients achieved at least a PR</td>
</tr>
<tr>
<td>Scarfone (unpublished data)</td>
<td>Topotecan 1.0, carboplatin AUC = 5, paclitaxel 175 (over 3 hours)</td>
<td>Topotecan on days 1-3, carboplatin and paclitaxel on day 3</td>
<td>ORR = 88%</td>
</tr>
</tbody>
</table>

Abbreviations: AUC = area under the curve; CR = complete response; G-CSF = granulocyte colony-stimulating factor; i.v. = intravenous; MTD = maximum tolerated dose; ORR = overall response rate; PR = partial response; q = every; SD = stable disease.

*Indicates only patients who completed the study (n = 6).
Engelholm reported the results (via personal communication) of a recent study of topotecan-based triplet therapy in 37 previously untreated stage IIB to IV ovarian cancer patients. Escalating doses of topotecan (1.0 to 2.0 mg/m²) were given orally on days 1 to 5, and carboplatin was administered to an AUC of 5 with paclitaxel, 135 to 175 mg/m² (over 3 hours), on day 5. All 37 patients in the study were reported to have achieved at least a PR, although preliminary data are not yet published. The treatment was well tolerated.

Finally, in a phase II study, 20 patients with suboptimal ovarian cancer received topotecan, 1 mg/m² for 3 days, followed by paclitaxel, 175 mg/m² given over 3 hours, and carboplatin, given to an AUC of 5 on day 3 (Scarfone, personal communication). Dose reductions were required in 30%-50% of patients due to neutropenia. Five patients received G-CSF support. An ORR of 88% was similar to the response rates reported in previous studies. Four patients achieved a PCR.

In summary, the three-drug combination appears to result in both a significant response and toxicity—a clinical scenario observed previously with the introduction of platinum agents into the front-line setting. However, toxicity may be significantly reduced in the current setting with further elucidation of the platinum agent, infusion schedules of both paclitaxel and topotecan, and the sequence of platinum relative to topotecan.

### Topotecan Consolidation Regimen

A third approach to integrating topotecan into front-line treatment of ovarian carcinoma involves its use as consolidation therapy following several courses of platinum plus paclitaxel. Two studies have evaluated the feasibility of single-agent topotecan in consolidation therapy following carboplatin plus paclitaxel, and the results are summarized in Table 3 [35, 36]. In the first study, 30 previously untreated patients with stage II to IV ovarian cancer were treated with paclitaxel, 175 mg/m² given over 3 hours, and carboplatin, AUC 6, every 3 weeks for 5 cycles, followed by 5 cycles of topotecan, 1.25 to 1.5 mg/m²/day every 3 weeks [35]. The MTD for topotecan, defined as the dose at which 33% of patients experienced grade 4 toxicity (myelosuppression) for more than 7 days, was 1.5 mg/m². The recommended dose of topotecan for further evaluation in a consolidation setting was 1.25 mg/m² on days 1 to 5 of a 21-day course. Response data from this trial are not available.

A phase II study evaluated the antitumor activity and toxicity of a regimen of two courses of paclitaxel, 60 mg/m² over 1 hour, and carboplatin, AUC 2, weekly for 6 weeks, followed by four courses of topotecan, 1.5 mg/m² × 5 days every 21 days [36]. Of the 37 patients with suboptimally debulked (>1 cm residual) advanced disease who completed the initial portion of the regimen (i.e., carboplatin plus paclitaxel), complete responses and PRs were observed in 32% and 46% of patients, respectively. Following completion of the topotecan sequence, 40.5% of patients had achieved a CCR and 27% had a PR. The 1-year survival associated with this regimen was 75%.

The preliminary results of using topotecan in consolidation therapy have been encouraging, and this approach warrants further evaluation. In particular, the consolidation regimen may be useful in patients who achieve a complete response with carboplatin and paclitaxel due to the lack of cross-resistance between paclitaxel and topotecan.

### Sequential Doublets of Topotecan/Paclitaxel with Platinum

Attempts to add topotecan directly to paclitaxel and cisplatin in a triplet regimen have been fraught with toxicity challenges, although the regimens had been associated with good antitumor activity (Table 2, [30-32] and Engelholm and Scarfone, personal communications). The sequential doublet combination may minimize toxicities associated with the triplet regimen and reduce the likelihood that patients with topotecan- or paclitaxel-resistant tumors will fail to benefit from treatment. A number of phase I/II studies are investigating sequential topotecan/platinum and paclitaxel/platinum courses, and the results are summarized in Table 4 [37, 38].

### Table 3. Role of topotecan in front-line ovarian carcinoma—consolidation regimen

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose, mg/m²</th>
<th>Schedule</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chan et al. [35]</td>
<td>Topotecan 1.25-1.5, carboplatin AUC = 6, paclitaxel 175 (over 3 hours)</td>
<td>Carboxplatin + paclitaxel q 3 weeks × 5 cycles, followed by topotecan × 5 days × 5 cycles</td>
<td>Topotecan MTD = 1.5 mg/m², 33% grade 4 toxicity</td>
</tr>
<tr>
<td>Gonzalez-Beca et al. [36]</td>
<td>Topotecan 1.5, carboplatin AUC = 2, paclitaxel 60 (over 1 hour)</td>
<td>Carboxplatin + paclitaxel weekly for 6 doses × 2 courses, followed by topotecan × 5 days × 3 weeks × 4 courses</td>
<td>Following carboplatin + paclitaxel regimen: CR = 32.4%, PR = 45.9%. Following topotecan: CR = 40.5%, PR = 27%. Overall 1-year survival = 75%</td>
</tr>
</tbody>
</table>

Abbreviations: MTD = maximum tolerated dose; AUC = area under curve; q = every; CR = complete response; PR = partial response.
In an attempt to limit the toxicities associated with a three-drug combination, the National Cancer Institute of Canada Clinical Trials Group investigated the feasibility of administering topotecan along with carboplatin and paclitaxel in sequential couplets of cisplatin/topotecan, followed by paclitaxel/cisplatin, in 44 patients [37]. Cisplatin, 50 mg/m², was administered on day 1, and topotecan, 0.75 mg/m², on days 1 to 5, with cycles repeating every 21 days for four cycles. Interval debulking surgery was performed as needed following the four cycles. Paclitaxel, 135 mg/m², was then administered over 24 hours on day 1 with cisplatin, 75 mg/m², given on day 2, with cycles repeating every 21 days for four cycles. Forty (91%) patients completed all eight cycles. The ORR was 78%. Progression-free survival was 15.3 months, and overall survival had not yet been reached. Of 32 patients undergoing interval cytoreduction after the topotecan/cisplatin couplet, five (16%) had a PCR and 16 (50%) a PR. The major toxicity observed with cisplatin/topotecan and paclitaxel/cisplatin was grade 4 myelosuppression occurring in 79% and 75% of patients, respectively.

In another recent study by Gordon et al. [38], the feasibility of alternating courses of topotecan plus carboplatin and paclitaxel plus carboplatin was investigated in previously untreated patients with advanced ovarian cancer. Carboplatin (AUC 4 to 5) was administered on day 1 with topotecan (0.6 to 1.0 mg/m²) for 3 days of cycles 1, 3, 5, and 7. Paclitaxel (175 mg/m² over 3 hours) was administered with carboplatin (AUC 5 to 4) on day 1 of cycles 2, 4, 6, and 8. The courses were planned to run for 21 days. The major toxicity was myelosuppression. DLT observed at level 0 (topotecan, 0.75 mg/m² days 1 to 5, and carboplatin, AUC 5) caused the investigators to reduce both the number of daily topotecan infusions (to 3 days) and the dose (to 0.6 mg/m²). In addition, thrombocytopenia-associated hematologic toxicity further necessitated a dose reduction in carboplatin (to AUC 4) in both couplet strategies. However, a higher dose of topotecan was possible following these modifications, and the MTD was identified as topotecan 1.0 mg/m² on days 1 to 3 without G-CSF support. Although prophylactic G-CSF administration ameliorated delays caused by myelosuppression, further dose escalation of topotecan was not possible due to thrombocytopenia. This novel alternating doublet regimen was associated with a progression-free survival of 20.5 months, and elevated pretreatment cancer antigen 125 (CA 125) levels normalized in 29 of 34 (85%) patients. The investigators suggested that further evaluation of this regimen should use topotecan at 1.0 mg/m² daily on days 1 to 3.

The sequential doublet regimen appeared to be active and generally well tolerated. In theory, this regimen has advantages over the replacement regimen because there is reduced concern about tumor-resistance development, as both paclitaxel- and topotecan-resistant tumors are treated. Additionally, the design of this schedule may alleviate some of the toxicity associated with the triplet regimen and may be a more acceptable regimen for delivery of all three agents. Based on the antitumor activity and tolerability profile of this regimen, many of the ongoing and planned studies of topotecan in front-line ovarian cancer incorporate this regimen.

**CONCLUSIONS**

On the basis of the in vitro and in vivo data presented, topotecan appears to be a credible candidate for investigation in front-line ovarian cancer treatment protocols. Although the preliminary work shows significant antitumor responses with topotecan, it is too early to determine which treatment strategy is optimal. The clinical trials outlined have used varied schedules—different doses of

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**Table 4. Role of topotecan in front-line ovarian carcinoma: sequential doublets**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose, mg/m² Schedule</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Hoskins et al. [37]</td>
<td>Topotecan 0.75, cisplatin 50-75, paclitaxel 135 (over 24 hours) A: Topotecan on days 1-5, cisplatin 50 day 1 q 21 days × 4 cycles followed by B: Paclitaxel day 1, cisplatin 75 day 2 q 21 days × 4 cycles</td>
<td>ORR = 78%</td>
</tr>
<tr>
<td>Gordon et al. [38]</td>
<td>Topotecan 0.75-1.0, carboplatin AUC = 4 or 5, paclitaxel 175 (over 3 hours) A: Topotecan on days 1-3 or 5, carboplatin (AUC = 4) on day 1 q 21 days during cycles 1, 3, 5, 7 alternating with B: Carboplatin (AUC = 5), paclitaxel on day 1 q 21 days during cycles 2, 4, 6, 8</td>
<td>MTD = topotecan 1.0 mg/m², carboplatin (AUC = 4), paclitaxel 175 mg/m²; Grade 4 neutropenia = 42% of courses. PFS = 20.5 months. CA 125 response = 85%</td>
</tr>
</tbody>
</table>

Abbreviations: AUC = area under curve; CA-125 = cancer antigen 125; MTD = maximum tolerated dose; ORR = overall response rate; PFS = progression-free survival; q = every.
topotecan, platinum, and paclitaxel—in varied patient populations, making comparisons difficult. Additionally, many of the studies were modest or small in size and lacked long-term follow-up. As a consequence, a number of larger, multicenter, randomized trials of front-line topotecan combinations are under way (Fig. 2). The results of these studies will further elucidate the efficacy of topotecan in front-line ovarian cancer therapy and will provide a larger body of data from which to base important treatment decisions.

ACKNOWLEDGEMENT
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SELECTED READING

