Cancer Chemother Pharmacol (2011) 68:457–463
DOI 10.1007/s00280-010-1510-y

ORIGINAL ARTICLE

Phase 1/pharmacology study of intraperitoneal topotecan alone and with cisplatin: potential for consolidation in ovarian cancer

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Received: 30 July 2010 / Accepted: 26 October 2010 / Published online: 11 November 2010

Abstract
Purpose Most ovarian cancers recur after first-line treatment. We studied the pharmacology, tolerability, and therapeutic potential of intraperitoneal (IP) topotecan, alone and with IP cisplatin.
Methods Patients received IP topotecan 1.5 mg (flat dose) daily on days 1–5 (level 0) via IP catheter. Subsequent cohorts received IP cisplatin 50 mg/m^2 on day 1 added to topotecan 1.5 mg on days 1–3 (level I), topotecan 1.25 mg on days 1–3 (level II), or topotecan 1.25 mg on days 1–5 (level III). Plasma and IP concentrations of total and lactone (E-ring closed) topotecan were measured on days 1 and 2 in cycles 1 and 2.
Results Sixteen patients (15 tubo-ovarian, 1 gastric cancers) were entered at levels 0 (3), I (4), II (4), or III (5). Dose-limiting neutropenias occurred in seven patients at dose levels I and III; grade 3 thrombocytopenia occurred in two at level III. Other toxicities included grade 1 hives in two, serum creatinine elevations in two, and *Staphylococcus epidermidis* and chemical peritonitis (one each). A median progression-free survival of 13 months was recorded among ovarian cancer patients who had minimal (6) or no residuum (3) after platinum-based induction; 5 are alive at 4 years. Topotecan's AUC IP/AUC plasma ratios ranged from 13 to 119.
Conclusion Topotecan IP for 3–5 days is tolerable; occasionally, myelosuppression is dose-limiting. Topotecan 1.25 mg (days 1–3) with IP cisplatin 50 mg/m^2 (day 1) is a regimen suitable for consolidation in phase 3 trials.

Keywords Intraperitoneal · Ovarian cancer · Topotecan · Cisplatin

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Introduction

The underlying pharmacologic principles of intraperitoneal (IP) drug delivery were formulated by Dedrick et al. [1] nearly three decades ago. Howell developed the pharmacologic basis for IP cisplatin in a series of studies mostly applied to ovarian cancer patients. Platinum-containing regimens building on Howell's initial experience [2] included their use in consolidation and exploring modulation of drug resistance with alpha-interferon [3] or cyclosporine [4]. Additionally, gemcitabine [5], docetaxel [6], and irinotecan [7] have been recently the subject of phase 1 and pharmacologic evaluations. However, the strongest support for pursuing this route of administration comes from results of phase 3 studies as described in the next two paragraphs.

In the 1990s, further pursuit of this strategy was questioned [8–10]. Randomized trials eventually yielded the proof-of-concept impact of IP cisplatin-based chemotherapy on survival [11]. In two of these trials (GOG104/SWOG8501 and GOG172), IP cisplatin (100 mg/m^2) for

six cycles was administered after surgery, whereas in another trial (GOG114) the six cycles of IP cisplatin were given after two cycles of intravenous (IV) carboplatin [12–14]. Meta-analyses of IP versus IV treatment and a National Cancer Institute Clinical Alert support a significant reduction in hazard risks for recurrence and death favoring first-line IP therapy of ovarian cancer [15–17]. Current trials (e.g., GOG252) are exploring whether IP carboplatin can be substituted for cisplatin, and whether bevacizumab adds to either IV or IP platinum/taxane combinations.

The IV/IP arm of GOG114—which, incidentally, had a 28-month median relapse-free survival, the longest of the trials of front-line IP therapy for stage III ovarian cancer—raises the possibility of using IP therapy for consolidation, thus extending the role of IP drug delivery beyond those optimally cytoreduced at the initial surgery [14]. Consolidation following negative reassessment after six cycles of IV platinum-based chemotherapy had been studied in an EORTC trial in which patients were randomized to receive IP cisplatin 90 mg/m^2 for four cycles or no further therapy following their initial platinum-based induction. This trial closed after 9 years because of slow accrual and poor compliance, in large part attributed to poor tolerance of the regimen, with 56% of the patients completing four IP cycles; only a trend was noted in favor of IP consolidation [18].

Consolidation regimens with IV topotecan or other drugs, vaccines, or IP radioimmunoconjugates were all found wanting in randomized phase 3 trials (cited by WP McGuire [19]). IP therapy as consolidation for residual ovarian cancer at reassessment has been reported in one randomized phase 2 trial [20] and several nonrandomized studies [2–6, 21–29]. Carboplatin by itself and in combination with etoposide [17, 21], paclitaxel by itself or with cisplatin [29], floxuridine alone or in combination with either cisplatin or carboplatin [23, 24], and mitoxantrone [21] are among the drugs that have undergone phase 1/2 studies of IP therapy. The study described here evaluated the tolerability and pharmacology of IP topotecan alone and with IP cisplatin as a potential regimen for consolidation after induction with platinum and taxanes. Both topotecan and another camptothecin analog, 9 AC, have undergone preliminary evaluation via the IP route with no local dose-limiting toxic effects (DLT) [30]. Their single-agent activity, persistent bioavailability of the active lactone form in direct contact with peritoneal surfaces, and potential synergy with cisplatin as predicted preclinically [31] support exploration of the use of topoisomerase-1-targeted camptothecin derivatives for consolidation after first-line therapy. We hypothesized that we could overcome partial platinum resistance still present at reassessment in minimal peritoneal disease by achieving high exposures to cisplatin coupled with introduction of a new agent (topotecan) working synergistically with cisplatin. In the trial design, we aimed at delivering topotecan in its preferred daily × 3–5 days schedule that also is more suitable for an eventual IP versus IV proof-of-concept comparison.

Patients and methods

Baseline eligibility requirements included adequate bone marrow granulocytes (>1.0 × 10^9/L) and platelets (>100 × 10^9/L), calculated creatinine clearance ≥60 mL/min (by the Cockroft-Gault method), serum bilirubin ≤1.5 mg% and aspartate aminotransferase ≤3 × upper limit of normal, and peripheral neuropathy not exceeding grade 1. A Port-A-Cath device, if not already present, was placed at the time of open laparotomy or laparoscopically within 8 weeks prior to initiating therapy.

Except for the first three patients, who received IP topotecan by itself, all patients received a combination of IP topotecan and IP cisplatin. IP cisplatin was given on day 1 at a dose of 50 mg/m^2 in 1 L of isotonic saline solution following administration of an antiemetic (usually an oral 5HT antagonist) and IV prehydration (1 L of isotonic saline solution with 2 grams of magnesium sulfate and 20 meq KCL) at 200 mL/hr. Additional hydration and antiemetics were given as required for emesis, though hospitalization was rarely necessary. The cisplatin was followed immediately by IP administration of topotecan in 500 mL isotonic saline solution. On subsequent days, IP topotecan was delivered in 1.5 L of isotonic saline solution with either oral or IV antiemetics and without prehydration. Treatment was given for four to six cycles to patients with detectable disease after induction, and for two cycles to patients without detectable disease after induction; it was to be discontinued for severe toxic effects occurring despite dose modifications.

After establishing that IP topotecan 1.5 mg alone daily for 5 days was tolerable (dose level 0), we embarked on a 3 + 3 dose escalation design for the combination of IP topotecan with a fixed dose of IP cisplatin (50 mg/m^2). The recommended phase 2 dose was defined as the dose level at which no more than one DLT episode occurred during the first two cycles in a cohort of six patients (or no DLT episodes in a cohort of five patients) and at which the next higher dose (i.e., the maximum tolerated dose) involved at least two patients experiencing a DLT episode, defined as a grade 3 nonhematologic toxic effect or any grade 4 toxic effect, in the first two cycles. Patients were assigned sequentially to cohorts on the four dose levels described in Table 1. Dose level 0 consisted of topotecan 1.5 mg (flat dose) on days 1–5 without cisplatin. Dose level I consisted of topotecan 1.5 mg delivered on days 1–3 with cisplatin 50 mg/m^2 on day 1. Because of excessive myelosuppression

Table 1 Dose levels: topotecan alone and with cisplatin

Dose level	IP Cisplatin	IP Topotecan (flat dosing)				
	Day1 (mg/m^2)	Day 1 (mg)	Day 2 (mg)	Day 3 (mg)	Day 4 (mg)	Day 5 (mg)
0	–	1.5	1.5	1.5	1.5	1.5
I	50	1.5	1.5	1.5	–	–
II	50	1.25	1.25	1.25	–	–
III	50	1.25	1.25	1.25	1.25	1.25

IP intraperitoneal

on this regimen, topotecan dose was reduced to 1.25 mg on days 1–3 for dose level II [24]. When dose level II proved to be tolerable, we explored extending the topotecan again through day 5 (dose level III).

In the event of a grade 3 or 4 toxic effect, dose modifications were made as follows: neutropenia and/or thrombocytopenia required reduction by one dose level (at dose level III) or a 33% decrease of topotecan dose (at other dose levels). Treatment-related renal effects or neurotoxic effects (persistent elevation of creatinine [>1.8 mg%] and/or grade ≥ 3 neuropathy) required withholding therapy until resolution. If abnormalities persisted beyond 6 weeks, reduction of cisplatin dose by 50% (for reversible toxicity) or omission of cisplatin (for irreversible toxicity) was considered for subsequent cycles. If cisplatin was omitted, topotecan was to be administered at dose level 0. Cisplatin and/or topotecan doses were also to be adjusted in the event of severe gastrointestinal symptoms (nausea, vomiting, diarrhea, mucositis).

For antitumor effect assessments—since low-volume peritoneal disease does not lend itself to the usual RECIST criteria of response—we focused on treatment-free interval and on surrogate indicators of antitumor activity such as CA125 levels and status of peritoneal cytology (after documented negative cytologic studies on at least two occasions). Surgery or CT scans supplemented assessment of disease progression in specific instances.

The protocol was approved by the Protocol Review and Monitoring Committee of the NYU Cancer Center and by the Institutional Review Board (IRB); all patients signed an informed consent prior to entry. The trial was not registered with cancer.gov, since the study was completed before this became a requirement of our Clinical Trials Office.

Pharmacokinetics

Analysis of the E-ring closed and open forms of topotecan from serial peritoneal fluid and plasma sampling was performed by HPLC during the first two cycles. On day 1, the patient's peripheral blood was sampled at the following time points: pre-dose, end of infusion, and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 21–24, and 45–48 h following the end of infusion. On day 2, a limited sampling was carried out at pre-dose, end of infusion, and 0.25, 0.5, 1, 2, 3, and 4 h following the end of infusion. When possible, peritoneal fluid was sampled at pre-dose, end of infusion and 0.5, 1, 2, 4, 8, 21–24, and 45–48 h following the end of infusion. The topotecan levels were determined by a methodology previously reported [32], with the following modifications: 1 mL of plasma or IP fluid was stabilized for analysis of the closed form by addition of 1 mL of a buffer containing 0.1 M ammonium phosphate and 25 mM diisooctyl sulfosuccinate (pH 6.0) containing 10 ng of camptothecin internal standard. The samples were processed through a Varian 300-mg solid-phase extraction column. For determination of total drug in the samples, 100 μL of the extracted sample was mixed with 50 μL 0.05 M phosphoric acid. After 0.5 h, 100 μL of this mixture was subjected to high-performance liquid chromatography (HPLC) analysis. A dual range of topotecan level standards comprised 2.5–50 ng/mL for the low range (plasma samples) and 50–1,000 ng/mL for the higher range (IP fluid). In general, the closed form averaged above 70%. The closed forms of topotecan from the plasma and IP decay data were best fit with nonlinear models available in WinNonlin ver 5.1 (Pharsight, Mountain View, CA).

Results

Sixteen patients (14 ovarian, one fallopian tube, and one gastric cancer) were enrolled between January 2001 and July 2005. A gastric cancer patient was the first patient enrolled following documentation of peritoneal implants at surgical staging. All subsequent patients had a nonuterine gynecologic cancer and had received prior IV carboplatin or cisplatin induction therapy. All were eligible for toxicity evaluation, the primary objective of our study (for patient characteristics, see Table 2). The gastric cancer patient was not included in the progression-free survival analysis, a secondary study objective, because of withdrawal from protocol treatment prior to any relapse. Response parameters based on CA125 level, radiologic imaging, and cytologic findings from peritoneal fluid samples taken prior to each IP treatment were followed, if applicable.

Hematologic toxicity

Among the three patients accrued at dose level 0, only one had a grade 3 or 4 hematologic toxic effect: grade 3 neutropenia occurring on day 22 of cycle 3 (C3D22). Myelosuppression was documented at all doses when cisplatin was included (Table 3). At dose level I, three of four patients developed grade ≥ 3 neutropenia (two, grade 4) on days 21–24 of cycle 1 (median absolute neutrophil count [ANC]

Table 2 Patient characteristics: adenocarcinomas of likely gynecologic origin (excludes one patient with gastric cancer)

Number entered	15
Diagnosis	13 epithelial ovarian cancer high-grade serous (7), adenocarcinoma NOS (4), endometrioid (2) 1 fallopian tube adenocarcinoma (adeno NOS) 1 primary peritoneal or ovarian signet ring adenocarcinoma
Median age, years	49 (range 36–71)
Stage	III: 14 IV: 1
Performance status	All 0–1
Second look (consolidation)	6 (2 microscopic; 4 ≤ 1 cm residuum) 3 (no residual disease following resection)
Metastatic/recurrent disease	6
Prior first-line treatment (patient number/total patient cycles)	Cisplatin or carboplatin/paclitaxel (12/68) Cisplatin/capecitabine (1/3) Carboplatin/cyclophosphamide (1/9) Cisplatin/topotecan (1/6)

NOS not otherwise specified

Table 3 Cumulative toxicity results: grade 3 or 4 only

Dose level	0 ($n = 3$)	I ($n = 4$)	II ($n = 4$)	III ($n = 5$)
Anemia	0	2 G3	0	0
Neutropenia[a]	1 G3	1 G3; 2 G4	3 G3	2 G3; 2 G4
Thrombocytopenia	0	0	0	2 G3
Nausea/vomiting	0	0	0	0
Abdominal pain	0	0	0	0
Diarrhea	0	1 G3	0	0
Headache	0	0	0	0
Fatigue	0	0	0	0
Mucositis	0	0	0	0
Neuropathy	0	0	0	0
Other	0	1 (G2 ↑ creatinine)	1 (G2 hives) 1 peritonitis (*S. epidermidis*)	1 (G2 hives) 1 (G2 ↑ creatinine)
Total number of DLT episodes[b]	0	2 (neutropenia) 1 (diarrhea)	0	2 (neutropenia)

G grade, *DLT* dose-limiting toxicity

[a] G3 neutropenic fever in two patients at dose level 1 (C3D28) and dose level 2 (C2D14)

[b] Defined as grade 3 nonhematologic toxic effect or any grade 4 toxic effect in the first two cycles

nadir 0.814×10^9/L), necessitating a 1-week dose delay in all three. The first two went on to complete five and three cycles, respectively, after a 33% dose reduction in topotecan, before disease progression. The third patient also required 33% dose reduction of topotecan (to 1.0 mg) due to grade 3 neutropenia and fever after cycle 3, which resolved with filgrastim and antibiotics; subsequently she completed a total of five cycles.

Because of these toxic effects at dose level I, dose level II utilized a reduced topotecan dose (1.25 mg) in this 3-day treatment schedule. Three of four patients at this dose level developed grade 3 neutropenia, on C6D24, C2D21, and C1D21 (median ANC nadir 1.062×10^9/L), but there were no DLT episodes. The third patient, after completing her second cycle, was hospitalized for *Staphylococcus epidermidis* peritonitis on C2D10, requiring removal of her catheter and discontinuation of study treatment. This patient had to be replaced with a fourth study entry for full two-cycle evaluability. Four of the five patients treated at dose level III developed grade ≥ 3 neutropenia, on C2D19, C1D17, C1D15, and C1D17 (median ANC nadir 0.854×10^9/L), two of which necessitated reduction of the topotecan. Both went on to complete five or six cycles without further severe toxic effects or the need for growth factors. Other hematologic toxic effects were infrequent; at dose level III, grade 3 thrombocytopenia was seen concurrently during two of the neutropenic periods; anemia, possibly attributable to treatment, was only moderate, and red

Table 4 Therapeutic outcomes

Dose level	0 ($n = 3$)	I ($n = 4$)	II ($n = 4$)	III ($n = 5$)
Cycles received	4, 2, 3	6[a], 4, 5, 3	6, 5, 6[b], 2	6[b], 4, 3, 5, 5
Patients recurrence-free (weeks)	1 (NE) 1 (25)	1 (*266+*)	2 (*209+*, *86+*)	
Patients progressing (weeks)	1 (52)	3 (*57*, 16, 15)	2 (5, *29*)	5 (*56*, *52*, *34*, 163, *108*)

Italics values denote therapy delivered in consolidation setting

NE not evaluable (gastric cancer—see text for nonevaluability)

[a] Topotecan dose reduced by 33%

[b] Cisplatin discontinued after three or four cycles (see text)

cell transfusions were not required, although recombinant erythropoietins were used on occasion.

Nonhematologic toxicity

The most common nonhematologic toxic effects were relatively mild, comprising mainly transient grade ≤ 2 nausea, vomiting, and abdominal pain readily treatable with supportive measures and antiemetics. One episode of grade 3 diarrhea (dose level I) was reversible with loperamide. Hives occurred in two patients immediately upon receiving IP cisplatin (one on cycle 3, dose level II, and the other one on cycle 4, dose level III). Gradual resolution occurred a few hours after treatment with steroids and antihistamines. Both continued on IP topotecan monotherapy without further severe toxic effects. Two patients had reversible cisplatin-induced serum creatinine elevations to 2.0 and 2.1 at dose levels I and III, respectively, leading to treatment discontinuation. Each had underlying co-morbid conditions: one diabetes and hypertension, the other ureteral obstruction due to tumor recurrence.

Antitumor effects and survival

Eight stage III and IV ovarian cancer patients entered the protocol as a 'consolidation' treatment following induction with 6–9 cycles of carboplatin or cisplatin + paclitaxel (7 patients), or cisplatin + cyclophosphamide (1) patient. One patient initially suspected to have a gastrointestinal primary (but later diagnosed as a 'signet ring' primary peritoneal or ovarian adenocarcinoma) received 3 cycles of cisplatin/capecitabine prior to protocol entry (Table 2). Six had minimal residual disease and 3 no residuum after their reassessment. A median progression-free survival of 13 months was recorded among these patients (in italics, Table 4). The median overall survival exceeded 4 years with 5 of these patients still alive at that landmark. Three remain disease-free, one was rendered disease-free by resection of a CT scan-isolated perihepatic recurrence at 5.5 years, and the fifth manifested disease after 18 months of protocol treatment and died at 6.2 years since entry. The six other patients with ovarian and tubal cancer entered the protocol with minimal residual disease after platinum-based induction treatment, followed by one or more treatments for recurrence. Three experienced surrogate evidence of antitumor activity (see below) with eventual progression at 6 months, 1 year, and 3 years, while the others progressed prior to 4 months (nonitalics, Table 4). These six patients died of disease at a median of 12 months from progression (range 5–56 months).

The CA125 level was abnormal (45–67 units/mL) at baseline in six patients, including three in the consolidation group: nadir CA125 levels of 9.4–16 units/mL were observed in four. One patient in the consolidation group who had only a transient decrease in CA125 level from 67 units/mL to a nadir of 51.7 units/mL, and another patient had continued rise in CA125 levels to over 200 units/mL before going off study; they both had documented progression by imaging.

One patient with gastric cancer was treated with three cycles of topotecan monotherapy (dose level 0) for residual subcentimeter peritoneal implants after gastrectomy. Though he experienced no significant toxic effects and was disease-free, he was taken off study and treated with three subsequent cycles of IP floxuridine. He remained disease-free for 5.5 years before a documented recurrence at the proximal anastomosis.

Pharmacokinetics

Pharmacokinetic studies of topotecan were performed on 15 patients spanning all dose levels. Peak IP and plasma levels ranged from 208 to 1166 ng/mL and 6 to 23 ng/mL, respectively. Figure 1, a plot from a patient on dose level II, demonstrates this 2-log differential in topotecan levels. IP/plasma area under the curve (AUC) ratios ranged from 13 to 119 over the three dose levels (Table 5).

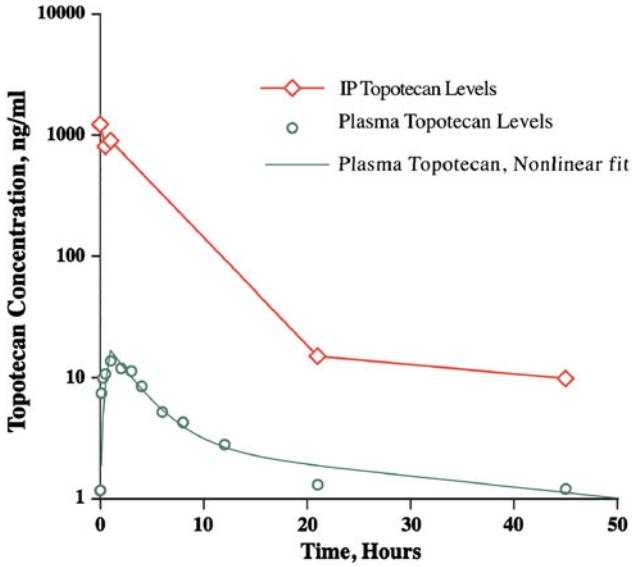

Fig. 1 Comparison of IP/plasma pharmacologic advantage. Plot of topotecan levels IP and in plasma (patient on dose level II)

Table 5 Topotecan pharmacokinetic data

Dose level	Plasma AUC (ng/mL × hr), range	IP AUC (ng/mL × hr), range	IP/plasma ratio, range
0	21–32	2,320	72–110
I	21–70	2,507	35–119
II	44–55	1,320–2,139	24–48
III	39–51	2,415–3,032	13–80

AUC area under the curve

Discussion

The study described here documents the toxicity pattern of IP topotecan on a daily 3- to 5-day schedule when given by itself or in combination with IP cisplatin (50 mg/m^2 on day 1) for as many as six cycles. In the three combination levels explored, the only consistent DLT was myelosuppression, requiring relatively minor reductions in topotecan dose to be tolerable. The 3-day schedule of the combination with 1.25 mg of topotecan and 50 mg/m2 of cisplatin (dose level II) was associated with no DLTs in three fully evaluable patients, whereas a dose of 1.5 mg topotecan (dose level I) caused DLTs in 3 patients. This finding, and consistent toxic effects on dose level III, led us to conclude that dose level II is a suitable starting dose for consolidation, with the suggestion that an additional 1–2 days of IP topotecan treatment be considered for subsequent cycles for individual patients experiencing no myelosuppression.

Antitumor activity was observed at all levels, as manifested by the lowering of CA125 levels in four of six patients who began with an abnormal baseline level. Among the nine patients in whom the regimen was used as consolidation therapy, the median PFS exceeded 1 year, and four of these patients were alive at 4 years (three recurrence-free).

The pharmacologic data indicate a median pharmacologic advantage (AUC IP/IV) about 100-fold for the active lactone form of the drug. While other studies with IP topotecan utilized different schedules, their reported tolerance and pharmacology findings are consistent with ours [33, 34]. When used as part of a consolidation regimen in 20 women who had residual disease after induction, IP topotecan 20 mg/m^2 every 3 weeks yielded a 24 month median progression-free survival at a median overall survival of 30 months from second-look surgery [35].

IV topotecan was used as consolidation in two phase 3 studies that yielded negative results [36, 37]. An IP topotecan regimen that also contains IP cisplatin, however, continues to have potential interest as a regimen to test consolidation after first-line treatment. Furthermore, significant tumor growth delays and survival following IP topotecan or IP cisplatin compared to their respective IV counterparts have been shown in a murine model when these treatments were coupled with IV antivascular endothelial growth factor antibody [38]. Our regimen uses daily IP topotecan on the schedule approved for the systemic use of this agent, and combines it with IP cisplatin in the sequence that is most effective (i.e., cisplatin preceding topotecan), albeit more myelotoxic [31].

In conclusion, the tolerable toxicity profile across all dose levels, coupled with encouraging outcomes in this phase 1 study, offers the possibility of choosing dose level II for phase 2/3 consolidation trials, with an allowance to extend topotecan to 5 days per cycle if the first cycle is tolerated. The topotecan levels achieved in the peritoneal cavity may enhance the therapeutic index of this agent, which is known to give very troublesome myelosuppression even in low doses when it precedes cisplatin [31]. Further trials testing such a strategy are warranted and may be reinforced depending on the results of the ongoing Gynecologic Oncology Group (GOG 252). This phase 3 study in advanced stage ovarian cancer that has been optimally cytoreduced is comparing two IP regimens to the standard IV carboplatin plus paclitaxel, all three adding bevacizumab.

Acknowledgments Supported in part by grants from Glaxo SmithKline, The Chemotherapy Foundation, and the GCRC M01 RR00096.

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